MEMORY STORAGE: EVIDENCE THAT CONSOLIDATION
CONTINUES FOLLOWING ELECTROCONVULSIVE SHOCK

by

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ABSTRACT

Recent experimental evidence indicates that the effectiveness of posttraining electroconvulsive shock in disturbing retention is not constant but highly variable. One factor which appears to contribute to this variation is the strength of the electroshock current. Currents of higher intensity or of longer duration have generally been found to be more effective in disturbing retention. Indirectly, this evidence suggests that an electroshock treatment does not invariably stop memory consolidation. It appears that following a weak electroshock treatment, the interference with consolidation is not complete and that consolidation may continue afterwards.

This possibility was directly examined in the present experiment with a one-trial passive avoidance task. The results showed that rats given one electroconvulsive shock 5 min after the passive avoidance training suffered only a slight loss of retention. However, when a second electroconvulsive shock was given at 1 hr after training, there was a significantly greater retention loss than that following one electroconvulsive shock at 5 min or at 1 hr. Additional results indicate that the disruptiveness of the second electroconvulsive shock is time-dependent and that the retention deficit does not appear to be due to punishing or disinhibitory effects of the electroconvulsive shocks. These findings are interpreted as indicating that memory consolidation can continue after electroconvulsive shock.

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Consolidation theory, which postulates that memory is susceptible to disruption shortly but not long after learning, has generally been the most successful way of accounting for the disturbances of retention found when electroconvulsive shock (ECS) is given after training. The recent accumulation of evidence that the effectiveness of ECS (and other amnesic agents as well) in disrupting retention is not constant but highly variable (Chorover and Schiller, 1965; Quartermain, Paolino, and Miller, 1965; Carew, 1970; Kopp, Bohdanecky, and Jarvik, 1966; McGaugh, 1966; Robustelli, Geller, and Jarvik, 1969) suggests that the time-dependent processes involved in consolidation may be influenced by many variables. This evidence has provided fruitful ground for a further elaboration of consolidation theory to account for this variability and has also led to the development of alternatives to the consolidation hypothesis as a basis for explanation.

A review of the experimental literature indicates three sources of evidence which appear to provide the best explanations for the apparent variation in the length of ECS-induced amnesia gradients. The first of these suggests that the variation is due to differences to which consolidation is disturbed and to which another process, "incubation" of a conditioned emotional response (CER), is interrupted. The second hypothesis suggests that the variation is really due to changes in the susceptibility of the consolidation process to disruption as a consequence of variations in what is learned and how it is learned. The third hypothesis suggests that the variation in amnesia gradients is due substantially to variations in the severity of the amnesic agent. The evidence for each of these explanations will now be presented and evaluated.

The Incubation Hypothesis

The first hypothesis is an alternative to a simple consolidation theory in that it postulates that two time-dependent processes rather than only one are interfered with by a disturbance of brain activity which occurs following acquisition (Spevack and Suboski, 1969). One of these is the well-known consolidation process but this is considered to be very brief (less than 1 minute). The other and longer process is incubation which can take several hours (Pinel and Cooper, 1966a). Descriptively, incubation is the gradual increase in the strength of a conditioned emotional response that takes place over time following the training trials. The variation in the length of ECS-induced amnesia gradients, according to this hypothesis, is due to differences in the extent to which response incubation is involved in the tasks studied. If no incubation is involved, the amnesia gradient will reflect only the short-duration consolidation process, while if incubation is present, the amnesia gradient will be much longer since the longer time-course incubation process will be interfered with.

This point of view is known as the incubation hypothesis and is derived mainly from the following evidence. In certain instances of passive avoidance learning (Pinel and Cooper, 1966a), there appears to be a period following training when a newly acquired passive avoidance response appears to spontaneously increase in strength (the incubation effect). When this gradient of incubation is compared to the gradient obtained by giving ECS at various times following passive avoidance training, the incubation and ECS-induced amnesia gradients are found to be practically identical. On the basis of these results,

Pinel and Cooper (1966b) and Pinel (1968) have suggested that in experiments where ECS is given after training as the interrupting agent, the performance deficit observed upon retesting could be due to the interference with incubation rather than to an impairment of memory. The possibility that the ECS-induced performance deficit in the passive avoidance task is due to a disturbance of incubation was subsequently strongly supported by Chorover and Schiller's (1966) finding that if the development of a conditioned emotional response which occurs during passive avoidance learning is prevented, a large part of the disruptive effect of ECS upon retest performance is eliminated. More recently, Spevack and Suboski (1969) have pointed out that in instances of appetitive or discrimination learning where little or no incubation occurs, ECS gradients are invariably short.

The foregoing summary indicates that the incubation hypothesis can assimilate into its framework a substantial part of the evidence on time-dependent disturbances of memory caused by ECS. However, there is also a considerable volume of equally reliable evidence in the consolidation literature which is completely inconsistent with the incubation hypothesis. This conflicting evidence concerns the very heart of the hypothesis, the proposition that any long amnesia gradients obtained with ECS are due to the interference with incubation and not consolidation. For example, Cherkin (1970) found that response incubation does not occur in his avoidance task and yet long gradients of amnesia can still be found. Similarly, McGaugh (1966) reported results indicating an amnesia gradient which is longer than the incubation gradient for his task. In a recent experiment with discriminated avoidance learning, Barrett, Hughes, and

Ray (1971) also found a long amnesia gradient that did not parallel the incubation curve. Tenen (1965a, b) using a one-trial appetitive task with no punishing experience to induce CER incubation reported a long amnesia gradient of 3 hours. These results on ECS-induced retention deficits with long time gradients cannot be accounted for by an incubation interpretation. Thus, although the incubation hypothesis has been useful in emphasizing the possibility that confounding variables (i.e., incubation) may be involved in the amnesia gradients obtained with ECS in some tasks, in general, the variation in the length of the amnesia gradients found with ECS does not seem attributable to the presence or absence of an incubation process.

Task Variation and Amnesia Gradients

The second way of accounting for the variation in ECS-induced amnesia gradients is not a formally elaborated hypothesis but a collection of evidence suggesting that the variation in amnesia gradients is systematically related to certain task and treatment variables. This evidence suggests that differences in the complexity of different tasks and in the strength of the reinforcer used during training are related to the length of the amnesia gradient. We will first examine this evidence and then suggest how it can be incorporated into consolidation theory.

With respect to task complexity, the following evidence has been reported. Chorover and Schiller (1966) have reported some results which indicate that passive avoidance learning involving the inhibition of stepping off a pedestal is less susceptible to disruption by ECS than passive avoidance of stepping through a hole into a dark chamber.

Similar results were also found by Carew (1970). Recently, the findings of Lewis, Miller, and Misanin (1968) and of Miller (1970) suggest that these task-associated differences in susceptibility to ECS interference may be related to the manner in which the relevant information about the learning task is acquired. Both Lewis et al and Miller found that increasing the animal's familiarity with the training apparatus prior to training significantly decreased the disruptive effect of ECS given following learning. Miller went on to show that as the complexity of the training environment is increased, a much greater amount of familiarity with the training apparatus is needed to offset the disruptive effects of ECS. Consistent with this evidence are the early results of Russell (1949) who found that the retention of more difficult maze learning was significantly more susceptible to interference by ECS. From these results, it appears clear that variation in learning tasks is one cause of the variation in amnesia gradients. However, whether one can attribute specifically the cause of the variation in amnesia gradients to the complexity of the training environment at the time of response acquisition will have to be verified by additional evidence varying complexity across a greater variety of training conditions.

The other characteristic of tasks that has been related to the susceptibility to disturbance by ECS is the amount of reinforcement used during training. Ray and Bivens (1968) reported that when higher foot-shock intensities were used during training, ECS is less disruptive of retention. Robustelli, Geller, Aron, and Jarvik (1969) varied the delay between the step-through response and the punishing stimulus during

passive avoidance training and found the responses acquired with the longer delays of punishment more susceptible to the amnesic effects of ECS. These results also suggest that there is a relation between training conditions and the length of amnesia gradients. However, at the very least these experiments will have to be done using positive reinforcers before differences in reinforcement per se can be seriously inferred to be the critical variable.

Overall, these experiments on task differences do indicate that the variation in amnesia gradients found with ECS is at least partly due to the variation in training conditions and in the response being acquired. The experimenters who have produced these results have avoided speculating on how these task differences affect the consolidation process. Lewis (1969) has come close to such speculation with his proposal that the way in which information is "registered" and "integrated into an existing cognitive complex" is directly affected by conditions present during training. However, in terms of consolidation, the most straightforward interpretation of this evidence would seem to be that the rate or speed of consolidation is affected by the learning conditions and the actual response learned. Thus, for example, simple response learning in familiar situations may be both assimilated faster (as Lewis suggests) and consolidated faster and therefore is less susceptible to interference by an amnesic agent after acquisition.

The suggestion that the rate of the consolidation process may differ between tasks is supported by a substantial number of experiments whose results tend to indicate that the rate of consolidation can be experimentally manipulated. Gerard (1955), for instance, has provided

some evidence that consolidation may be prolonged by a period of hypothermia given shortly after training. If hamsters were made hypothermic shortly after training, the period following training when an ECS could effectively disrupt retention was significantly increased. Davis, Bright, and Agranoff (1965) have subsequently made the same observation in goldfish. Using a similar experimental design, Albert (1966a) found that if a brief period of cortical spreading depression was given to rats shortly after training, the period following training when a second treatment of spreading depression could disrupt retention was similarly greatly increased. One way of interpreting these findings (Albert, 1966a) is that consolidation is slowed such that the processes which underlie consolidation progress at a slower pace and therefore, are susceptible to interference for a longer period after training.

There is also some evidence which suggests that consolidation can be speeded up. Albert (1966b) has reported that a short period of anodal polarization of the cortex following training shortened the time following training when a treatment of cortical spreading depression could normally disrupt retention. More recently, Bloch, Deweer, and Hennevin (1970) found that low level stimulation of the reticular formation immediately following training also attenuated the amnesic effects of a normally disruptive treatment of flurothane anaesthesia given 1 minute after training. Similarly, attenuating effects upon the disruption caused by ECS have also been found with injections of stimulant drugs. Weissman (1967) administered strychnine sulphate or pentylenetetrazol to rats just after training and before an ECS treatment and found some attenuation of retrograde amnesia upon retest the

next day. Bivens and Ray (1966, cited in McGaugh, 1968) administered strychnine sulphate to mice 10 minutes before passive avoidance training followed by ECS within 30 seconds and also found an attenuation of retrograde amnesia on a retest 24 hours later. McGaugh and Hart (cited in McGaugh, 1968) in a similar experiment also found that an injection of strychnine sulphate 10 minutes before training decreased the amnesic effects of an ECS administered 18 seconds or 1 minute following one-trial inhibitory avoidance training. Recently, Essman (1966) and Essman and Golod (1968) found the injection of tricyanoaminopropene and Essman, Steinberg, and Golod (1968) found the injection of nicotine before passive avoidance training also reduced the amnesic effect of ECS in mice. Because tricyanoaminopropene and nicotine are found respectively to increase significantly the ribonucleic acid content of the brain and to alter the biogenic amine changes caused by an ECS, these investigators suggested that changes in the content of brain ribonucleic acid and in biogenic amine (i.e., serotonin) activity may be two factors which are involved in antagonizing the amnesic effects of ECS.

The attenuation of amnesia found in all of these experiments is suggestive of the possibility that memory storage processes (i.e., consolidation) are facilitated or accelerated by these various experimental manipulations. Considered together, this evidence suggests that the rate of consolidation is variable and that it might, therefore, be affected by the conditions of training and reinforcement.

Electroconvulsive Shock Parameters

The third hypothesis accounting for the variation in the length

of ECS-induced amnesia gradients suggests that the amount of retention impairment observed in any experiment is directly related to the severity of the amnesic treatment (Alpern and McGaugh, 1968; Miller, 1968). This hypothesis arose from experimental evidence indicating that the disturbance of retention following an amnesic treatment was generally partial and related to the severity of the amnesic treatment. The more severe the amnesic treatment, the higher was the probability that the disturbance would be sufficient to impair retention.

A survey of the literature indicates substantial evidence supporting this proposal. Of the experiments using ECS as a disturbing agent, Weissman (1965), Miller (1968), Pagano, Bush, Martin and Hunt (1969), Ray and Barrett (1969), Jarvik and Kopp (1967), Dorfman and Jarvik (1968) and Lee-Teng (1969) have all found that with increases in the intensity of the electroshock current there is a corresponding increase in the amount of interference with retention. The only exception to this general pattern of results is an earlier experiment of Weissman (1963) which did not observe an increase in retrograde amnesia following large increases in the ECS current intensity. In experiments where the duration instead of the intensity of the electroshock is varied, the evidence is substantially less clear. Alpern and McGaugh (1968) have found significantly more retrograde amnesia following longer duration ECS currents. However, a subsequent experiment by Paolino, Quartermain, and Levy (1969), which also varied the duration of the ECS current, did not find any apparent change in the amount of amnesia following a four-fold increase in the duration of the ECS.

Besides the evidence with electroshock experiments, there is a

substantial body of findings from experiments using other amnesic agents which also tends to support the hypothesis that the amount of retention interference is directly related to the severity of the amnesic treatment. Albert (1966a) and Burésóva and Burés (1971) have found greater interference with increased durations of spreading depression. Cherkin (1969) increased both the duration and the concentration of the convulsant flurothyl and found much greater retention interference. Alpern and Kimble (1967) found that the disruptiveness of diethyl ether was related to its temperature. Quinton (1966) and Beitel and Porter (1968) respectively found that increasing the time of exposure to carbon dioxide or to hypothermia following training correspondingly increased the amount of retention interference. Flexner, Flexner, and Stellar (1965) have reported that as the concentration of the antibiotic puromycin was increased, its disturbance of memory became progressively more effective.

In summary, although the evidence is not unanimous, the bulk of it, both with ECS and other amnesic agents, seems to favor the conclusion that there is a direct relationship between the severity of the amnesic treatment and the amount of retention interference. This evidence seems to verify the suggestion that the disturbance of consolidation by an amnesic agent is not an all or none phenomenon. Rather it appears that the amount of disruption of consolidation is a function of the magnitude of the disruptive effects induced by the amnesic agent.

It is important that the experiments which have shown a direct relationship between the intensity or the duration of the amnesic treatment and the amount of retrograde amnesia have not usually presented

evidence indicating that the more intense or longer duration amnesic treatment created more severe disturbances of neural activity. Of the experiments cited above, only the Flexner et al. (1965) study provided some evidence that the increase in the disruptiveness of the amnesic agent, puromycin in this case, upon memory was correlated with correspondingly greater biological disturbances (i.e., the elevation in the degree and the duration of cerebral protein synthesis inhibition following injections of more concentrated puromycin solutions). In terms of consolidation theory, such evidence seems to be essential in order to show that there is an actual physiological basis for the greater disturbance of retention following more severe amnesic treatments. There is in the literature some independent experiments which do indicate such a relation for several amnesic agents. Minz and Domino (1953), for example, have found that electrocortical seizures of increasing strength and duration were induced by more intense as well as by longer durations of electrical stimulation of the brain. Zornetzer and McGaugh (1970) have found that increasing electroshock intensity produced a more severe disturbance of brain activity in terms of increased seizure discharges and heightened frequency of spike activities. The longer durations of cortical spreading depression are found to be associated with a longer period of depression of neural activity (Burés, 1959). Higher concentrations of flurothyl have been found to produce higher frequency of spike discharges (Herz, Spooner, and Cherkin, 1970). Severe hypothermia is found to produce a greater flattening of the EEG indicating an absence or large decrease in neural activity (Horsten, 1949).

A clear indication of the way in which more severe amnesic treatments cause more memory deficits is not yet available, but several authors have suggested some interesting possibilities. Albert (1966a) and Cherkin (1969) have proposed that the reason there is more retention following a weak amnesic treatment is that these weak treatments slow but do not stop consolidation. Post-treatment consolidation thus can be the cause of the subsequently observed retention. As more direct evidence for the possibility that consolidation does continue following an amnesic treatment, Albert (1966a) has provided some results showing that a brief period of cortical spreading depression, which was not in itself sufficient to impair retention, enabled a later period of spreading depression to produce a loss of retention at a time when the second spreading depression treatment by itself would normally be ineffective. Albert suggested that while the first period of spreading depression was not sufficient to impair retention, it did disturb consolidation in a latent way which allowed the second period of spreading depression to actually stop the consolidation process and prevent retention.

Alpern and McGaugh (1968), Miller (1968), and Ray and Barrett (1969) have each suggested that the differences in effectiveness found with ECS treatments of various parameters are due to the variation in the amount of current which passes through the brain. They suggest that this results in varying degrees of disturbance of neural activity. In a somewhat more precise elaboration of this general line of thinking, Ray and Barrett (1969) have reasoned that retention circuits may be in areas of the brain which are not, or are only slightly, affected

by low levels of ECS current applied to the entire brain. With higher currents, these areas of the brain are presumably also disturbed and this could be one factor which contributes to the differences in amnesia induced by ECS of varying parameters. Alternatively, it is also possible that, with more intense or longer duration electroshock currents, the total amount of physiological disturbance created within the same brain structures is greater so that the consequent amount of retention interference induced is also larger.

The Present Experiment

Of the three explanations examined, the last two, variations in task variables and in disturbing-agent parameters, appear to provide the most substantial basis for explaining the obtained variation in ECS-induced amnesia gradients. The effects of both these variables seem to make sense in terms of the consolidation hypothesis. Differences in tasks might well be expected to have some effect upon the ease with which information is assimilated and consolidated following acquisition. Differences in the severity with which an amnesic agent disturbs some aspect of neural processes seem to follow the pattern that would be expected if the neural substrate of memory storage processes is being interrupted.

The intent of the present experiment is to look more closely at the question of how more severe disturbances of neural processes cause correspondingly more severe disturbances of consolidation. The above evidence on variation in amnesic agent parameters and the amount of retrograde amnesia is all in agreement with the general conclusion that weaker disturbances of neural activity are less effective in

disrupting retention because they do not invariably stop the consolidation process. The present experiment investigates the possibility that memory consolidation continues following a single ECS. The method for examining this possibility was to administer an ECS at a training-ECS interval where only a small retention loss occurs, and then a second ECS at a longer post-training interval. It was reasoned that if consolidation is only partially disturbed by the first ECS, the additional interference produced by a second ECS might be sufficient to actually stop the process and prevent retention.

Method

Subjects

The subjects were 128 naive, male, black hooded rats (200-300 grams) purchased from the Quebec Breeding Farm. They were housed in individual cages and maintained on a 23-hr water deprivation schedule throughout the experiment.

Surgical Procedures

Three days before approach training in the alley, ECS screw electrodes were implanted in the animals' skulls. A screw electrode consisted of a 2 cm long steel pin connected by a thin, stainless steel wire to a jeweller's screw. While the rat was anaesthetized with sodium pentobarbital (Nembutal, 40 mg/kg), its skull was exposed, and bilateral screw electrodes were threaded just through the skull at 3 mm lateral and 1 mm posterior to bregma. Two supporting screws were similarly turned into the skull just anterior to the coronal suture. Dental acrylic was then applied to cover completely the supporting and electrode screws, and the whole wound area.

Apparatus

The passive avoidance apparatus consisted of a wooden alley (104 cm by 14 cm by 20 cm high) with a mesh runway leading to a gridded goal area (last 19 cm of the alley) where a water spout protruded from the end wall. Footshock (2 ma ac, 1 sec) was delivered by electrifying the gridded goal area with a power transformer supplying 420 V. Electroconvulsive shock (25 ma, 0.4 sec) was generated through a 60 Hz, 820 V source which was connected in series to a 33,000-ohm resistor and the screw electrodes implanted in the animal's skull. ECS delivered in this manner reliably produced tonic-clonic seizures.

Experimental Procedures

Forty-eight hr after surgery, the animals were placed on a 23-hr water deprivation schedule which continued for the remainder of the experiment. Twenty-one hr later (Day 1), the animals began approach training in the alley. On Day 1, they were given a 5-min habituation trial. Then from Day 2 to Day 6, each animal was placed into one end of the alley facing the goal and left for 1 min. The latency following the release of the animal until it started drinking at the goal was recorded with a stop watch. Animals which did not drink were assigned a score of 60 sec. Three such trials, each separated by about 20 min, were given daily. On the basis of the mean latencies to drink from Day 2 to Day 6, the animals were divided into matched groups.

On Day 7, the animals were "treated". Prior to their being placed into the alley on Day 7, all animals had wire leads attached to their skull electrodes (this did not prevent the animals from approaching the water spout promptly). Every animal which received passive avoidance

training was permitted to approach the goal area as previously. Three sec after the animal crossed into the goal area, it received a footshock (FS) via the grid floor. Fifteen sec after the FS, the animal was taken from the alley and returned to its cage. The wire leads on the animal's skull electrodes were not removed until after the first ECS or sham ECS treatment 5 min after the training. Animals not treated at 5 min had their wire leads removed during the transfer back to their cages (see Figure 1 for a description of the experimental paradigm).

The footshock control group (FS-only) received a sham ECS (no current passed) 5 min following the FS.

Group 5-min-ECS was given an ECS 5 min after the FS. The purpose of this group is to show that a single ECS administered at a fairly short training-ECS interval does not produce a substantial interference with retention.

To examine the possibility that memory consolidation is not suppressed completely by the single ECS at 5 min after training, group 5-min-1-hr-ECSs received a second ECS 1 hr after the FS. To see if the effect of the second ECS was time-dependent, group 5-min-24-hr-ECSs was given the second ECS 24 hr after the FS.

Finally, three other groups were included. Group 1-hr-ECS was given a single ECS 1 hr after the passive avoidance training to assess the disruptive effect of a single ECS at 1 hr after training. Group 24-hr-25-hr-ECSs was administered two ECSs separated by one hr, 24 hr after training, to control for possible disinhibitory effects of two closely paired ECSs. The last group, No-FS-5-min-1-hr-ECSs, was a control for any aversive effects of the paired ECSs alone. Animals

in this group were not footshocked, but were removed from the alley 3 sec after they crossed into the goal. ECS was administered 5 min and 1 hr later.

Forty-eight hr (Day 9) after training, the animals of each group with the exception of those belonging to group 24-hr-25-hr-ECSs were returned to the alley for three 60-sec test trials. The mean approach latency on the three test trials was scored for each animal as a measure of retention. Group 24-hr-25-hr-ECSs was retested 72 hr (Day 10) after training in order to maintain an ECS-retest interval approximately equal to that of the other groups.

Statistics. Statistical analyses were performed using two-tailed Mann-Whitney U tests.

Results

The results are summarized in Figure 1. A single ECS at 5 min after the training (5-min-ECS group) did not significantly reduce the retest approach latencies below those of the FS-only group ($p < 0.10$). However, a second ECS at 1 hr after the FS (5-min-1-hr-ECSs group) significantly increased the disruptive effects of the ECS treatment. The retest score for the 5-min-1-hr-ECSs group was significantly lower than that of the 5-min-ECS group as well as that of the FS-only group (both $p < 0.002$). That the disruptive effect of the second ECS is time-dependent is shown by the performance of the 5-min-24-hr-ECSs group, which received the second ECS 24 hr after the training. The approach latencies for the 5-min-24-hr-ECSs group were not significantly different from those of group 5-min-ECS.

Figure 1. Median approach latencies for each experimental group on the retention test. All groups (except group 7) were given a FS in the passive avoidance apparatus followed by ECS or sham ECS treatments. These treatments were as follows: Group 1, ECS at 5 min and 1 hr after the FS; Group 2, ECS at 5 min and 24 hr after the FS; Group 3, ECS at 5 min after the FS; Group 4, ECS at 1 hr after the FS; Group 5, ECS at 24 hr and 25 hr after the FS, and Group 6, a sham ECS at 5 min after the FS. Group 7 did not receive a FS but was given an ECS 5 min and 1 hr after the removal from the avoidance apparatus.

The possibility that the second ECS for the 5-min ECS groups was affecting a time-dependent process is supported by the finding that the retest approach latencies of the 24-hr-25-hr-ECSs group, which received the paired ECSs 24 hr after training, were not significantly different from those of the FS-only control. This finding suggests that the poor retest performance for the group 5-min-1-hr-ECSs is not due to possible disinhibitory effects of the ECSs (Poslums and Vanderwolf, 1970). In agreement with the recent findings by Kesner, Gibson, and LeClair (1970) the paired ECSs alone (group No-FS-5-min-1-hr-ECSs) did not appear to have any effect upon the approach response which could be attributed to inhibitory or aversive effects of ECS.

Figure 1 also shows that a single ECS by itself at 1 hr after training only slightly interfered with retention (1-hr-ECS vs FS-only, $p < 0.10$). However, the disruptive effect of an ECS at 1 hr after training was significantly increased when it was preceded by another ECS at 5 min after training (1-hr-ECS vs 5-min-1-hr-ECSs, $p < 0.05$). This indicates that although the ECS administered at 5 min after training did not greatly disrupt retention, it did in some way increase the effectiveness of a second ECS given at 1 hr. This enhancement of the effectiveness of a second ECS in disrupting retention seems to last at least 1 hr but less than 24 hr.

In order to delimit more precisely the duration of the increased susceptibility to disruption induced by the first ECS at 5 min after training, several additional groups of rats were run in the way described previously and were given an ECS 5 min after the passive avoidance training. A second ECS was then administered at varying times

Figure 2. The effect of an ECS at 5 min following footshock on the length of time afterward when a second ECS can be given and impair retention (dash line). The horizontal line represents the maximum retention expected of the two ECS groups as estimated from the effect of a single ECS at 5 min. The curve (solid line) showing the effect of a single ECS given at varying times following learning is presented to show how much the administration of two ECSs rather than one increased the time following footshock when a treatment could be given and still impair retention. To complete the one ECS curve, a group (n=9) which received a single ECS at 2 sec following footshock has been added.

after the first ECS. The results are presented in Figure 2. There was a significant interference with retention when the second ECS was administered at 2 hr (n=11) (5-min-ECS vs 5-min-2-hr-ECSs, $p < 0.002$) after training, but at 3 hr (n=12) or 6 hr (n=12) the effectiveness of the second ECS had dissipated.

Figure 2 also summarizes the results of the present experiments. It illustrates how much the administration of two ECSs, rather than one, increased the time following the FS when an ECS treatment could be given and still disturb retest performance.

Discussion

Memory consolidation appears to continue following a single ECS given at 5 minutes after passive avoidance training. The evidence for this is that while a single ECS at 5 minutes after training does not greatly disrupt retention, a second ECS given some time after the first ECS drastically increases the loss of retention. Since the second ECS impairs retention in a time-dependent manner and appears to be independent of disinhibitory and punishing effects, its disturbance of retention is consistent with memory consolidation theory. The finding that retention is disrupted at all by the second ECS suggests that consolidation is not stopped following the first ECS.

Within the context of consolidation theory, the present finding of an extended amnesia gradient with the two ECSs appears explainable in several reasonable ways. One possibility is that the first ECS while itself not completely disrupting consolidation does produce effects which potentiate the disruptiveness of the second ECS. The enhanced effectiveness of the second ECS in disturbing retention may be due to

certain physiological and metabolic changes caused by the first ECS which then potentiate the disturbing effect of the second ECS and allow it to disrupt more completely the consolidation process. For example, brief periods of energy reserve depletion in the brain have been found following a single ECS (King, Lowry, Passonneau, and Venson, 1967; Ferrendelli and McDougal, 1971). If this metabolic depletion is prolonged or increased by a second ECS, the disturbing effect upon consolidation may become sufficient to prevent retention. In addition, the biochemical effects produced by an ECS is not restricted to a disturbance of energy reserves. Disturbances of protein synthesis (Cotman, Banker, Zornetzer, and McGaugh, 1971), free fatty acids pool (Bazán, 1971), serotonin, norepinephrine and 3,4-dihydroxyphenylethylamine levels (Hineslay, Norton, and Aprison, 1968; Essman, 1970) and acetylcholine activity (Adams, Hoblit, and Sutker, 1969) have been found. The disruption of consolidation by the ECS treatments observed in the present experiment may involve any or all of these biochemical disturbances.

Alternatively, the results of the present experiment may be due to the first ECS partially disrupting and slowing consolidation such that the overall duration of the consolidation process is prolonged. This prolonging of the consolidation process thus makes possible the disruptive effect of a second ECS even when it is given at a time after learning when by itself it would be quite ineffective in disturbing retention. In an earlier experiment with cortical spreading depression as the disturbing agent, Albert (1966a) has found essentially the same results. When a brief period of spreading depression,

which did not by itself disturb retention was given shortly after training, it enabled a later period of spreading depression to disrupt retention at a time when the second treatment of spreading depression by itself was not effective. Albert interpreted these results as suggestive of a slowing effect upon consolidation induced by the first treatment of spreading depression. Recently, Cherkin (1969) has similarly suggested that under certain conditions an amnesic treatment may only slow memory consolidation. His results with the convulsant flurothyl suggest that a slowing effect upon consolidation occurs following less potent or less severe amnesic treatments.

The occurrence of slowing and potentiation effects may not be mutually exclusive. The amnesia found following the two ECSs at 5 minutes and 1 hour, for instance, could be the result of both these effects occurring together. The extent of the present findings, however, do not permit a definitive evaluation of this possibility nor for that matter of the slowing effect or the potentiation effect alone as the more likely explanation for the present findings. However, all of these explanations are consistent with the conclusion that consolidation continues following the first ECS.

Considered outside the framework of consolidation theory, the strongest alternate explanation for the present findings seems to be that suggested by Wiener (1970). He proposed that ECS-induced retention deficits are due to the fact that ECS alters brain cholinergic activity following learning. There have been a number of results suggesting that changes in brain cholinergic activity is reflected in performance variations. Deutsch (1971) has recently summarized this

evidence which suggests that cholinergic activity immediately after learning is very high, but then declines over a number of hours following learning. However, this decline gradually dissipates again over time (up to 14 days). Apparently, if experimental manipulations such as anticholinesterase injection (Deutsch, 1971) or ECS (Adams et al., 1969) which increases acetylcholine levels in the brain are given at times when acetylcholine levels are high following learning, they can interfere with retention performance. Wiener's results suggest that this is the manner by which ECS treatments interfere with retention. Wiener found that a series of 5 ECSs given at 5 minutes, 30 minutes, 7 days, and 14 days after training interfered with retest performance but not if the ECSs were given 1 day, 3 days, 5 days, or 31 days after training. This pattern of results is essentially identical to that found with anticholinesterase drugs (Deutsch, 1971) and it reinforces the possibility that ECS-induced retention losses are due to the alteration of cholinergic activity in the brain.

Implications for Recent Findings

The conclusion drawn from the present findings that consolidation can continue following an ECS provides a useful and parsimonious theoretical basis for interpreting several recent discoveries reported in the consolidation literature. The following discussion suggests how the evidence provided by the present experiment makes possible the assimilation of these findings within consolidation theory.

a) The variation in amnesia gradients

The present finding that memory consolidation can continue following an ECS treatment suggests one possible way of resolving the evidence on

the differences in amnesia gradients obtained following variations in ECS parameters (Alpern and McGaugh, 1968; Miller, 1968; Pagano et al., 1969; Ray and Barrett, 1969). It appears that the differences in amnesia gradients may be resolved as an effect due to the differential effectiveness of ECS (with different parameters) in stopping consolidation; that is, the greater retention usually found (in terms of shorter amnesia gradients) following weaker ECS treatments may be best explained as a result of the amount of consolidation which continues following the ECS treatment. Presumably, this post-treatment consolidation makes possible retention upon retesting. This interpretation follows from the previous discussion that the effect of an ECS may only slow or partially disturb consolidation such that the consolidation process itself is not disrupted completely.

With respect to the variations in amnesia gradients found in separate experiments (i.e., short amnesia gradients: Chorover and Schiller, 1965; Quartermain et al., 1965; long amnesia gradients: Kopp et al., 1966; McGaugh, 1966), it seems that if the ECS treatment used in each of these experiments are also differentially effective in stopping consolidation, the amount of amnesia found following the ECS would be directly related to the amount of consolidation which takes place after the ECS treatment. The more effective an ECS is in suppressing consolidation, the greater is the probability of finding more severe retention interference (i.e., in finding a longer amnesia gradient).

b) Recovery from retrograde amnesia

Recently several experiments reported a recovery from ECS-induced

retrograde amnesia (Zinkin and Miller, 1967; Kohlenberg and Trabasso, 1968). According to consolidation theory, ECS-induced retrograde amnesia is the result of the ECS disrupting consolidation before the processes which are involved in memory storage have been completed. This type of interference presumably should be permanent because if memory storage processes were disrupted by the ECS, the physical basis for recall would not have been formed and no recovery from amnesia should, therefore, occur. The recent findings that recovery from ECS-induced amnesia can occur is not consistent with this formulation of the consolidation theory.

The two most reasonable explanations offered for these findings on the recovery from ECS-induced retrograde amnesia appear to be 1) the retrieval interference hypothesis of Weiskrantz (1966) and 2) the incomplete disruption of consolidation hypothesis of King and Glasser (1970). The retrieval interference hypothesis proposed that post-training ECS interferes with recall by creating high levels of "noise" in the memory retrieval system. As this "noise" level decreases over time, the interference with recall is reduced and recovery from amnesia occurs. The second hypothesis attributes the recovery from amnesia to the incomplete disruption of consolidation by an ECS. It suggests that in cases where consolidation is only partially disrupted, recovery of memory may occur spontaneously or after repeated exposure to stimuli associated with the original learning situation. Apparently the incomplete disruption of consolidation enables the establishment of some memory components which make possible the recovery from amnesia. Evidence on the relationship of the effectiveness of ECS and the

efficacy of the recovery from amnesia (Pagano et al., 1969; Miller, 1968) are cited in support of this alternative explanation.

The results of the present experiment are apparently more consistent with the second explanation for the recovery phenomenon. The findings of this experiment that retention was disrupted by the ECSs given at 5 minutes and 1 hour but not at 24 hours and 25 hours after training indicates that the ECS-induced amnesia is not attributable to an interference with retrieval because the ECS-treatment-retest intervals of the present experiment are the same (48 hours) following both ECS treatments so that at the time of retention testing, the level of interfering "noise" in the memory retrieval system, if induced, would be equivalent. If the effect of the ECSs, according to Weiskrantz's formulation (1966), is to disturb memory retrieval rather than memory consolidation, the amount of retention disturbed or not disturbed following these ECS treatments should, therefore, be the same. The nature of the present results suggests that the recovery from ECS-induced amnesia is more likely due to processes (i.e., consolidation) which occur after the ECS treatment. A component which may be formed during this post-ECS consolidation period and which may serve to mediate the recovery from amnesia is a residual memory trace. (This concept will be discussed further in the next section). Obviously, if the formation of this residual memory trace occurs subsequent to the ECS treatment, it will be dependent on the degree of consolidation which can go on following the ECS. Miller (1968) and Pagano et al. (1969) have both provided results which indicate that the rate of recovery from ECS-induced amnesia is related to the severity of the ECS stimulation. No recovery or very little recovery may follow when a high intensity ECS is given after learning, but when a low

intensity ECS is administered, recovery from amnesia is quite strong. Considered with the evidence of the present experiment, it seems possible that the greater efficacy of the recovery from amnesia following weaker ECS treatments may be directly related to the amount of post-ECS consolidation activities. The amount of post-treatment consolidation activity presumably is greater following a weaker ECS. This interpretation is generally consistent with that of King and Glasser (1970) who suggested that the recovery from amnesia is due to the incomplete disruption of consolidation by the ECS treatment.

c) The reminder effect

The present evidence that memory consolidation can continue following an ECS also provides a useful theoretical basis for resolving within a consolidation framework some other recent findings which are not easily assimilated into consolidation theory. Firstly, Nachman and Meinecke (1969), Pfingst and King (1969) and Kesner, McDonough, and Doty (1970) have each reported that if animals were trained in an avoidance response with a one-trial learning paradigm and then given an ECS within seconds of this training, amnesia was observed as usual with this type of experimental procedure upon retest 24 hours later. But if the same animals were trained again and again given an ECS immediately after the training, very little or no amnesia was found upon a second retest. Secondly, Lewis, Misanin, and Miller (1968) and Quartermain, McEwen, and Azmitia (1970) have described conditions under which memory lost after ECS can be restored following appropriate reminders. Animals were trained in passive avoidance and amnesia was induced by post-training ECS. When the animals were then given a reminder shock (a footshock given outside

the training apparatus after the retest trial) a recovery of retention was observed. It appears from these results that ECS disruption of retention was not total, and that residual memory expressed through a recovery of memory following a reminder or following a second training-ECS pairing can survive the effects of the initial ECS treatment. Both of these groups of findings are not apparently consistent with consolidation theory because according to the consolidation theory, the effects of the ECS administered immediately following training or immediately following a second training trial should prevent retention by disrupting consolidation; no residual memory should be present once consolidation is disrupted by ECS.

That this conclusion is not invariably true is suggested by the evidence of the present experiment. Because memory consolidation seemingly can continue following an ECS, it follows from this that a residual memory trace might be formed as a result of consolidation activity which occurs following the ECS treatment. As discussed above, this post-ECS consolidation may be behaviourally expressed as a spontaneous recovery from amnesia; alternatively, it may consist of the formation of processes which are the basis upon which a reminder foot-shock or a second training trial (followed by ECS) can bring about retention

The significance of a residual memory trace in attenuating the effects of a second ECS in disturbing retention is central to Kesner et al.'s (1970) interpretation of their findings. They suggest: "It... seems probable that an ECS does not destroy information but blocks full development or alters the accessibility of such information. Similar information received at a later time may then functionally interact with

that from the previous experience". This interpretation is supported by their finding that when information storage was blocked more effectively by giving the ECS very shortly (0 to 0.5 second) after training, more training-ECS pairings can be given before significant retention of the training occurs. From one point of view, it appears from these results that certain essential components of the memory trace are established very rapidly after acquisition. Although these components of the memory trace are not sufficient to enable the expression of memory in some situations (for example, following the first training-ECS pairing), they are nevertheless sufficiently established to attenuate greatly the effects of a second ECS as shown by the experiments of Nachman et al. (1969), Pfingst et al. (1969), and Kesner et al. (1970).

Previously, Albert (1966b) has provided some results which similarly suggest that some components involved in memory storage are formed rapidly after learning. Like the memory components described by Kesner et al. (1970) which do not appear to be susceptible to ECS-induced disturbances, Albert found memory components which are immune to the disruptive effect of spreading depression or cathodal polarization since if anodal polarization is applied shortly after a spreading depression or cathodal polarization treatment, the usually induced amnesia is largely reversed. Presumably, the memory components not destroyed by spreading depression or by cathodal polarization are those components which enabled the attenuation of amnesia produced by anodal polarization. Albert (1966b) suggested that these memory components may consist of intracellular molecular changes acting as information holding mechanisms because this type of information holding mechanisms (molecular changes) seems to be

the sort which may be able to withstand the kinds of electrical disturbances such as those created by ECS, spreading depression, or cathodal polarization.

However, the residual memory components which seem to be responsible for the attenuation of the amnesic effects of a second ECS found in the experiments of Kesner et al. (1970), Pfingst et al. (1969), and Nachman et al. (1969) may not necessarily be formed before the onset of the ECS treatment as suggested by Kesner et al. In view of the present evidence that consolidation can continue after ECS, it is possible that the processes which are involved in the formation of a residual memory trace may also occur following the ECS treatment. Of course, if an ECS of a certain parameter is very effective in disturbing consolidation processes or if the ECS is given very immediately following acquisition (i.e., 0-0.5 second as in Kesner et al.'s experiment), it is probable that memory consolidation can be completely disrupted. The results of Kesner et al. (1970) described above illustrates this possibility very precisely.

If post-ECS memory consolidation occurs in the experimental situations discussed above, the idea of some residual memory having a major function in attenuating the effects of the second ECS treatment appears to be more in line with consolidation theory which assumes that establishing memory components require a prolonged gestation period.

There is some evidence which suggests that the processes which seem to underlie the recovery from ECS-induced amnesia following a reminder footshock (and possible also following a second training-ECS pairing) may involve consolidation. Quartermain et al. (1970) found that the amnesic agent cycloheximide which has been found to disrupt

consolidation after training (Barondes and Cohen, 1968) disturbed in a similar manner when injected before the reminder trial the processes which are essential in retention recovery following the reminder stimulus. This finding suggests that the recovery of memory initiated by a reminder may also involve consolidation activity since if this restarted recovery process is preceded by a cycloheximide injection, the recovery of the memory is prevented. Of course, this evidence is only tentative, and additional experimental verification is required.

Conclusion

The present thesis has considered one way of interpreting some of the data on the disruption of retention induced by an amnesic agent. A number of recent results including those of the present experiments are consistent with the possibility that memory consolidation may continue following a single ECS. Together, these results suggest that the effect of many amnesic treatments may be to disturb the conditions for consolidation rather than to destroy the information being stored. According to this point of view, it appears possible that if the necessary conditions (which may consist of biochemical [Byrne, 1970] or bioelectrical [John, 1967] changes) for consolidation can be re-established following an amnesic treatment, the development of long-term memory would be possible. In the case of the present experiment, presumably, these conditions are not completely destroyed by the first ECS or are re-established spontaneously such that post-treatment consolidation makes possible the retention found following the single ECS treatment given at 5 minutes after training. In several other recent experiments, there is some evidence that these conditions can be re-

established artificially by administering various agents following an amnesic treatment. McGaugh (1968) has reported that the administration of a central nervous system stimulant, strychnine sulphate, can attenuate the amnesic effect of an ECS when given within 3 hours of the ECS treatment. Albert (1966b) has found that the disruptive effects of cortical spreading depression or of cathodal polarization are greatly reduced when anodal polarization is applied within several hours afterward. Barondes and Cohen (1968) have found that manipulations which generate "arousal" (i.e., footshock, amphetamine) can re-establish long-term memory following a period of cerebral protein synthesis inhibition induced by cycloheximide.

This evidence suggests that some initial components which are involved in memory storage are not susceptible to the same disturbance as is consolidation. It appears that these components (i.e., information holding mechanisms) may consist of independent and distinct processes which are parts of a very complex sequence of events leading to the eventual storage of information. This general interpretation is in agreement with several more precise elaborations formulated previously (i.e., Albert, 1966b; John, 1967).

It should also be pointed out that the supporting evidence upon which all the issues considered here are based, although substantial, are certainly not complete. The present interpretation acknowledges alternative explanations (i.e., Neilson, 1968; Pinel, 1968; Schneider and Sherman, 1968; Spevack and Suboski, 1969; Wiener, 1970) suggested for the basis of the retention deficits produced by amnesic agents.

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