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EFFECTS OF STIMULATION AND SUPPRESSION OF THE HIPPOCAMPUS ON LEARNING AND MEMORY

by

MAURO CAUDARELLA

Department of Psychology, University of Toronto

A Thesis submitted in conformity with the requirements for the Degree of Doctor of Philosophy in the University of Toronto

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SCHOOL OF GRADUATE STUDIES

PROGRAM OF THE FINAL ORAL EXAMINATION

FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

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EFFECTS OF STIMULATION AND SUPPRESSION

OF THE HIPPOCAMPUS ON LEARNING AND MEMORY

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Effects of Stimulation and Suppression of the Hippocampus on Learning and Memory

Mauro Caudarella

ABSTRACT

The role of the hippocampus (HPC) in reinforcement was investigated in several ways. First, it was shown that electrical stimulation of the dorsolateral hippocampus could reinforce a T-maze discrimination directly by serving as a reward when no conventional reward (such as food) was present. Secondly, the application of hippocampal (HPC) stimulation in a learning paradigm which included a conventional reinforcer had different effects depending on the type of learning and the timing of HPC stimulation. (a) When 0.5 sec of HPC stimulation followed each lever press along with a food pellet in a Skinner box (contingently stimulated group), there were no significant differences in rate of acquisition of lever pressing compared with a randomly stimulated group and an implanted but unstimulated group. However, a retention test conducted 24 hr after any stimulation and with no food or stimulation present

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indicated that memory was significantly impaired in the contingently stimulated group compared with the unstimulated control group. These results are consistent with reports that HPC stimulation disrupts long-term memory without affecting immediate memory. The HPC stimulation was subsequently shown to be rewarding in self-stimulation tests. (b) In one-trial passive avoidance learning, HPC stimulation significantly improved memory whether it was self-administered or administered by the experimenter shortly after the single conditioning trial.

Thirdly, the effect of diazepam (Valium), a drug which suppresses HPC activity, was investigated in direct HPC reinforcement (self-stimulation) and in passive avoidance learning. If stimulation of the HPC is rewarding and if associations are established and reinforced through HPC activity, then disruption of HPC function should suppress both self-stimulation and long-term memory formation. (a) Diazepam (1 and 2 mg/kg) significantly and drastically suppressed HPC self-stimulation; a lower dose (0.5 mg/kg) of diazepam had very small effects. That diazepam did not merely depress motor performance is indicated by the increase in self-stimulation seen with preoptic

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and lateral hypothalamic stimulation sites under the influence of diazepam (1, 2 and 3 mg/kg). (b) Diazepam (5 mg/kg) also produced anterograde amnesia in one-trial passive avoidance learning compared with a vehicle solution (propylene glycol + ethanol) when injected 30 min before the trial. The disruption of learning produced by diazepam did not appear to be state-dependent or due to diminished sensitivity to footshock.

Taken together, the results suggest that the activity of the hippocampus is important in reinforcement; that is, in establishing the neural representation of associations between stimuli and responses.

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INTRODUCTION

The present investigation is concerned with the role of the hippocampus in reinforcement, a key aspect of learning and memory. In recent years the hippocampus has received a great deal of attention. The anatomy and physiology of hippocampal circuits have been described in great detail. An important role of the hippocampus in learning and memory has long been suspected and recent studies of brain plasticity have focused on this structure. In this dissertation, I approach the study of hippocampal function from a behavioral perspective and I employ behavioral tests of learning and memory in combination with physiological and pharmacological manipulations to examine the function of the hippocampus.

First, I will define what I mean by reinforcement and discuss some of the historical and theoretical background which has culminated in some recent attempts

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at a direct manipulation of the neural processes underlying reinforcement as I am defining it. Next, I will discuss what is meant by the term "hippocampus" and outline the functional anatomy of this complex structure. Then, I will review some recent experimental evidence that the hippocampus exhibits a remarkable degree of plasticity and thus may be critically involved in learning and memory.

The methods used in this investigation are electrical stimulation of the hippocampus and pharmacological treatment with diazepam, combined with several different behavioral tests of learning. Therefore, I will also review the behavioral effects of hippocampal stimulation and then present the reasons for using diazepam, its pharmacological and physiological properties, and its behavioral effects, with particular emphasis on suppression of memory formation and suppression of hippocampal activity.

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Reinforcement: the strengthening of associations.

I will use the terms "reinforcement" and "reinforcing event" in the broad sense to refer to any event or process which strengthens associations, and hence aids memory formation. The term "reinforcer" will denote a positive or negative reinforcer in the standard usage of operant conditioning: a reinforcer is a stimulus whose presentation ("positive reinforcer" or, "reward") or termination ("negative reinforcer") strengthens (i.e., increases the probability of) a response which it follows (see, e.g., Smith and Moore, 1966).

Reinforcement in the broad sense first used by Pavlov (1927) has been defined by Berlyne as "whatever has to be added to contiguity to obtain learning" (Berlyne, 1969b, p. 179). When a particular response occurs in the same place and at about the same time as a set of stimulus conditions, learning may take place, depending on how closely and how often the conditions are paired. By "learning" I mean a relatively permanent change in behavior or behavior potential (see G. Kimble, 1961). Often, however, no learning occurs when a

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stimulus and a response are paired unless a reinforcing event occurs at about the same time (Berlyne, 1971). What kind of event provides reinforcement, and thus acts to strengthen stimulus-response associations, depends on the kind of learning situation. In classical conditioning, the reinforcing event is the unconditioned stimulus. In operant conditioning, the reinforcing event is the satisfying condition (e.g., giving sweetened milk or withdrawing a painful stimulus) which follows the response. In human verbal and intellectual learning, the reinforcing event is probably some factor which alters attention (Berlyne, 1967).

Spencer (1888) was perhaps the first psychologist to set out a physiological theory of reinforcement based on the much older account of the control of behavior by pleasure and pain. According to Spencer, a certain response to a stimulus would occasionally lead to pleasurable sensations accompanied by an increase in neural activity in the parts of the nervous system involved in performing the response. The resulting facilitation (described by Spencer in terms of increased "permeability" of the neurons to "molecular motion") ensured that the same response was more likely

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to be repeated on subsequent appearances of the same stimulus conditions (Spencer, 1888, Vol. I, p. 545). Thorndike (1898) shared Spencer's mechanistic view that an animal's learned behavior came about through automatic strengthening of accidental associations of stimuli and responses through reinforcement rather than the teleological opinion prevalent at the time (Bolles, 1967) that an animal's behavior was determined by foresight or conscious memory of the pleasurable consequences. Before he formulated the well-known behavioral version of his Law of Effect (Thorndike, 1911, 1933), Thorndike (1905) first advanced a Law of Effect as one of his Laws of Brain Action which described the physiological action of the nervous system at the neuronal level. The Law of Acquired Brain Connections, or Law of Association, was stated in part as follows:

> When any neurone group, A, is stimulated, the nervous impulse will be transmitted to the neurone group ... which has been aroused by A most frequently, with most satisfaction to the individual ... (Thorndike, 1905, p. 167).

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The Law of Effect, one component of the Law of Association, stated that when a neuron is stimulated, it transmits the stimulus along the line of strongest connection; that is, "other things being equal, that [line] resulting in the greatest satisfaction to the animal" (Thorndike, 1905, p. 166). Both Spencer and Thorndike believed that the close association of stimuli and responses in time and space set up "reverberatory waves" (Spencer, 1888) of neural activity, or weak neural traces, that could be strengthened by the presence of "a pleasant mental state" (Thorndike, 1905), "satisfactory consequences" (Thorndike, 1911), or, as we would say today, "reward" (Berlyne, 1971).

Ever since Spencer and Thorndike first pointed out that the addition of a pleasurable event to the contiguity of stimulus and response could assist the formation and registration of new associations, many theorists have stressed the close connection between reinforcement and memory formation (e.g., Berlyne, 1967, 1971; Hebb, 1955; Hull, 1943; Huston, Mueller & Mondadori, 1977; Milner, 1970; Olds & Olds, 1961; Routtenberg, 1974). Huston and his collaborators have recently been conducting direct experimental tests

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of the idea that presentation of a reinforcer can enhance memory processes. In the first such experiment, Huston, Mondadori and Waser (1974) found that passive avoidance learning was facilitated when food reward was administered shortly after the footshock in a one-trial step-down task. Subsequent experiments (Mondadori, Ornstein, Waser & Huston, 1976; Mueller, Huston & Mondadori, 1977; Huston & Mueller, 1978) showed that rewarding brain stimulation administered through an electrode in the lateral hypothalamus could also facilitate the learning of one-trial and multiple-trial avoidance tasks as well as appetitive T-maze learning. The experimenters concluded that these results provide evidence for a theory of reinforcement which postulates that reinforcers normally strengthen behavioral propensities "by a direct facilitative action on immediate memory traces; i.e., by preventing the trace from fading or being disrupted" (Huston & Mueller, 1978, p. 265). Similar facilitatory effects of posttrial lateral hypothalamic stimulation have been reported by Major and White (1978) who used a one-trial appetitive learning task followed by a short session of self-stimulation, and Destrade and Soumireu-Mourat (1977) who used both avoidance and appetitive tasks followed by experimenter-delivered stimulation. White

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and Coulombe (1979) have recently extended this series of studies to include improvement of memory by rewarding hypothalamic stimulation in a variety of learning situations: secondary reinforcement, conditioned emotional response, acceleration of extinction, and visual discrimination in a T maze. In all these experiments the animals were trained on a given task in a test apparatus and were then allowed to self-stimulate (1000 lever presses) in a different apparatus; the facilitation of memory was observed 24 hours after the hypothalamic stimulation. Memory improvement in a one-trial appetitive task was also observed with a posttrial treatment of 30 trains of experimenter-delivered stimulation (White & Major, 1978).

In the present investigation, electrical brain stimulation is administered after presentation of the conditioning stimuli in three different situations -- viz., spatial discrimination learning, lever pressing for food reward, and passive avoidance learning -- in an attempt to determine whether such stimulation disrupts, facilitates or has no effect on learning and memory.

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Functional anatomy of hippocampal circuits.

The hippocampus is an archicortical convolution which in mammals is completely rolled into the inner area of the cerebral hemisphere and in primates is restricted to the medial area of the temporal lobe. It forms a prominent part of the limbic lobe - a region of archicortex and paleocortex which forms a border and, hence, a transitional zone between the diencephalon and the higher neocortical areas. Because of this anatomical situation, the hippocampus appears to be an ideal structure in which to place functional circuits that perform a reinforcement function in learning; that is, that process diencephalic and brain-stem information about biological drives and rewarding events and modulate cortical memory formation processes (see Green, 1964; P. Milner, 1970).

Although the anatomy of the hippocampus has been extensively studied and described many times since the late nineteenth century discovery of the Golgi silver staining method (Blackstad, 1956; Crosby, Humphrey & Lauer, 1962; Chronister & White, 1975; De Groot, 1975; Gottlieb & Cowan, 1974; Green, 1960;

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Hamilton, 1976; Haug, Blackstad, Simonsen & Zimmer, 1971; Hjorth-Simonsen, 1973; Isaacson, 1974; Lorente de No, 1934; Ramon y Cajal, 1893, 1901, 1911; Sidman, Angevine & Taber Pierce, 1971; Shepherd, 1979; Swanson & Cowan, 1975, 1977), there remains much confusion and inconsistency in the nomenclature and exact definition of what constitutes the "hippocampal convolution", "hippocampal formation", "Ammon's horn", "Ammon's formation", "hippocampal gyrus" or "hippocampus" (see Green, 1964; Isaacson, 1974). Part of the difficulty in nomenclature arises from the fact that the total hippocampal formation is a continuous sheet of phylogenetically old cortex extending from the entorhinal cortex (also called piriform cortex or parahippocampal gyrus) of the basolateral temporal lobe, through the subiculum, the hippocampus proper (C-shaped region of neatly stratified pyramidal cells) and ending in the dentate gyrus (or fascia dentata). During prenatal development, this continuous sheet becomes so rolled up into the lateral ventricle that the dentate gyrus comes full circle, is shifted slightly and merges (exchanging direct fiber connections) with the entorhinal cortex where the hippocampal convolution begins.

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Following the pioneering work of Ramón y Cajal (1893, 1901, 1911) a classical picture emerged of functional hippocampal anatomy which described the fornix as the major efferent pathway carrying most of the axons of hippocampal pyramidal cells directly to the mammillary nuclei of the hypothalamus, synapsing there and relaying information to the anterior thalamus by way of the mammillothalamic tract (bundle of Vicq d'Azyr). Some of the fornix fibers went instead to the septum. The input to the hippocampus was seen as arising from the cingulum and from the secondary olfactory areas of the cortex, principally the entorhinal cortex (Barr, 1972; De Groot, 1975; Green, 1964). This classical picture was often simplified by authors reviewing hippocampal anatomy so that until recently it was generally believed that the hippocampus received a principal afferent input from the temporal cortex and discharged its efferent fibers principally, if not entirely, through the fornix to the hypothalamus (Green, 1964).

Crosby et al. (1962) have reviewed the wealth of anatomical and physiological data that indicate that the connections of the hippocampus are much more complex than previously believed. For example, the hippocampus receives inputs through the fornix (from

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the septum), and through the dorsal fornix or induseum griseum (e.g., the dorsal noradrenergic bundle from the nucleus of the locus coeruleus-Ungerstedt, 1971) whose fibers course dorsal to the corpus callosum. The simplified classical picture has been recently further upset by reports by Swanson and Cowan (1975, 1977) that autoradiographic methods show that the fornix fibers which project to the hypothalamus do not arise from the hippocampus at all, but instead have their cell bodies in the subicular cortex. Swanson and Cowan have therefore concluded that what has been described as one of the best known pathways - the projection from the hippocampus proper to the mammillary nucleus - does not, in fact, exist (Cowan, Note 3; Swanson & Cowan, 1975, 1977).

The basic hippocampal circuit (Chronster & White, 1975; Shepherd, 1979) appears to start in the entorhinal cortex which conveys information to the granule cells of the dentate gyrus through the perforant path - a monosynaptic excitatory connection. The dentate granule cell probably has an inhibitory feedback circuit through an axon collateral that synapses onto a basket cell which in turn synapses back onto the granule cell body. The granule cell also receives inputs from the

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septum and from the hippocampus proper (CA4). The granule cell's main output axon is the so-called mossy fiber which synapses onto the cell body of pyramidal neurons in cell field CA3 of the hippocampus proper. The CA3 neuron also receives input from the entorhinal cortex by way of the perforant pathway and from the septum by way of the fornix and fimbria. The CA3 pyramidal neuron sends an axon called a Schaffer collateral to stimulate the CA1 pyramidal neurons. The pyramidal neurons, like the granule cells, probably have inhibitory feedback circuits mediated by basket cells. The CA1 and CA3 pyramidal neurons send some axons through the alveus, fimbria and fornix to the lateral septum (the only subcortical projection of the hippocampus) but the vast majority of CA1 axons terminate in the subiculum (Hjorth-Simonsen, 1973; Swanson & Cowan, 1977). The CA1 neurons also receive other inputs by way of the alvear pathway from the entorhinal cortex. In addition to the specific inputs mentioned, all regions receive extensive commissural connections from the contralateral hippocampal formation. Also, noradrenergic fibers from the locus coeruleus and serotonergic fibers from the raphe nuclei of the midbrain project to the hippocampus and dentate gyrus (Ungerstedt, 1971; Moore, 1975). Mesolimbic

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dopaminergic fibers apparently project only to the ventral hippocampus (Hökfelt, Ljungdahl, Fuxe & Johansson, 1974; Hokfelt, Fuxe, Johansson & Ljungdahl, 1974). Morphologically, the largest neurons in the hippocampal formation are the pyramidal cells of CA3 (called "giant pyramidal cells"). Both pyramidal and granule cells are very rich in dendritic spines that usually show a "spine apparatus" and often a "spinule" that protrudes into the presynaptic terminal.

In reporting behavioral studies that use hippocampal stimulation, investigators and reviewers have not always been careful to distinguish the important subdivisions of the hippocampal formation. For example, many reviews (e.g., McGaugh & Gold, 1976; McGaugh & Herz, 1972; Kesner & Willburn, 1974) report results obtained with "hippocampal" stimulation, even though the area stimulated was the dentate gyrus, the subiculum or the entorhinal cortex. The assumption of homogeneity of function of the hippocampal formation no longer seems warranted. First of all, the dorsal and ventral areas of the hippocampal formation have different anatomical connections (Cragg, 1965; Lorente de Nó, 1934; Siegel & Edinger, 1973; Siegel & Tassoni, 1971 a & b), different electrophysiological responses

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to stimulation (Coyle, 1969; Racine, Rose & Burnham, 1977) and different monoamine fiber inputs from the brain stem (Hokfelt, Fuxe et al., 1974). Also, several behavioral experiments have found different, sometimes opposite, effects (within the same experiment) of stimulation of these areas (e.g., Kesner & Doty, 1968; Wyers, Peeke, Williston & Herz, 1968) and of lesions of these areas (Nadel, 1967, 1968; O'Keefe & Nadel, 1978). Secondly, within the dorsal hippocampal formation, a distinction must be made among the dentate gyrus, hippocampus proper (cell fields CA1 to CA4) and subiculum on the basis of cell types and functional connections (Blackstad, 1956; Ramón y Cajal, 1893; Swanson & Cowan, 1975; White, 1959) as well as behavioral results (Milgram, 1969; Zornetzer, Chronister & Ross, 1973). Thirdly, cell fields CA1 and CA3 of the hippocampus proper have long been distinguished on the basis of anatomical (Blackstad, 1956; Gotlieb & Cowan, 1974; Green, 1964; Lorente de Nó, 1934) as well as behavioral results (Buzsaki, Acsadi & Jani, 1980; Jarrard, 1976); CA1 and CA3 correspond, respectively, to the extensively described regio superior and regio inferior of Ramón y Cajal (Green, 1964; Hjorth-Simonsen, 1973).

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The hippocampus: possible role in brain plasticity, learning and memory processes.

An important role of the hippocampus in learning and memory processes has been proposed by many reviewers on the basis of experimental animal studies and human experimental and neuropathological studies (e.g., Butters & Cermak, 1975; Black, Nadel & O'Keefe, 1977; Douglas, 1967; Green, 1960, 1964; Kimble, 1963, 1975; Kimble & Pribram, 1963; Livesey, 1975; Milner, 1972, 1974; Nadel, 1967; Olds & Olds, 1961; Scoville & Milner, 1957; Thompson, 1976). Using new approaches, a number of recent studies have found evidence of the involvement of the hippocampal formation in learning and memory. Berger and collaborators have recently recorded hippocampal unit responses (in CA1) which precede by 30 msec, and accurately predict, the appearance of a classically conditioned nictitating membrane response in the rabbit (Berger & Thompson, 1978; Berger, Alger & Thompson, 1976; Thompson, 1976). The hippocampal unit activity is not related to the motor control of the performance of the rabbit's response (i.e., blinking the third eyelid, called the nictitating membrane) since no such electrical activity

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occurs when the nictitating membrane response occurs spontaneously or is triggered by an air puff in an unpaired control test.

Other experimenters have been studying the plasticity of synaptic transmission in hippocampal circuits with a view to elucidating brain mechanisms that may underlie learning and memory. It has been discovered that if the fibers connecting the entorhinal cortex with the dentate gyrus (the monosynaptic perforant path) are stimulated at a frequency of 10-15 pulses per second or higher, the postsynaptic response evoked from the dentate gyrus granule cells is potentiated for a period of several hours or even days (Bliss & Lomo, 1970, 1973; Bliss & Gardner-Medwin, 1971, 1973; Douglas & Goddard, 1975; Lomo, 1971; Cotman & McGaugh, 1980). Unlike the long-lasting potentiation seen in hippocampal pathways, facilitation (or, post-activation potentiation) in mammalian peripheral and spinal synapses and in invertebrate preparations has been reported to last for only a few seconds or minutes, at most (Eccles, 1977; Katz, 1966; Mountcastle & Baldessarini, 1968). Douglas and Goddard (1975) reported very long-lasting potentiation of the perforant path-granule cell synapse response: they found

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that trains of stimulation presented only once a day for ten days produced an increase in the population excitatory postsynaptic potential (EPSP recorded from the granule cells of the dentate gyrus) that lasted for twelve days in most cases and, in a few cases, as long as two months. It is interesting that such long-lasting potentiation should be found with daily trains of stimulation, since this procedure, called "kindling" (Goddard, McIntyre & Leech, 1969), results in permanently lowered thresholds for epileptiform afterdischarges and convulsions (Goddard et al., 1969; Racine, 1972 a & b) and has been proposed as a model of brain plasticity that may underlie learning and memory (Goddard & Douglas, 1975; Goddard, McNaughton, Douglas & Barnes, 1978; Racine, Gartner & Burnham, 1972; Racine, Newberry & Burnham, 1975; Racine & Zaide, 1978; Racine, Tuff & Zaide, 1975).

The fact that long-term synaptic potentiation of the type seen after "kindling" stimulus trains or other types of high frequency stimulation may represent one of the processes that underlie learning and memory is further suggested by the recent correlational studies of Barnes (1979). Barnes found a positive correlation, using both young and old rats,

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between performance on a complex circular maze and the degree of long-term potentiation of responses evoked in the dentate gyrus by high frequency stimulation of the perforant path; that is, fast learners showed more potentiation and slow learners showed less. Furthermore, the old rats which learned the maze more slowly than the young rats, also showed less overall synaptic potentiation in the same hippocampal pathway.

Potentiation in the perforant path apparently leads to morphological postsynaptic changes: Fifkova and van Harreveld (1977) reported significant enlargement of dendritic spines of granule cells in the dentate gyrus of the mouse following potentiating stimulation of the entorhinal cortex. The enlarged spines were observed in brains removed from two minutes to twenty-three hours after the potentiating trains of entorhinal stimulation (Fifkova, Note 4). Lee, Oliver, Schottler, Creager & Lynch (1979) have reported that potentiating high frequency stimulation of the intrinsic synaptic connections of the hippocampus proper (the commissural Schaeffer collateral projections from CA3 to CA1) increased the number of synaptic contacts on dendritic shafts by 50 percent and also significantly increased the ratio of shaft

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to spine synapses in adult rats both in vivo and in the hippocampal slice preparation. Low frequency stimulation (0.25 Hz) produced neither potentiation nor morphological synaptic changes. Lee et al. (1979) suggest that this kind of structural modification of hippocampal synapses may account for the long duration of the synaptic potentiation effects typically found in hippocampal circuits.

Electrical stimulation of the hippocampus: Effects on behavior

A. General effects

Unlike its close neighbors, the amygdala and septum, the hippocampus does not appear to produce any consistent behavioral changes if stimulated with a low-intensity electrical stimulus which does not trigger afterdischarges (Morin, 1971; Vinogradova, 1975). In human patients, hippocampal stimulation produces no major or consistent behavioral effects; researchers have not found any sexual responses,

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rage reactions, touch sensations, hallucinations or gross behavioral changes (Pampiglione & Falconer, 1960).

The hippocampus has a very low seizure threshold in both humans and animals (Green, 1964) and after-discharges spread quickly from the stimulated side to the contralateral hippocampus (Racine, 1972 a & b). In experiments on animals, stimulation that produces afterdischarges in the hippocampus has been correlated with cessation of movement and staring fixedly into space followed by pouncing, patting the air, "wet-dog shaking", piloérection, salivation, grooming and penile erection (Green, 1964; Morin, 1971; Racine, 1972 a & b). Poststimulation feeding behavior (Milgram, 1969) and "pleasure" reactions (Morin, 1971) have also been noted. Stimulation of the hippocampus has also been reported to increase secretion of growth hormone (a stress-related hormone) (Willoughby & Martin, 1978). The hippocampus has been described by many authors as inhibiting the secretion of stress-induced adrenocortical hormone activity (see Bohus, 1975; van Hartesveldt, 1975; Willoughby & Martin, 1978) but the effects of stimulation of the hippocampus are apparently very complex; for example, Kawakami, et al.

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(1968, reported in van Hartesveldt, 1975) found that stimulation of dorsal CA2 and CA3 hippocampal cell fields (but not stimulation of alveus or dentate gyrus - Willoughby & Martin, 1978) produced an increase in adrenal corticosteroid hormone activity ten minutes after stimulation, but a decrease four hours after stimulation. Others have reported that low frequency stimulation of the hippocampus prevented an increase in adrenal corticosteroid activity in response to stress, whereas high frequency stimulation increased the hormonal response to stress (van Hartesveldt, 1975). Moreover, after habituation to hippocampal stimulation, no changes were observed in hormonal responses to stress (Bohus, 1975). The involvement of the hippocampus in the pituitary-adrenal system response to stress is further indicated by the finding that it is the region of the brain which accumulates the highest concentration of corticosterone, the glucocorticoid hormone that is released by the adrenal cortex in response to ACTH secreted by the pituitary gland (McEwen, Gerlach & Micco, 1975), and the finding that corticosterone binds tightly and selectively to the nuclei of hippocampal pyramidal cells and dentate granule cells (Bohus, 1975; McEwen et al., 1975). The behavioral significance of putative glucocorticoid

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receptors in the hippocampus is unclear (see McEwen et al., 1975), but it is interesting to note, in light of the possible role of the hippocampus in learning and memory processes, that implantation of corticosterone directly into the hippocampus prevented retention of a passive avoidance trial as measured 24 hours later, although no memory deficit was seen during an immediate retention test (Bohus, 1975).

B. Effects on learning and memory.

Many experiments have indicated that electrical stimulation of the dorsal hippocampus, both with and without elicited afterdischarge activity, disrupts the memory of recently learned behaviors (see reviews by Kesner & Wilburn, 1974; McGaugh & Gold, 1976; McGaugh & Herz, 1972; Gold, Zornetzer & McGaugh, 1974; Livesey, 1975), although there have been reports of facilitation of memory with hippocampal stimulation (Destrade & Cardo, 1974; Destrade & Jaffard, 1977, 1978; Destrade, Soumireu-Mourat & Cardo, 1973; Erikson & Patel, 1969; Jaffard, Destrade & Cardo, 1976; Landfield,

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Tusa & McGaugh, 1973; Stein & Chorover, 1968).

Olds and Olds (1961) reported that dorsal hippocampal stimulation delivered throughout the training session prevented the learning of novel discriminations although the performance of already learned responses was not disrupted. Livesey (1975) found some disruption of learned responses under the effects of similar continual hippocampal stimulation but also found that new learning could be prevented by delivering hippocampal stimulation either (a) for only two seconds, five or ten seconds after each response or (b) only between the presentation of the discriminative cue and the rat's response. Livesey concluded that in both his studies and the Olds' experiments the animal appeared to be unable to use its previous experience in order to decide which discriminative cue signalled reward.

The presence of seizure activity in the hippocampus does not necessarily disrupt learning even though hippocampal stimulation that is below after-discharge threshold does interfere with acquisition or memory within the same experiment (Kesner & Doty, 1968; Kesner & Wilburn, 1974). Flynn and Wasman (1960) showed that avoidance learning could occur when the

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conditioning trials were presented during the presence of generalized EEG seizure discharges recorded from the hippocampus and other structures. McIntyre (1976) reported that the memory of passive avoidance learning was not disrupted by posttrial convulsions which had spread throughout the brain by "kindling" the amygdala. These reports of failure to disrupt learning and memory with hippocampal seizures stand in marked contrast to the reports of disruption of one-trial avoidance learning by a single pulse or brief train of stimulation, of the dorsal hippocampal formation, that was below after-charge threshold (e.g., Lidsky & Slotnick, 1970; Shinkman & Kaufman, 1972; Sideroff, Bueno, Hirsch, Weyand & McGaugh, 1974; Zornetzer, Chronster & Ross, 1973).

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The effect of diazepam on human memory formation

Diazepam, a drug widely used in humans because it suppresses the emotions of anxiety and fear, has an unusual effect on human memory formation: in doses within the range of human therapeutic use, diazepam produces a profound amnesia in man. The ability of diazepam to induce amnesia for the events which occur from about two minutes to about thirty minutes (depending on the dose) after its intravenous administration is well established in the clinical literature (Brown & Dundee, 1968; Clarke, Eccerseley, Frisby & Thornton, 1970; Dundee & Haslett, 1970; Dundee, Haslett, Keilty & Pandit, 1970; Dundee & Pandit, 1972; Driscoll, Smilack, Lightbody & Fiorucci, 1972; Foreman, 1974; Fox, Wynands & Bhumbhami, 1968; Goneim & Medwaldt, 1975, 1977; Gregg, Ryan & Levin, 1974; Grove-White & Kelman, 1971; Keilty & Blackwood, 1969; O'Neill & Verril, 1969; O'Neill, Verril, Aellig & Lawrence, 1970; Pandit, Dundee & Keilty, 1971). In fact, the amnestic properties of diazepam, at doses far below those required to produce anesthesia, have made this drug extremely popular in the practice of dental surgery in many different countries (Foreman,

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1974; Gregg et al., 1974).

Of particular interest, a moderate (0.1-0.3 mg/kg) intravenous dose of diazepam temporarily produces the type of global anterograde amnesia which is reminiscent of the relatively pure anterograde amnesia seen in patients with bilateral hippocampal lesions (see Green, 1964; Milner, 1970, 1972, 1974): the patients appear to be normal, conscious, and responsive (they engage in conversation and may even assist the dental surgeon), yet hours or days after their experiences, they are unable to remember anything that happened while under the effects of diazepam. The patients (as I can attest from personal experience) usually claim that they were asleep through the entire procedure. Under diazepam, immediate recall appears to be unaffected, whereas long-term memory of auditory, visual and painful stimuli is severely impaired whether tested with recall or recognition techniques (Clarke et al., 1970; Gregg et al., 1974; Grove-White & Kelman, 1971). These authors attribute the memory deficits under diazepam to a failure of consolidation of labile short-term memory traces.

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Similar anterograde amnesia is seen in patients with bilateral hippocampal lesions. Since extensive temporal lobe lesions not involving the hippocampus did not result in an amnesia syndrome, Scoville and Milner (1957), Penfield and Milner (1958) and others (see Green, 1964; Milner, 1970) concluded that normal functioning of the hippocampus is necessary in order for labile memory traces to be "consolidated", or stored permanently in the brain. In reviewing studies of patients with unilateral left or right temporal lobectomies, Milner (1974) concluded that the severity of memory deficit was proportional to the amount of the hippocampus that was removed. Anterograde amnesia syndromes also result from such other types of neuropathological conditions as encephalitis, Alzheimer's disease and Korsakoff's syndrome. The exact location of brain damage is often difficult to determine in these patients, but damage generally involves several parts of the limbic system, usually including the hippocampus (Morin, 1971; R. Swanson, 1976); moreover, the hippocampus appears to be particularly sensitive to the degenerative changes involved in these diseases as well as to such conditions as anoxia (lack of oxygen) and ischemia (restriction of blood flow) (Cotman &

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McGaugh, 1980; Green, 1964). Electroconvulsive shock also results in amnesia, and in this instance also several lines of evidence suggest that the critical structure involved in the memory deficit is the hippocampus (Douglas, Pagano, Lovely & Peterson, 1973; Hostetter, 1968). It thus appears that global anterograde amnesia produced by any of a number of traumatic events usually involves disruption of hippocampal circuits.

Since global anterograde amnesia can also be produced by intravenous administration of diazepam, it is tempting to assume that diazepam has this amnestic action because it disrupts activity in hippocampal circuits. Before reaching such a conclusion, however, it would be necessary to demonstrate, among other things, that diazepam does suppress hippocampal activity.

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Pharmacology of diazepam and suppression of hippocampal activity.

Although the mechanisms of any of the actions of diazepam, including amnesia, are not yet understood, there is evidence that this drug acts selectively on the limbic system (Foreman, 1974; Greenblatt & Shader, 1974, pp. 103-104; Hernandez-Peon, Rojas-Ramirez, O'Flaherty & Mazzuchelli-O'Flaherty, 1964; Parkes, 1968; Racine, Livingstone & Joaquin, 1975; Randall & Schallek, 1968; Schallek, Zabransky & Juehn, 1964; Zbinden & Randall, 1967, pp. 239-246) and, in particular, that it acts selectively to suppress activity in the hippocampus (Adamec, McNaughton & Livingston, Note 1; Mathews & Con nor, 1976; Olds & Olds, 1969; Wolf & Haas, 1977). The inhibition of hippocampal pyramidal cells apparently occurs through a facilitation of GABA-mediated recurrent inhibition (Haefely, 1978; Guidotti, 1978); that is, diazepam appears to act on the basket cells (inhibitory interneurons that use GABA as a neurotransmitter-Andersen, 1975; Curtis, Felix & McLennan, 1970) potentiating their inhibitory influence on the activity of the pyramidal cells (the primary units

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of the hippocampus) and thus suppressing hippocampal information processing and output (Wolf & Haas, 1977). Recently, moreover, the existence of benzodiazepine (the small class of drugs of which diazepam and chlordiazepoxide are the principal members) receptors in several brain areas has been demonstrated by in vitro and in vivo receptor-binding studies (Duka, Hollt & Herz, 1979). The largest number of benzodizepine-specific receptor sites in rats was found in the hippocampus.

The present investigation

The evidence reviewed suggests the hypothesis that the hippocampus is involved in the establishment, processing and strengthening of the neural trace which is set up during conditioning and learning. The present investigation is concerned with procedures which attempt to intervene during the initial phases of memory formation (i.e., learning).

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A. Part I

The first three experiments of Part I use electrical stimulation of the dorsal hippocampus of rats. In the first experiment, each rat is presented with a stimulus condition, a T maze, and is given a choice of two responses: walking into the left or right goal box. Both responses must be performed at least once before any brain stimulation is administered. The purpose of the experiment is to see whether, in the absence of any conventional reward, it is possible to strengthen the association between presentation of the T maze and the selection of a particular goal box (the "correct" one) by stimulating the hippocampus after each spatiotemporal association has occurred (i.e., after each accidental entry into the "correct" goal box). In other words, the first experiment attempts to discover whether dorsal hippocampal stimulation is both reinforcing, in the broad sense, and rewarding, in the special Skinnerian sense.

Besides the stimulus, the response and the brain stimulation, the second and third experiments

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introduce a fourth event in the operant conditioning paradigm: a conventional reinforcer. Dorsal hippocampal stimulation administered during the learning trials has been reported to disrupt the acquisition of appetitive learning; hippocampal stimulation shortly after the completion of a conditioning trial in a passive avoidance paradigm has been reported to prevent the formation of long-term memory. The second experiment attempts to determine whether dorsal hippocampal stimulation reinforces or disrupts appetitive learning in the Skinner box using food reward; the third experiment examines whether such stimulation reinforces or disrupts the learning of a passive avoidance response when presented after the conditioning trial.

B. Part II

It will be shown in Part I that hippocampal stimulation is reinforcing in the special situations of the first and third experiments, but not in the second experiment. Since diazepam suppresses hippocampal function-- regardless of whatever additional

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actions it may have in the brain-- this drug should suppress the two kinds of learning that are shown to be reinforced by hippocampal stimulation in Part I of the present investigation, viz., learning with no conventional reward (essentially "self-stimulation") and facilitation of passive avoidance learning. Accordingly, the fourth experiment examines the effect of diazepam on lever pressing rewarded only by hippocampal stimulation and the fifth experiment investigates the effect of diazepam on passive avoidance learning. If the hippocampus normally functions to reinforce conditioned associations, then administration of diazepam should prevent the learning of such associations whether an appetitive of aversively motivated task is involved.

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GENERAL METHODS

Subjects. All subjects were male hooded rats of the Long Evans strain obtained from Canadian Breeding Farms and Laboratories, Lachine, Quebec. They were 3-5 months of age and weighed 300-450 gm at the time of surgery. The rats were housed in individual stainless-steel cages and were given food (Master or Purina Rodent Chow) and water (fluoridated) ad libitum.

Surgery. Two types of electrodes were implanted with the aid of a stereotaxic instrument: a single strand of 220μ diameter 80% platinum-20% iridium wire insulated with clear vinyl for monopolar stimulation or a bipolar electrode made of two twisted strands of 225μ diameter Nichrome wire insulated with Formvar. Each rat was anesthetized with 60-80 mg/kg sodium pentobarbital (Nembutal) injected intraperitoneally along with 0.5 cc atropine sulfate (1% solution). The top of the head was sheared with electric clippers and disinfected by scrubbing with Proviodine. A midline incision was made in the scalp and the periosteal tissues removed with scalpel and gauze pads until the dorsal surface of the skull was fully exposed.

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Epinephrine solution (1:1000) was applied liberally to all exposed surfaces to stop bleeding and dry the exposed skull thoroughly. A small hole (about 1 mm) was made with a dental drill for the electrode and three or four similar holes were drilled more laterally for the stainless steel screws which were then screwed tightly into the skull at differing angles. If the electrode was of the single, monopolar type, one or more of the screws were wrapped with stainless steel wire to serve as the indifferent electrode. For recording, a similar indifferent skull-screw electrode was used along with a depth bipolar electrode. All hippocampal electrodes were aimed at cell field CA3 of the dorsal hippocampus according to the following coordinates: 3.8 mm posterior to Bregma, 4.2 mm lateral to the midline and 3.3 mm below the dura mater, with the skull level. About half the electrodes were always implanted in the left hippocampus and half in the right one. The actual electrode placement as determined by histology is shown in Fig. 1; all electrode tips were located in regio inferior (CA3) or immediately adjacent fimbria. The electrode hole was plugged with bone wax and the electrode was then lowered through the wax to minimize bleeding onto the skull surface. When the electrode was in place, dental

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Fig. 1 Location of electrode tips in the hippocampus. For convenience, all electrodes are shown on the same side and only the stimulation electrodes are shown. The sections are redrawn from Pellegrino & Cushman (1967).

A. Experiment 1

B. Experiment 3A

C. Experiment 3B

D. Experiment 4

E. Photomicrographs of sample electrode tips (Exp. 2). Small DC lesions were made through the electrode.

Symbols:

HPC	Hippocampus
FI	Fimbria
DG	Dentate Gyrus
▲	a self-stimulation site
△	not a self-stimulation site
④	indicates that 4 electrode tips were located at the same site and the site was a self-stimulation one.

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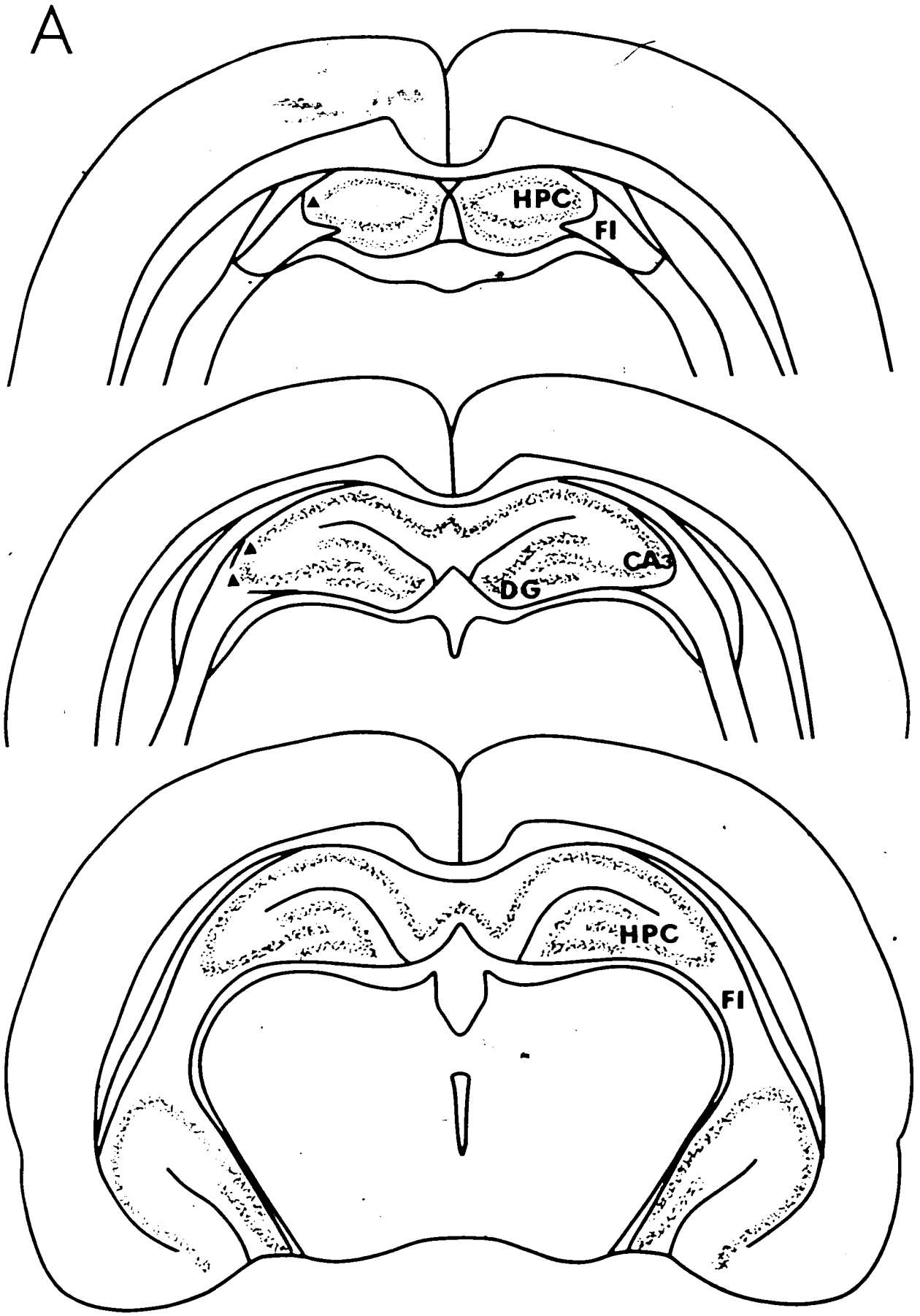

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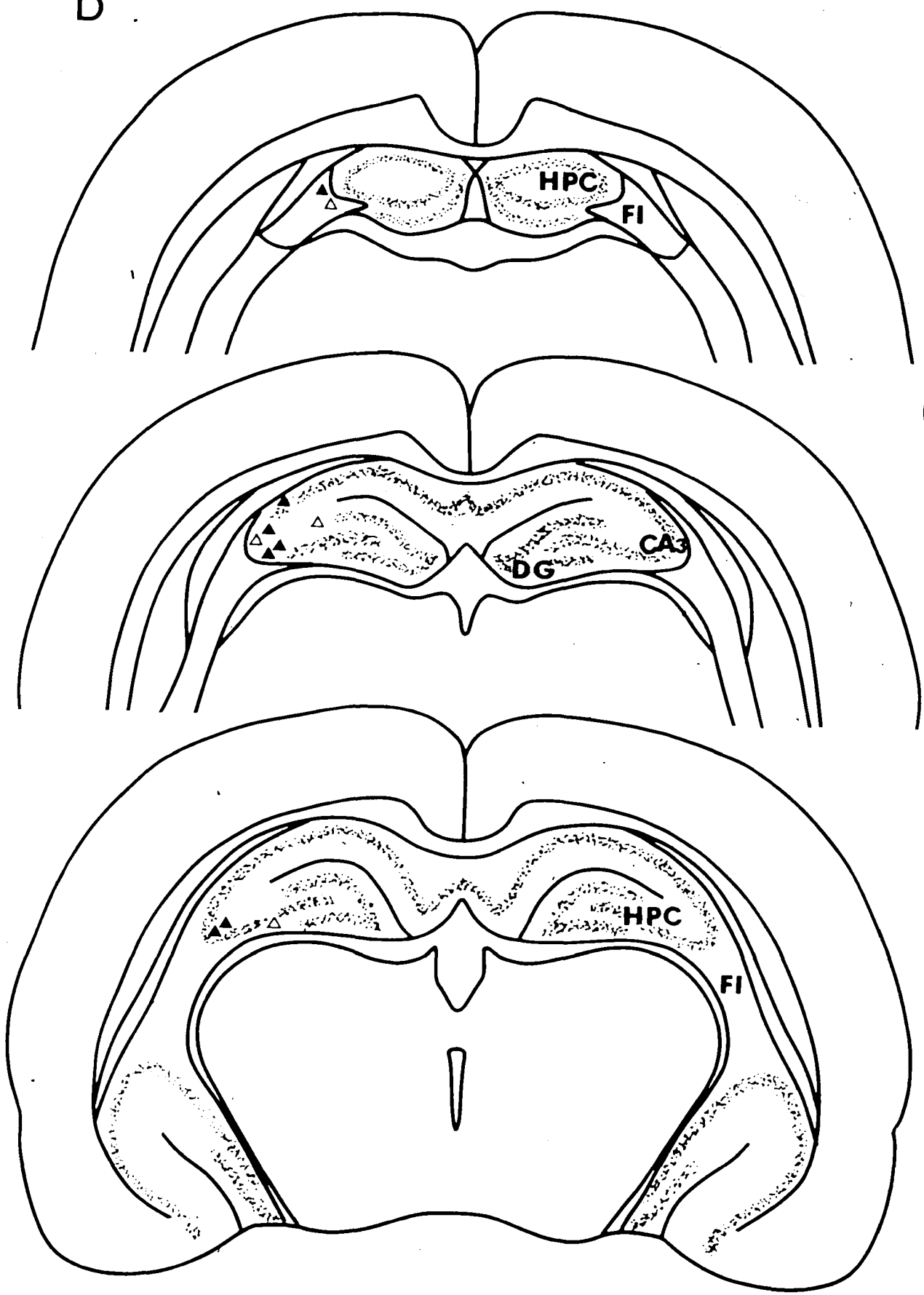

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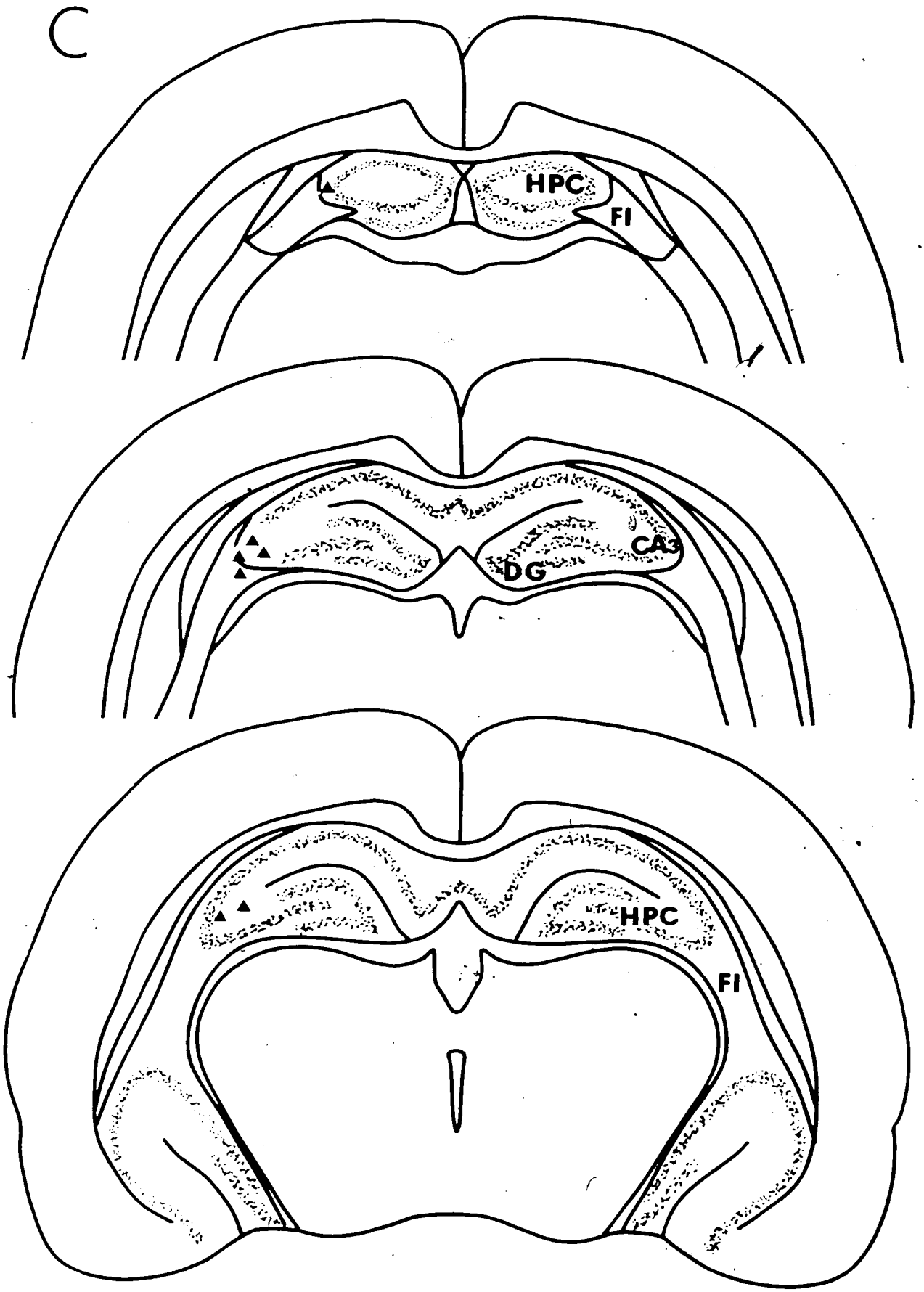

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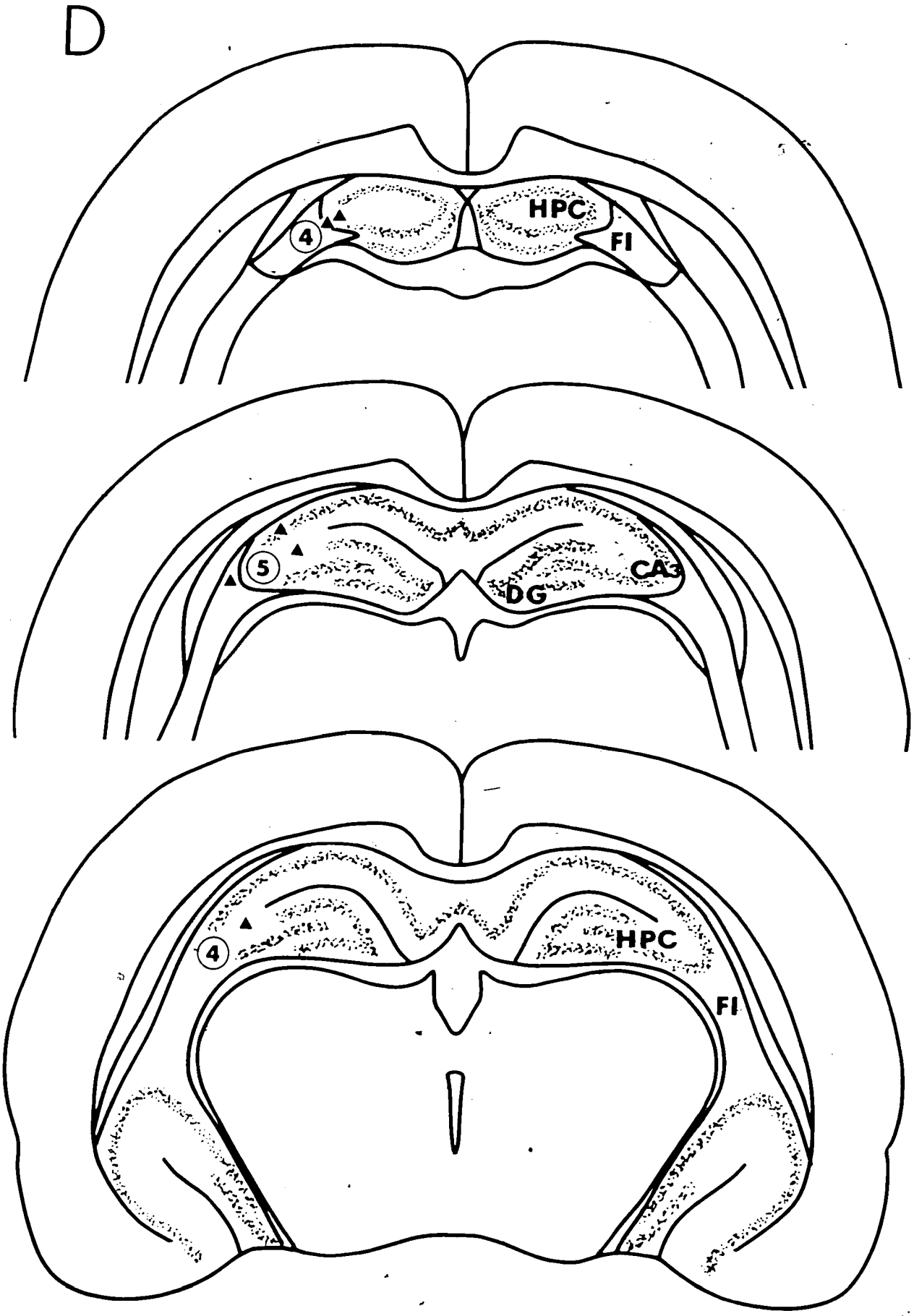

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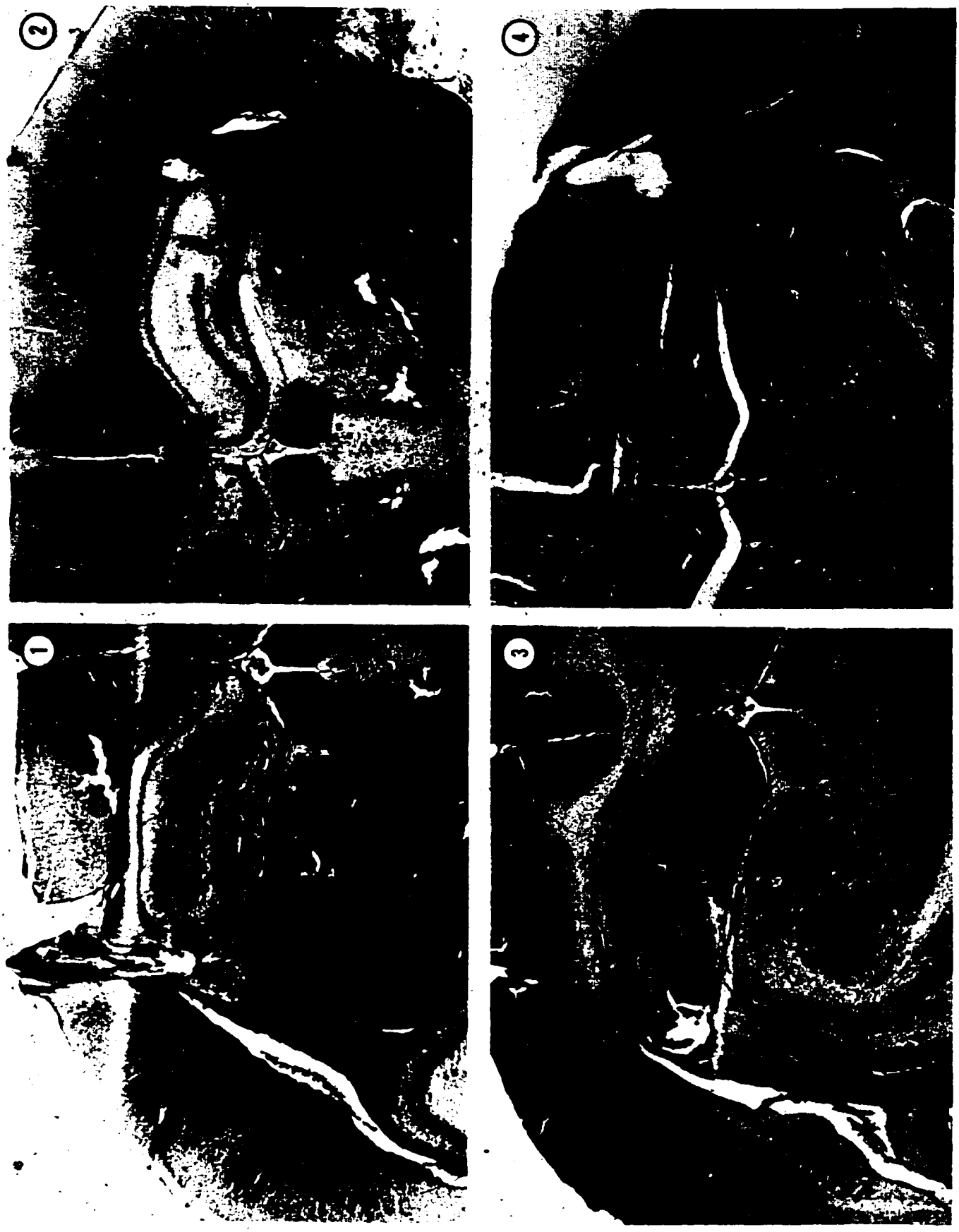
GREY PHOTO



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acrylic cement (Caulk Grip cement) was placed around the electrode and all the skull screws. The incision was then closed around the cement with three or four stitches and the animals were allowed to recover for at least two weeks before behavioral testing began.

Histology. Upon completion of the experiment each animal was killed with an overdose of Nembutal (1 cc or more) or with exposure to CO_2 for a few minutes. The brain was perfused with 10% formalin by injection into the left ventricle of the heart of the animal and was then removed from the cranium and stored in a 10% formalin solution. A 1-2 cm segment of brain containing the electrode track was frozen and sliced in an Ames Cryostat microtome. Sections around the electrode tip were mounted on glass slides, dried and stained with cresyl violet to show both cells and fibers. The atlas of Pelligrino and Cushman (1967) was used to identify brain structures.

Apparatus. Spatial discrimination training was conducted in a wooden T maze, painted black except for the white Plexiglas starting box. The long segment of the "T" measured 60 cm and the crossbar 19 cm; the width was 7 cm. Attached at each of the three points

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of the "T" was a 20 x 16 cm box. The boxes and runways were all 20 cm high.

Self-stimulation and lever pressing for food reward took place in clear Plexiglas Skinner boxes (each 30 x 18 x 62 cm high) fitted with a 3 cm wide lever, 4 cm above the floor, in the middle of one narrow wall. Each Skinner box was housed in a sound-attenuating chamber (61 x 46 x 92 cm high) which had a large two-way mirror that permitted viewing of the animal at all times. The inside of the chamber was illuminated by a 15 W fluorescent tube. Stimulation was delivered through a mercury commutator on top of the Skinner box by a constant-current sine-wave stimulator. Pressing the lever in the Skinner box activated both the stimulator and a counter. The lever had to be released before another stimulation could be delivered. Stimulation not delivered in the Skinner box occurred the same way except that the experimenter activated the stimulator and long leads were used instead of a commutator.

Passive avoidance training was conducted in an oblong black Plexiglas box (25 cm x 60 cm x 29 cm high). A black Plexiglas partition which divided the box in half was raised about 10 cm off the floor by the experimenter to begin the trial. The stainless steel rods

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(1.5 cm apart) which formed the floor of the box were connected to an 18 pin Cinch-Jones connector plugged into a Grason-Stadler scrambled shock generator (no. E1064GS). Only one half of the floor bars were electrified; this half of the box (the dark compartment) was covered with a sheet of clear Plexiglas with red acetate film on top. The other half of the box (the bright compartment) was covered by a steel grating (6.5 cm^2 holes). A 150 W reflector lamp stood approximately 50 cm above the floor of the bright compartment.

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Part I

ELECTRICAL STIMULATION OF THE HIPPOCAMPUS

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EXPERIMENT 1

A number of reports have indicated that rats will stimulate their brains electrically if the stimulating electrode is located in the dorsal hippocampus (Campbell, Milgram & Christoff, 1978; Campbell & Milgram, 1980; Caudarella, Milgram & Lomp, Note 2; Milgram, Server & Campbell, 1979; Olds, 1956a; Phillips, van der Kooy & Fibiger, 1977; Ursin, Ursin & Olds, 1966; van der Kooy, Fibiger & Phillips, 1977). All of these studies have reported only performance measures, mainly lever pressing rates, which, while they indicate that a hippocampal placement can support self-stimulation, do not provide adequate evidence of reinforcement and learning (see Berlyne, 1969a). Rigorous evidence of learning is particularly important in the case of hippocampal electrode placements since some researchers (Bruner, 1966; Newman & Feldman, 1964; Porter, Conrad & Brady, 1959) have suggested that hippocampal self-stimulation depends on abnormal seizure activity and others (see Olds, 1962) have suggested that such seizure activity might lead to repetitive automaton-like responding. Even without seizures, any kind of positive-feedback

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facilitation (i.e., a tendency for the stimulation to make the animal repeat whatever it has just been doing) might lead to an increase in lever pressing without any reinforcement or learning (Berlyne, 1969). Moreover, hippocampal stimulation is known to affect activity (Green, 1964), and an increase in general activity alone might account for increases in specific responses.

Several observations further suggest that hippocampal self-stimulation may be different from hypothalamic brain stimulation reward and from conventional reinforcers: animals receiving hippocampal stimulation take several sessions to learn and cannot be shaped (Milgram et al., 1979; Caudarella et al., Note 2). This behaviour is odd since a rapid response to shaping (i.e., the rewarding of successive approximations to the desired response) is generally characteristic of brain stimulation reward. The failure of shaping is, as far as I know, unique to the hippocampal placements. (A note of caution should be added here, however, since many experimenters reject animals that cannot be shaped within a few sessions and it is possible that some of these animals would self-stimulate if tested over a much longer period of time.) Even when hippocampal animals achieve stable self-

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stimulation rates, the rates are quite low (e.g., 100-300 lever presses in 30 min, continuous reinforcement schedule, 0.5 sec trains of stimulation). While self-stimulation rates are not necessarily correlated with reward value of the stimulation as indicated by preference tests (Hodos & Valenstein, 1962), some investigators and reviewers (e.g., German and Bowden, 1974; Ritter & Stein, 1973) reject placements that yield such low rates from consideration as self-stimulation areas.

On the other hand, there are observations which suggest that hippocampal stimulation is truly rewarding. First, hippocampal self-stimulators do not require priming to start them off at the beginning of a session, even after a delay of several weeks after the last self-stimulation session (Caudarella et al., Note 2). Also, very stable rates of lever pressing are maintained over long periods (at least several weeks).

Accordingly, in the first experiment to be described here, I compared the training of rats in a T-maze learning task rewarded by hippocampal stimulation with that of animals rewarded by food. If hippocampal stimulation could be used like food to reinforce a spatial discrimination, this would be good evidence that activation of the hippocampus can promote

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learning by serving as a positive reinforcer. Olds (1956) and Kornblith & Olds (1968) conducted simple maze-learning experiments using stimulation of the medial forebrain bundle in order to show that such stimulation was rewarding. However, Berlyne (1969a) criticized the use of speed of running as the dependent measure in Olds' experiment since an increase in running speed over days could be due to the conditioning of high arousal to the maze cues. Therefore, in the present experiment, a choice measure was used instead of running speed; correct choice of goal box is a measure that should not reflect conditioned arousal.

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METHOD

Three rats were implanted stereotactically with a single monopolar electrode as described. After recovery from surgery, each animal was placed in a Skinner box and was simply left there for 30-60 minutes a day until self-stimulation began. Training continued in daily 30-min sessions until relatively stable lever pressing rates were achieved. Three other rats were not implanted but were instead maintained on a restricted feeding schedule for about a week until their body weights had dropped 20-25 percent. Their weight was maintained at this level throughout the course of the experiment.

All Ss were placed in the start box of the T maze three times to allow them to become accustomed to the apparatus and to determine their preference for the left or right goal box. No reward of any kind was available in the goal boxes. The following day, each S was placed in the start box facing the runway and it was gently pulled by the tail to start it off into the runway. The food-reinforced animals were started off the same way. The goal box not preferred by the rat in the preliminary test was chosen as the

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"correct" one. When a rat in the brain stimulation group entered the correct goal box, it received four 30μA, half-second stimulations separated by 0.15 sec off-periods. When a rat in the food reward group entered the correct goal box, it received three 45 mg Noyes food pellets. The pellets were dropped into a glass dish only after the rat had completely entered the goal box so that the animal could not use odor cues to locate the correct goal box. For the same reason, a few pellets were scattered in the tray underneath both goal boxes in case any pellets were spilled by the rat and remained beneath the correct goal box. After 30 seconds the animal was removed from the goal box and after a delay of approximately 30 seconds the next trial was begun. Each stimulated animal was paired with a food-reinforced animal. If a stimulated animal refused to leave the start box for several minutes, the testing session was terminated for the day and the paired food-reinforced animal was stopped after the same number of trials. The criterion for learning the maze was nine out of ten correct choices. When animals met this criterion, training continued the next day with goal boxes reversed (in terms of delivery of reward). Reversal training occurred with two Ss in each group. Occasionally, a few more trials

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were allowed on a given day if the animal appeared to be nearing criterion and sometimes more trials were allowed to verify a consistent pattern of choices which were surprising (if all choices were correct on one day when they had been very erratic on previous days).

RESULTS AND CONCLUSIONS

The number of correct and incorrect choices made by the six animals on each testing day are shown in Table 1. The food-reinforced rats learned the initial spatial discrimination in 10-53 trials (Table 2). The rats that received only hippocampal stimulation as reinforcement also learned the discrimination, although somewhat more slowly, in 10-83 trials. Among the four animals that underwent reversal training, the food-reinforced rats both learned the reversal in the first training session, whereas one stimulated rat took 39 trials to learn the first reversal and the other had not learned after 32 trials. If one looks only at the first choice of each day (Table 3, I) and the first

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Table 1

The number of correct and wrong choices made on each testing day by pairs (A, B, C) of animals receiving food reward or hippocampal (HPC) stimulation.

(R) indicates reversal of correct and wrong goal boxes the day after the animal has met criterion.

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TABLE 1

PAIR	DAY	HPC STIMULATION NO. CORRECT	HPC STIMULATION NO. WRONG	FOOD REWARD NO. CORRECT	FOOD REWARD NO. WRONG	TOTAL NO. OF TRIALS
	1	4	3	5	2	7
	2	4	2	4	2	6
	3	6	4	8	2	10
A	4	8	0	3	2	5
	5	1	4	10	0	10
	6	5	6			11
	7	3	2			5
	8	9	1			10
	1	6	7	7	6	13
	2	4	6	6	4	10
	3	5	5	5	5	10
	4	3	7	6	4	10
	5	7	3	10	0	10
	6	5	5			10
B	7	8	2			10
	8	9	1			10
	9 (R)	4	7	(R) 8	3	11
	10	6	4	9	1	10
	11	3	8			11
	12	3	11			14
	1	15	0	14	1	15
	2 (R)	0	6	(R) 3	3	6
	3	0	6	10	0	-
	4	1	5			6
	5	6	5			11
	6	7	3			10
	7	10	0			10
C	8 (R)	0	11	(R) 7	4	11
	9	0	10	9	1	10
	10	10	0			10
	11	3	0			3
	12 (R)	0	6	(R) 4	2	6
	13	0	10	10	0	10

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TABLE 2

Total number of trials to criterion (9 out of 10 correct T-maze choices). Data from Table 1.

PAIR	HPC STIMULATION	FOOD REWARD
A	64	38
B	83	53
C	10	10
MEAN	52	34

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choice of the day after the session on which the learning criterion was met (Table 3, II), there is no significant difference between the stimulated and food-reinforced animals. The last measure is particularly interesting since it should measure only long-term memory, unconfounded by any immediate activating effects of brain stimulation or by any transient positive feedback effects (e.g., the tendency to repeat the last performed response regardless of reward contingencies).

DISCUSSION

Stimulation of the hippocampus was rewarding (i.e., it promoted the learning of a spatial discrimination). However, learning was somewhat slower with brain stimulation reward and sometimes more erratic, with a surprising pattern of errors; for example, brain stimulation animal "C" (Table 1) that persisted in making the "wrong" choice (previously "correct") on every trial (Days 8 & 9) and suddenly switched to making the "correct" choice on every trial (Day 10). No such pattern of errors was seen in the behavior of

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TABLE 3

Comparison of hippocampal stimulation reward and food reward in the T maze test.

I. The animals' first choices each day, excluding the first day. (Does not include reversal training). Totals for 3 rats in each group.

II. The animals' first choices of the days after the session on which learning criterion was met (i.e. of the days when reversal training was begun). Totals for 2 rats in each group (pairs B & C).

	HPC STIMULATION		FOOD REWARD		TOTAL
	NO. CORRECT	NO. WRONG	NO. CORRECT	NO. WRONG	(MAXIMUM SCORE)
I	5	5	6	4	10
II	4	0	3	1	4

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the food-reinforced animals.

Slower learning in the T maze is consistent with observations of slower learning in a Skinner box with hippocampal stimulation. The slower learning is perhaps not surprising if one considers that the stimulation may be activating several circuits, directly or indirectly, some of which may be reinforcing and some of which may have disruptive effects on performance or learning. Such mixed effects are theoretically possible with any conventional reinforcer but, if so, they may tend to be more subtle. For example, the initial presentation of food to a very hungry animal, although obviously rewarding, may be so arousing as to interfere with performance and learning if the animal attacks the food dispenser instead of making the appropriate association with the "correct" response which caused the delivery of food. The same behavior may sometimes be seen in the case of a hungry person confronted with an uncooperative vending machine: in this case also, less arousal might lead to more efficient learning of the appropriate responses (see Bindra, 1959; Hebb, 1955; Malmo, 1975).

In the case of hippocampal stimulation, what is perhaps more surprising is that learning is slower than that normally seen with rewarding hypothalamic

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stimulation). One difference between the effects of stimulation of these two brain structures is that hippocampal stimulation has often been reported to have amnestic effects whereas hypothalamic stimulation has been reported to have facilitatory effects on learning (e.g., Berman & Kesner, 1976). Possible amnestic effects of hippocampal stimulation are considered in the next two experiments.

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EXPERIMENT 2

Stimulation of the dorsal hippocampus was used successfully in Exp. 1 to reinforce spatial discrimination learning. Hippocampal stimulation has also been used to reinforce operant lever pressing in self-stimulation experiments. However, as has already been pointed out, animals with hippocampal electrodes learn relatively slowly to self-stimulate and then stabilize at low rates of lever pressing. Some of these effects may conceivably be produced by disruptive effects of the stimulation as observed in the experiments already mentioned in the general introduction - e.g., Olds and Olds (1961), Livesey (1975) - that showed that dorsal hippocampal stimulation delivered during the learning session or immediately afterwards interfered with learning. In view of these reports it is of interest to know whether hippocampal stimulation will disrupt appetitive learning when stimulation follows each lever press as in self-stimulation experiments.

A previous experiment (Caudarella, Campbell & Milgram, 1977) showed that a slight disruption of

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learning could be produced if rewarding hippocampal stimulation was delivered during acquisition of a food-reinforced lever press response. When 0.5 sec of 30μA unilateral hippocampal stimulation was contingent on the lever press, food-deprived rats showed slower acquisition when compared with a stimulated, "yoked" control group; however, all animals did learn the response. The same stimulation parameters were subsequently shown to support self-stimulation in the same animals. It seemed therefore that hippocampal stimulation which promotes learning (i.e., acts as a positive reinforcer) might actually interfere somewhat with learning that is motivated by a conventional reinforcer (food pellets). One problem with the study, however, was that a yoked control group proved to be inadequate since those control animals which were paired with experimental animals that hardly pressed the lever obviously did not receive much stimulation. Therefore, the following experiment attempted to replicate and extend the preliminary findings using a randomly stimulated control group.

Increased performance with practice is only one criterion of learning and it is usually preferable to demonstrate the presence of long-term memory as

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evidence that learning has occurred. Indeed, hippocampal stimulation has been shown to prevent long-term memory (24 hr) even though a short-term memory (90 sec) test indicates that learning took place (Berman & Kesner, 1976). Accordingly, in the present experiment a retention test of learning was conducted 24 hr after the last training session. No stimulation or food reward was delivered during the retention test so that only differences in learning (and not performance) would appear among the groups.

One additional manipulation involved pretreating about half the animals with brief daily stimulation (kindling). The work of Campbell et al. (1978) suggests that the effects of hippocampal stimulation change with increased stimulation experience; in particular, they found that animals which initially do not respond readily to hippocampal stimulation learn to self-stimulate more quickly if they are pre-treated with daily kindling stimulation. If hippocampal stimulation has unrewarding, amnestic effects which diminish with repeated stimulation, it may be possible to attenuate any such effects by allowing animals prior experience with hippocampal stimulation.

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METHOD

Procedure. Forty-two rats were stereotactically implanted with single bipolar electrodes aimed at the dorsolateral hippocampus as described. After recovery, 19 rats received a 1 sec train of 60 Hz, sine wave stimulation (30μA) in their home cages once a day for 24 days (kindling). The other 23 rats were handled identically, but were not stimulated. Both groups of rats were then deprived of food for two days and maintained at approximately 80 percent of their ad libitum body weight throughout the first learning phase of the experiment. The Ss were randomly divided into three treatment groups tested in identical Plexiglas Skinner boxes. One group ("contingently stimulated": unkindled n=9, kindled n=7) received both a 45 mg Noyes food pellet and 0.5 sec of 30μA, 60 Hz, sine-wave current immediately following each lever press; a second group ("randomly stimulated": unkindled n=7, kindled n=5) received a food pellet for each lever press as well as having 0.5 sec of stimulation delivered randomly such that the total number of stimulations in each session equalled approximately the average of the stimulations

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received by the contingently stimulated group; and a third group ("unstimulated surgical control"; unkindled n=7, kindled n=7) received only food pellets, without stimulation. After 15 minutes of magazine training (i.e., automatic food pellet delivery) on the first day, the rats were left unassisted to learn to press the lever. Lever presses and stimulations were recorded every 15 min during daily 30-min sessions. Four days after the beginning of training on the lever pressing task, a 10-min test without any stimulation or food reward was given with the animals still on a restricted feeding schedule but 24 hours after the last training session. Lever presses were recorded after 5 and 10 minutes. One animal in each of the three unkindled groups had not responded after four days and was shaped successfully by the method of successive approximations. These three rats were then tested as were the others in a 10-min test. To facilitate the transfer from food reward to stimulation reward, the animals were then allowed one more day (15-min session) with food reward. The next two days all animals received only 0.5 sec of stimulation after each lever press although they were maintained on food deprivation. Thereafter, the animals were returned to ad libitum feeding while testing continued

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daily (30-min sessions) until the rats reached a self-stimulation criterion of at least 90 lever presses in 30 minutes on three separate days; otherwise screening for self-stimulation continued for up to 24 days.

Statistical Analysis. Six animals were not used in the analysis even though their data did not differ noticeably from the others: five animals in the stimulated groups that showed no evidence of self-stimulation and one rat that died before self-stimulation could be determined.

A two-way factorial analysis of variance was first performed and pairwise comparisons made using randomization tests (Siegel, 1956). Since there were no significant ($p>.05$, two-tailed test) differences between the kindled and unkindled groups, the data were pooled and analyzed without kindling as a blocking factor. In cases where there appeared to be significant kurtosis (Blalock, 1960), the Mann-Whitney U test was used for pairwise comparisons, in preference to the randomization test. All significance tests were non-directional (two-tailed).

An acquisition criterion of 25 lever presses in 15 minutes was adopted based on preliminary analysis

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of the learning trends in the data of the unstimulated control animals. If a rat's response rate reached 25 lever presses or more in 15 minutes, its response rate usually showed a marked increase in subsequent 15-min periods. Consequently this level of responding was taken to be an indication of acquisition.

RESULTS AND CONCLUSIONS

Fig. 2 shows the mean number of 15-min periods required to reach the acquisition criterion by the three groups. There were no significant differences: the rate of acquisition appeared to be the same for all three groups. However, Table 4A indicates that there was a difference in one measure of performance in the fourth 15-min period (the last training session for the rats that learned rapidly): the contingently stimulated animals' lever pressing rate was significantly lower than that of the unstimulated surgical control group. The performance of the randomly stimulated animals was between that of the other two groups. Thus it appears that the delivery of hippocampal stimulation

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Fig. 2 The effect of hippocampal stimulation on rate of acquisition of food-reinforced lever pressing. Small bars indicate standard error of the mean (S.E.M.). The acquisition criterion was 25 or more lever presses in 15 min with no decrease on subsequent days. There were no significant differences ($p > .05$) among the group means.

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MEAN NO. OF 15–MIN. PERIODS TO REACH ACQUISITION CRITERION

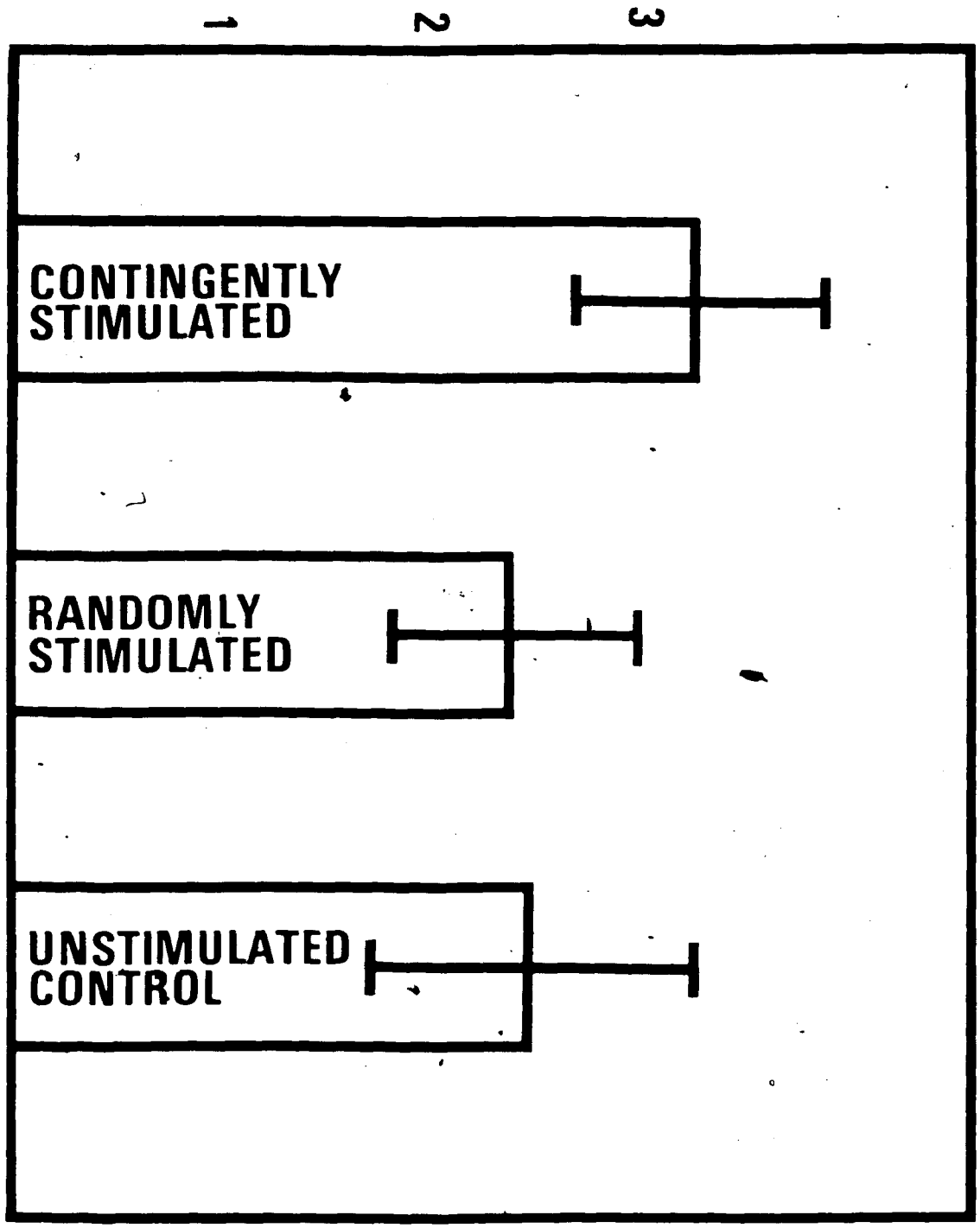

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TABLE 4

A. Number of lever presses in the fourth 15-min. period; i.e. the last training period for the rats that learned very rapidly.

B. Total number of responses by all Ss by the end of the training sessions.

		NUMBER OF LEVER PRESSES			
		A.		B.	
		FOURTH 15-MIN PERIOD		TOTAL NO. BY LAST DAY	
GROUP	n	$\bar{X}$	±S.E.M.	$\bar{X}$	±S.E.M.
CONTINGENTLY STIMULATED	16	*43.3	± 7.2	314.9	± 23.1
RANDOMLY STIMULATED	12	63.4	±13.3	296.8	± 26.7
UNSTIMULATED CONTROL	14	76.8	±13.7	386.6	± 30.8

* $p < .05$ (Mann-Whitney U) compared with unstimulated controls

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contingent on each lever press does disrupt performance to some extent. By the end of the training sessions, however, there were no significant differences among the groups in the total number of lever presses (Table 4B).

Table 5 presents the results of the 10-min test of learning (and memory) conducted one day after the last brain stimulation or food reward: the significantly lower number of lever presses (shown graphically in Fig. 3) indicates that the animals trained under contingent stimulation did not learn as well as the unstimulated control rats; once again, the randomly stimulated animals' mean score was intermediate.

Fig. 4 shows the mean number of 15-min periods to reach acquisition criterion as a function of kindling pretreatment and stimulation treatments. Kindling had no overall effect and there was no significant effect of kindling within each stimulation treatment (e.g., unkindled contingently stimulated vs. kindled contingently stimulated). Kindling had no significant effect on any of the other dependent measures already presented.

The five animals that did not show self-stimulation were distributed over the four stimulated groups and thus no meaningful statistical comparison can be made.

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TABLE 5

Number of lever presses in memory test one day after last stimulation/food reward. The data for the first five min are shown graphically in figure 3.

		NUMBER OF LEVER PRESSES			
		FIRST FIVE MIN.		TOTAL IN TEN MIN.	
GROUP	n	$\bar{X}$	±S.E.M.	$\bar{X}$	±S.E.M.
CONTINGENTLY STIMULATED	16	**35.7	± 7.9	**59.6	± 9.8
RANDOMLY STIMULATED	12	44.3	±11.7	71.3	±15.5
UNSTIMULATED CONTROL	14	69.9	±13.9	101.3	±15.8

** $p < .02$ (Mann-Whitney U) compared with unstimulated controls

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Fig. 3 Effect of hippocampal stimulation on food-reinforced lever pressing. The memory test took place one day after last administration of food pellets or brain stimulation. No reward was given during this test. Small bars indicate S.E.M. Contingently stimulated (n=16) vs. unstimulated surgical controls (n=14): $p<.02$.

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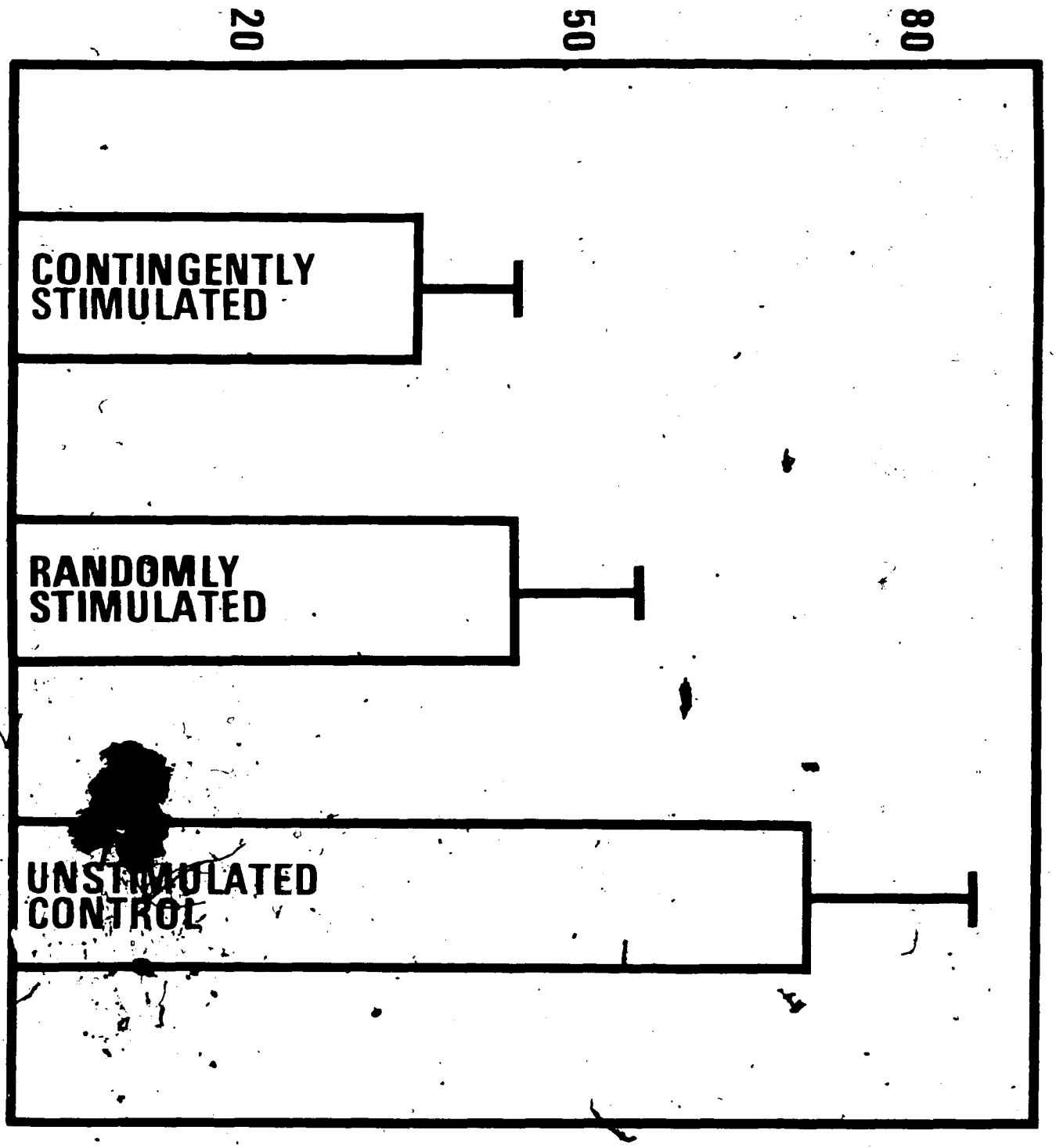

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Fig. 4 Effect of kindling pretreatment and stimulation condition on acquisition of lever pressing for food reward.

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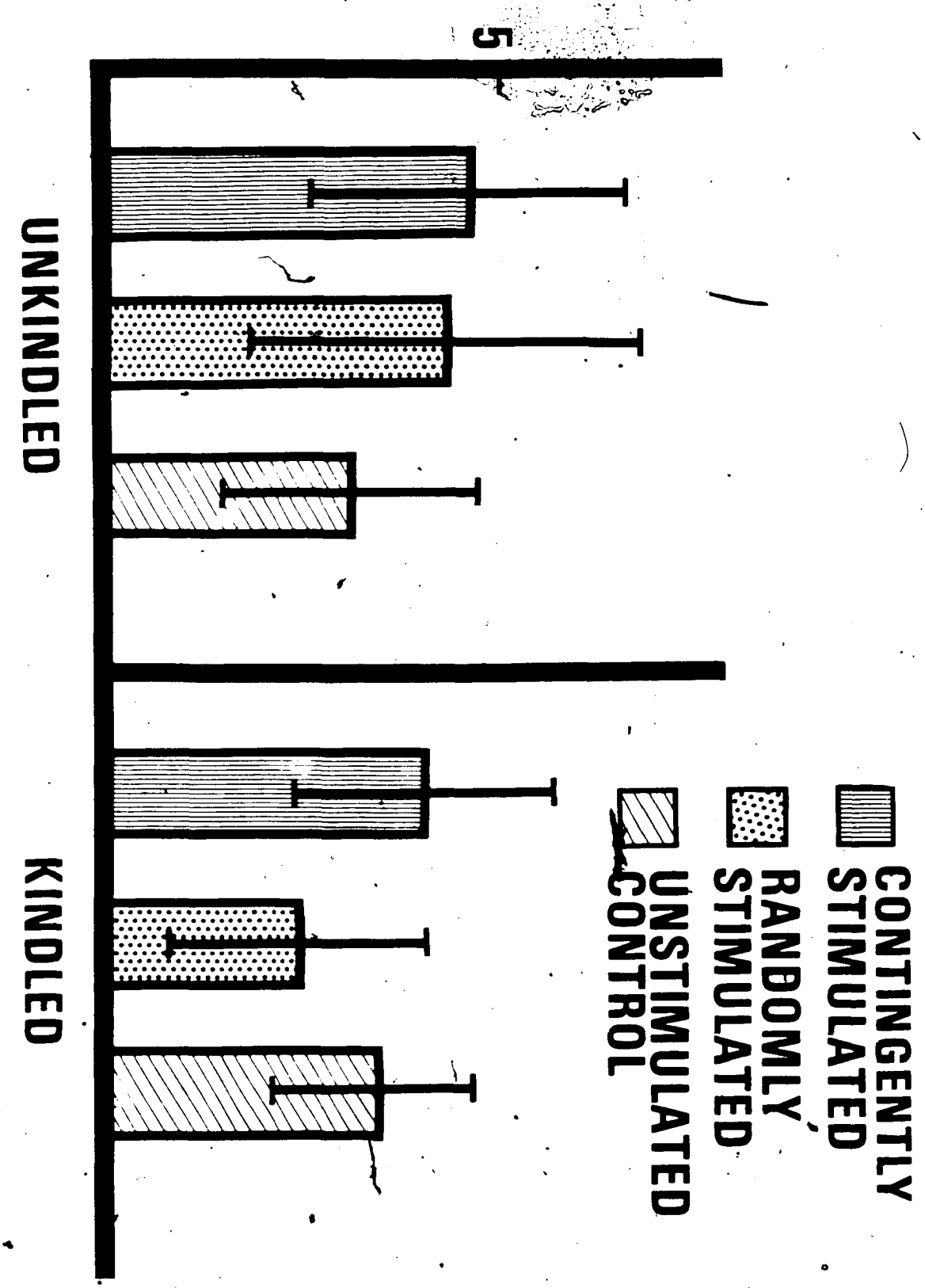
MEAN NO. OF 15–MIN. PERIODS TO REACH ACQUISITION CRITERION



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In looking at the individual data, no difference was evident between the performance of these animals and the similarly treated self-stimulators.

DISCUSSION

All of the animals tested in this experiment were able to learn the lever pressing task within a few days. However, hippocampal stimulation did disrupt learning slightly. Furthermore, the impairment was more pronounced if the 0.5 sec train of stimulation was delivered immediately after each lever press rather than randomly throughout the session (same total number of stimulations). These results are consistent with the previously reported preliminary results (Caudarella et al., Note 2) and resemble the results reported by Livesey (1975). In Livesey's experiments, however, the impairement in the acquisition of a discrimination was much more severe and could also be obtained with continual, but noncontingent, hippocampal stimulation (0.5 sec of stimulation every 3 sec throughout the session) as well as with discrete stimulation (2 sec train) after each response.

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Disruption of performance is interesting only if it accompanies impairment of learning (i.e., a relatively permanent change in behavior which outlasts such immediate effects of the stimulation as change in arousal, positive feedback or disruption of motor performance -- Berlyne, 1969a & b; Kimble, 1961) as indicated in a test of memory at least one day after the last stimulation. Therefore, it is particularly interesting that the animals previously trained with contingent hippocampal stimulation exhibited significantly poorer performance on the 10-min test of memory. This result combined with the observation of a lack of impairment in the measure of rate of acquisition (Fig. 2) is consistent with the results reported by Berman & Kesner (1976) indicating that posttrial hippocampal stimulation disrupts long-term (24 hr) memory of appetitive learning, with no evidence of impairment on a short-term (90 sec) test. As to the discrepancy in some of the results, it may be that the disruption of performance observed in the present experiment (Table 4A) is due to the presence of the stimulation during the training session rather than after the learning trial as used by Berman and Kesner. In support of this idea, White (Note 5) has found that facilitation of learning occurs only when rewarding

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brain stimulation is administered outside of the span of time of the conditioning sessions, and preferably in a different testing box, but that the same brain stimulation has disruptive effects if it is delivered within the learning session.

One unfortunate consequence of disruption of performance by the immediate interfering effects of the stimulation is that this effect introduces confounding: it may be that the contingently stimulated animals performed more poorly on the memory test simply because they experienced fewer conditioning trials during the learning sessions. In other words, if the stimulation has immediate disruptive effects on performance, a rat performs fewer responses, gets fewer rewards and therefore learns less well or less quickly. Unfortunately, there is no way to rule out this alternate explanation of the data within the confines of the present experiment.

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EXPERIMENT 3

Most experimenters reporting anmestic effects of hippocampal stimulation use simple, one-trial conditioning tasks that usually involve shock-motivated avoidance behavior (see Kesner & Wilburn, 1974; McGaugh & Herz, 1972). The brain stimulation is administered through previously implanted electrodes shortly after the animals are punished (shocked) when they perform some prefered and highly probable response such as entering a dark chamber, stepping down off a small platform or eating from an apparently ordinary food dish. Some disruption of learning was observed in Exp. 2 when hippocampal stimulation followed each reinforced response. However, since the immediate effects of the stimulation reduced responding, the slight disruption of learning observed may have been due to the smaller number of reinforced responses made by the stimulated animals.

Exp. 3 tests whether posttrial hippocampal stimulation will disrupt the learning of passive avoidance as has often been reported. The use of

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this simple one-trial learning paradigm should circumvent the kinds of performance effects encountered with operant conditioning in the Skinner box and should provide a test which is more comparable to the standard one-trial memory-disruption experiment.

Part A

The ability of hippocampal stimulation to serve as a reward presents a problem for the interpretation of the standard "amnesia" experiment using passive avoidance. It is possible that an animal that has been shocked when it performs a highly probable response will perform the same response again because the footshock was followed by a strong reward (i.e., brain stimulation), leading to the erroneous conclusion that the animal cannot remember being shocked; more specifically, that the animal cannot store or "consolidate" the association between response and footshock.

Only a few experimenters (e.g., Shinkman & Kaufman, 1972; Goddard, 1964) have attempted to rule out the rewardingness of the brain stimulation as an alternate explanation for the apparent amnesia, usually

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by testing for self-stimulation behavior well after the memory testing had been completed and sometimes in different animals. For example, Shinkman & Kaufman (1972) reported that posttrial hippocampal stimulation impaired consolidation of a conditioned emotional response. They admitted that their observation of a lack of shock-induced suppression of lever pressing would also occur if the hippocampal stimulation were rewarding and had no amnestic properties. To test for the rewardingness of the brain stimulation they conducted self-stimulation tests using current 50-77% of the intensity and 1.25% of the duration used in their memory experiments and only after the animals had undergone two conditioned suppression experiments as well as some undescribed preliminary tests of self-stimulation. In spite of a history of footshock administration during lever pressing (at least 14 daily pairings), the animals showed significant self-stimulation; however, on the basis of a nonsignificant correlation ($r = .36$, $n = 8$) between the rats' self-stimulation rate and suppression ratio (in the memory experiments), the authors concluded that the rewardingness of the stimulation could not account for the few cases of amnesia which they observed. They also noted that seizure thresholds during the self-stimulation

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tests were considerably lower than those recorded at the beginning of the experiment. In other words, Shinkman and Kaufman unfortunately dismissed the rewardingness of the hippocampal stimulation on the basis of self-stimulation control tests conducted with different current parameters in animals that had previously been shocked repeatedly during lever pressing and whose brain circuits had undergone a permanent functional change as evidenced by the lower seizure thresholds (i.e., "kindling").

No study that I know of has incorporated any specific control for the rewardingness of the hippocampal stimulation delivered after footshock in a one-trial passive avoidance or conditioned suppression task. Thus in this experiment an attempt is made to dissociate hippocampal stimulation from the response which the animal must learn to suppress. After the single learning trial, the rat is removed to a different testing box and allowed time to depress a lever which initiates a train of hippocampal stimulation. If the hippocampal stimulation is rewarding, it should be associated with pressing the lever and not with performing the response that is followed by footshock (in this case, entering a dark compartment). The dissociation should be further enhanced by using

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animals that have already had experience pressing a lever for hippocampal stimulation.

METHOD

Subjects. Twenty-three rats which had completed Exp. 2 were used - 14 selected randomly from among the self-stimulators and nine animals that had shown no evidence of self-stimulation.

Procedure. A one-trial step-through passive avoidance task was used in which rats were placed in the brightly lit half of the black Plexiglas box already described. The rat quickly entered the dark chamber through the small opening and, when all four paws were inside, received a strong 2 mA shock through the floor bars until it escaped to the bright (safe) compartment (1-2 sec). Latency to enter the dark chamber was measured with a stop-watch. The rat was then removed from the box, leads were attached to its electrode and the animal was quickly placed in a clear Plexiglas Skinner box. Pressing the lever activated the sine-wave stimulator which delivered a train of ten 1 sec

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stimuli separated by 0.5 sec off-periods. The 30 μA current level was set and monitored with an oscilloscope. Half the animals were stimulated in this way; half served as unstimulated controls which were treated identically except that the lever activated the noisy relay switches and timers without activating the stimulator. Twenty-four hours later (±15 min) each rat was again placed in the brightly lit compartment of the black box and latency to enter the dark chamber, up to a maximum of 300 sec, was recorded. In addition, the occurrence of defecation and the number of minutes of "freezing" were also recorded to provide a measure of emotionality and, hence, another index of learning.

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RESULTS AND CONCLUSIONS

On the second day, all animals stayed out of the dark chamber for a full five minutes (Table 6) indicating that hippocampal stimulation had not prevented the stimulated animals from remembering that they had been shocked in the dark chamber the day before. Included were a few animals that had shown evidence of seizure activity after the stimulation and one that had a generalized motor convulsion that lasted about 30 sec. (No. 22, Table 6). It can be seen from Table 8A, moreover, that some of the stimulated rats froze longer and defecated more than the unstimulated control group. Thus the hippocampal stimulation did not disrupt acquisition of a conditioned emotional response.

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TABLE 6

Latencies (in sec) to enter the dark chamber of the passive avoidance box. Maximum latency of 300 sec indicates retention of conditioned avoidance of the dark chamber.

	HIPPOCAMPAL STIMULATION			UNSTIMULATED CONTROL		
	S No.	Day 1 (TRAINING)	Day 2 (TEST)	S No.	Day 1 (TRAINING)	Day 2 (TEST)
Non-self-Stimulators	48	2	300	16	4	300
	46	4	300	54	9	300
	6	5	300	31	10	300
	60	19	300	36	16	300
	21	34	300			
Self-Stimulators	28	1	300	25	1	300
	15	3	300	20	2	300
	29	5	300	39	3	300
	24	7	300	59	3	300
	53	14	300	51	3	300
	19	19	300	38	12	300
	22	32	300	47	38	300

TABLE 8

Two behavioral indices of emotionality: freezing and defecation.

	EXP. 3A		EXP. 3B	
	HPC STIMULATION	CONTROL	HPC STIMULATION	CONTROL
MEAN TIME FREEZING ± S.E.M. (SEC)	93 ± 40	49 ± 30	180 ± 50	101 ± 46
PERCENTAGE OF RATS DEFECATING	67	55	75	50
TOTAL (n) NO. OF RATS	12	11	8	8

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EXPERIMENT 3, Part B

It is possible that the failure to observe amnesia in Exp. 3A was due to the successful dissociation of hippocampal stimulation and the shock compartment cues and that this better-controlled procedure accounts for the discrepancy in results between Exp. 3A and some reported studies in which footshock was simply followed immediately (or with a short delay) by hippocampal stimulation, resulting in no apparent evidence of memory (e.g., Brunner, Rossi, Stutz & Roth, 1970; Shinkman & Kaufman, 1972; Sideroff, Bueno, Hirsch, Weyand & McGaugh, 1974). In the next experiment, then, hippocampal stimulation was delivered shortly after footshock without allowing any intervening response by the animal. In this experiment, as in other similar studies, the brain stimulation was not delivered while the animal was still in the shock compartment since in that case the animal would be grounded through the floor bars and there would be a danger of electrocution.

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METHOD

Sixteen rats not used in Exp. 3A were randomly selected from the ones that had been found to be self-stimulators in Exp. 1; 8 were stimulated and 8 not stimulated (control group). The apparatus and procedure were the same as in Exp. 3A, except that as soon as each rat had been shocked upon entering the dark chamber of the passive avoidance box, it was removed, leads were attached to its electrode and it was held on a table just over the passive avoidance box while a train of stimulation was delivered 30 sec after footshock. The unstimulated control animals underwent the same procedure but with the stimulator turned off. On the second day, latency, defecation and freezing behaviors were recorded as in Exp. 3A.

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RESULTS AND CONCLUSIONS

Six of the stimulated animals avoided entering the dark compartment on the second day (Table 7). Two did enter the dark chamber but with latencies many times greater than on the first day (No. 3 and 50). The unstimulated control rats all stayed out of the dark compartment for the full five minutes. There is therefore no evidence that hippocampal stimulation as delivered here prevents the formation of retention of a conditioned avoidance. On the contrary, as in Exp. 3A, the stimulated animals appeared to be even more emotional than the control rats: Table 8B shows that some of the stimulated rats defecated more and froze longer.

DISCUSSION

Although the delivery of rewarding brain stimulation 30 sec after footshock in the present experiment did not lead to a disruption of aversive conditioning, it is still possible that the use of reward-

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TABLE 7

Latencies (in sec) to enter the dark chamber of the passive avoidance box. Maximum latency of 300 sec indicates good retention of conditioned avoidance of the dark chamber.

HIPPOCAMPAL STIMULATION			UNSTIMULATED CONTROL		
S No.	Day 1 (TRAINING)	Day 2 (TEST)	S No.	Day 1 (TRAINING)	Day 2 (TEST)
57	1	300	7	1	300
33	2	300	45	2	300
3	2	73	1	3	300
50	4	258	18	3	300
8	9	300	56	19	300
23	10	300	34	40	300
4	24	300	55	45	300
30	61	300	26	62	300

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ing stimulation could lead to incorrect reports of amnesia if somewhat different procedures were used. Stimulation of the hippocampus or other brain regions known to support self-stimulation (e.g., the amygdala--Wurtz & Olds, 1963) may have overridden or at least softened the effect of the footshock reinforcement, especially when the brain stimulation was applied within seconds of the footshock and in the same compartment (e.g., Brunner et al., 1970; McDonough & Kesner, 1971; Sideroff et al., 1974). It is interesting, moreover, that Koranyi and Endroczi (1965) found that active avoidance learning could be disrupted by dorsal hippocampal or amygdala stimulation as long as the stimulation was delivered in the original training box; if the rats were trained in one box but stimulated in a different box, no amnesia was seen 24 hr later.

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EXPERIMENT 3, Part C

In Exp. 3A and 3B, the animals that received hippocampal stimulation on the first day appeared to be more emotional than the unstimulated rats when placed in the testing chamber on the second day: they froze longer and defecated more than the control rats. These observations suggested that stimulated animals had developed a more profound conditioned emotional response but due to a "ceiling effect" no difference in latency to enter the dark compartment could be detected between them and the control rats within a maximum of five minutes. This suggestion was tested by waiting a week, during which the memory trace of the conditioned avoidance might become weaker and any effects of the brain stimulation on performance should subside, and retesting the animals in the same way (i.e., measuring latency to enter the dark chamber) but simply waiting until they did finally re-enter the dark chamber. This method allowed variance to occur among the latency scores and indicated a difference in scores due to the hippocampal stimulation.

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METHOD

Eighteen self-stimulators that had completed Exp. 3A and 3B were tested seven days after they had initially been introduced into the passive-avoidance apparatus. Six rats (3 stimulated, 3 control) were excluded because they had run back into the dark (shock) compartment on the first day before they could be removed from the apparatus. Thus, the animals used in the present follow-up test were ones that had been shocked only once. Since just three animals that did not self-stimulate remained, no meaningful comparison could be attempted between these and the self-stimulators and thus the follow-up test was conducted only with the eighteen self-stimulators.

Each rat was placed in the brightly lit chamber and simply left there until it entered the dark chamber (all four paws inside), with the exception of one rat that was removed from the box after one hour and assigned a latency of 60 min.

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RESULTS AND CONCLUSIONS

Fig. 5 presents the mean latency to enter the dark chamber for the 18 self-stimulators (9 stimulated and 9 control rats). The animals that seven days before had received 10 sec of hippocampal stimulation avoided entering the dark chamber significantly longer than the unstimulated control animals (Mann-Whitney U test, $p < .025$). The results were essentially the same for the two subgroups of self-stimulators that completed Exp. 3A (stimulation group: $\bar{X} = 1398 \pm 614$, control group: $\bar{X} = 365 \pm 170$, $n = 5$) and Exp. 3B (stimulation group: $\bar{X} = 2020 \pm 617$, control group: $\bar{X} = 302 \pm 121$, $n = 4$). It is also of interest that the only animal that showed a full-scale motor convulsion, when stimulated, entered the dark chamber with a latency of 351 sec, showing retention of the conditioned avoidance just slightly better than the mean of the control group (337 sec).

Thus, while all animals showed evidence of learning and memory on the second day (Exp. 3A and 3B), the animals that received unilateral hippocampal stimulation shortly after being shocked showed better retention than the control animals when a long testing

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Fig. 5 The effect of hippocampal stimulation on step-through passive avoidance learning. The latency to enter the dark (normally prefered) compartment seven days after a single foot-shock trial is shown along with S.E.M. The data are taken from animals that completed Exp. 3A and 3B. ($p < .05$).

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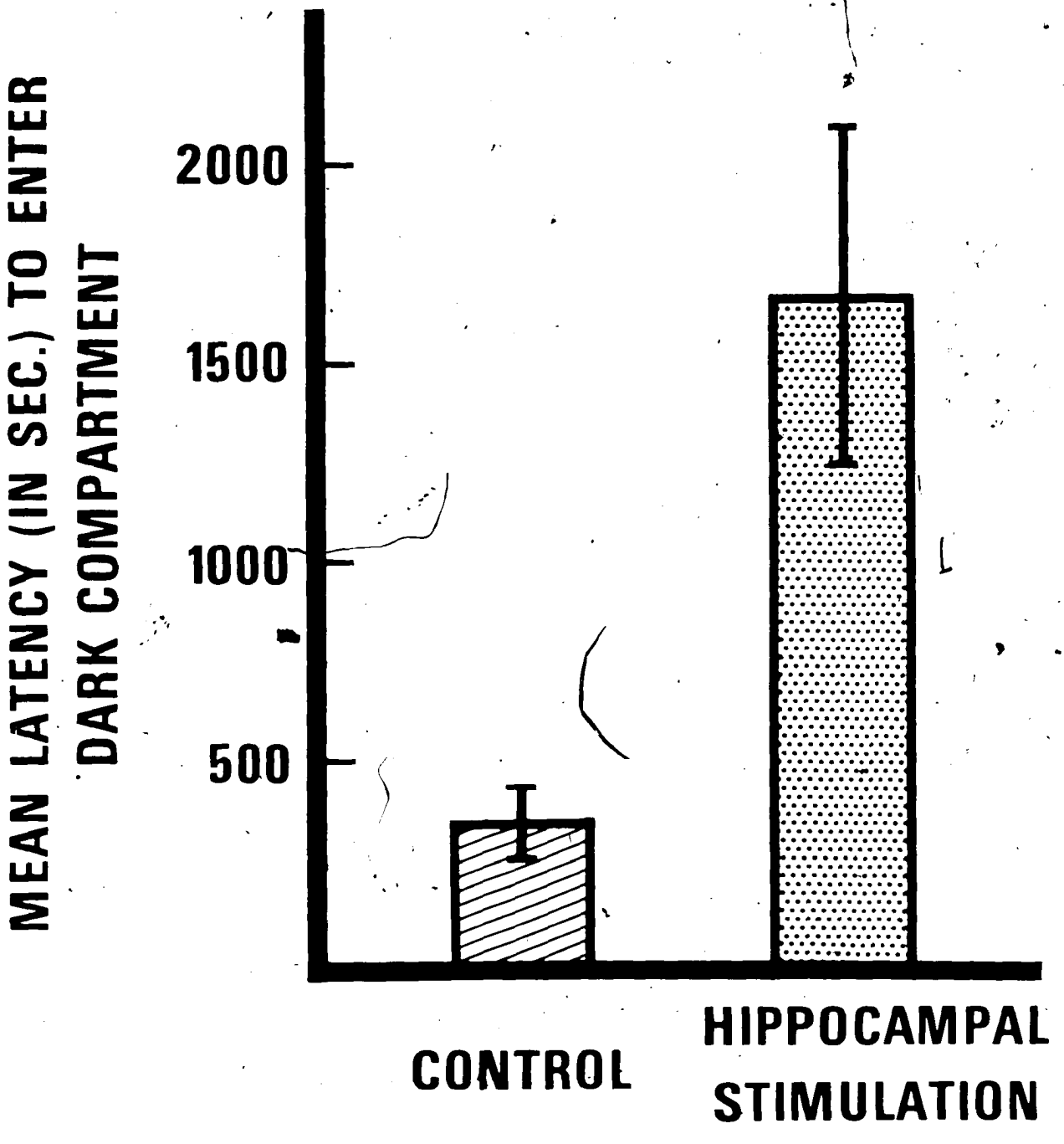

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session was allowed.

DISCUSSION: EXPERIMENT 3

Reports of facilitation of shock-motivated behavior by brain stimulation are open to the interpretation that the brain stimulation may merely be aversive and may "facilitate" learning only because it adds to the strength of the unconditioned stimulus (footshock). This interpretation cannot account for the results of the present experiment since all of the animals that showed facilitation also exhibited self-stimulation (at the same current intensity) before the passive avoidance test. In addition, the same type of hippocampal stimulation (4 one sec trains) was used in Exp. 1 to reinforce the learning of a spatial discrimination in a T maze.

The present results are essentially in agreement with the facilitation of long-term memory in mice recently reported by Destrade and Jaffard (1978) and Jaffard, Destrade and Cardo (1976). These investigators found that 80 sec of low-intensity stimulation of the dorsal hippocampus after step-through passive

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avoidance training resulted in improved performance in retention tests 24 hr later. In their case, however, the hippocampal stimulation was below afterdischarge threshold; in the present experiment, good retest performance was observed even after severe motor convulsions.

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PART II

SUPPRESSION OF THE HIPPOCAMPUS BY DIAZEPAM

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EXPERIMENT 4, Part A

The results of Exp. 1 indicate that hippocampal stimulation can serve as a reward. If the stimulation of the hippocampal pyramidal cells is indeed maintaining lever pressing behavior (self-stimulation) and if diazepam suppresses the activity of hippocampal pyramidal cells, then administration of diazepam should lead to a disruption of self-stimulation. This hypothesis was tested in the following experiment. A disruption of hippocampal self-stimulation would indicate that diazepam can suppress the ability of hippocampal stimulation to promote learning by serving as a reward.

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METHOD

Each animal was implanted with a single platinum-iridium or Nichrome electrode aimed at the dorsolateral hippocampus as already described. In a Skinner box inside a sound-attenuating chamber the animals were trained to deliver 0.5 sec of 30μA sine wave stimulation to their brain by pressing a small lever until reliable and stable lever pressing rates were achieved. Nineteen self-stimulators were randomly divided into three groups, each receiving a different dose of diazepam (undiluted Valium injection), viz., 0.5 mg/kg (n=7), 1 mg/kg (n=6), or 2 mg/kg (n=6), and a different volume of vehicle solution (40% propylene glycol + 10% ethanol) equal to the volume of drug administered to the same animal. Only low doses of diazepam were used to minimize sedative effects of the drug that might reduce motor responses. The same dosage of drug, or vehicle, was administered intraperitoneally 5 min before testing on three successive days. The sequence of three daily drug tests and three daily vehicle tests (one week apart) took place at each of two current intensities, 10μA and 50μA, approximately four weeks apart. The order

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of presentation of drug and vehicle and of low and high current intensity was counterbalanced and randomly determined. Each rat, then, was tested at both current intensities but received only one dose of diazepam (six times all together). Daily 20-min tests were conducted seven days a week and the number of stimulations received by the animal were automatically recorded. In three cases, when the current intensity was switched, 10μA was found to be below the animal's threshold for stable lever pressing and was therefore raised to 15-25μA for all test sessions.

EEG recording: To find out whether seizure activity is associated with hippocampal self-stimulation, sample EEG records were taken during self-stimulation from four animals with Nichrome bipolar electrodes. These animals were tested in a Plexiglas Skinner box housed in a shielded outer chamber which was otherwise identical to the box used during drug tests. EEG's were recorded only before and after the drug phase of the experiment. The animal was simply left to press the lever ad libitum while the EEG was recorded for 10-20 minutes. The current intensity was 30μA. EEG recordings were made through the stimulating electrode, fed through a Brush differential amplifier and displayed on a Brush oscillograph.

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A switching artefact in the EEG record prevented recording of activity for a period of approximately 0.5 sec after each stimulation

RESULTS AND CONCLUSIONS

The numbers of stimulations received in 20 minutes were averaged across the three administrations of the diazepam doses at each current intensity and are presented in Table 9. Fig. 6 shows the diazepam data expressed as a percentage of the averaged data on days when the vehicle only was injected. It is clear that 2 mg/kg of diazepam produced a pronounced suppression of self-stimulation rates ($p < .05$, Wilcoxon Matched-Pairs test - Siegel, 1956) at both current intensities. The 1 mg/kg dose produced a significant suppression ($p < .05$) only at the low current intensity. The difference between the low dose and vehicle control was not significant at either current intensity (even though at the low intensity five out of seven animals showed a slight decrease in self-stimulation rate when drugged).

Priming stimulation of the hippocampus did not arouse the animals that were inactive under the

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TABLE 9

Mean number of lever presses (± S.E.M.) made in 15 min by three groups of rats with hippocampal electrodes. Each group was tested with only one dose of diazepam at each of two current intensities. These data are presented in Fig. 6 as a percentage of vehicle response rates.

	DOSE (mg/kg)		
	0.5 (n=7)	1.0 (n=6)	2.0 (n=6)
LOW INTENSITY			
DIAZEPAM	92 ±17	85 ±33	19 ±13
VEHICLE	106 ±12	144 ±21	119 ±25
HIGH INTENSITY			
DIAZEPAM	134 ±21	167 ±13	32 ±20
VEHICLE	145 ± 7	194 ±19	112 ±20

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Fig. 6 Effect of three doses of diazepam (independent samples) on hippocampal self-stimulation at two current intensities (repeated measures) expressed as a percentage of control (vehicle) rates. Each point is based on 3 drug and 3 vehicle tests.

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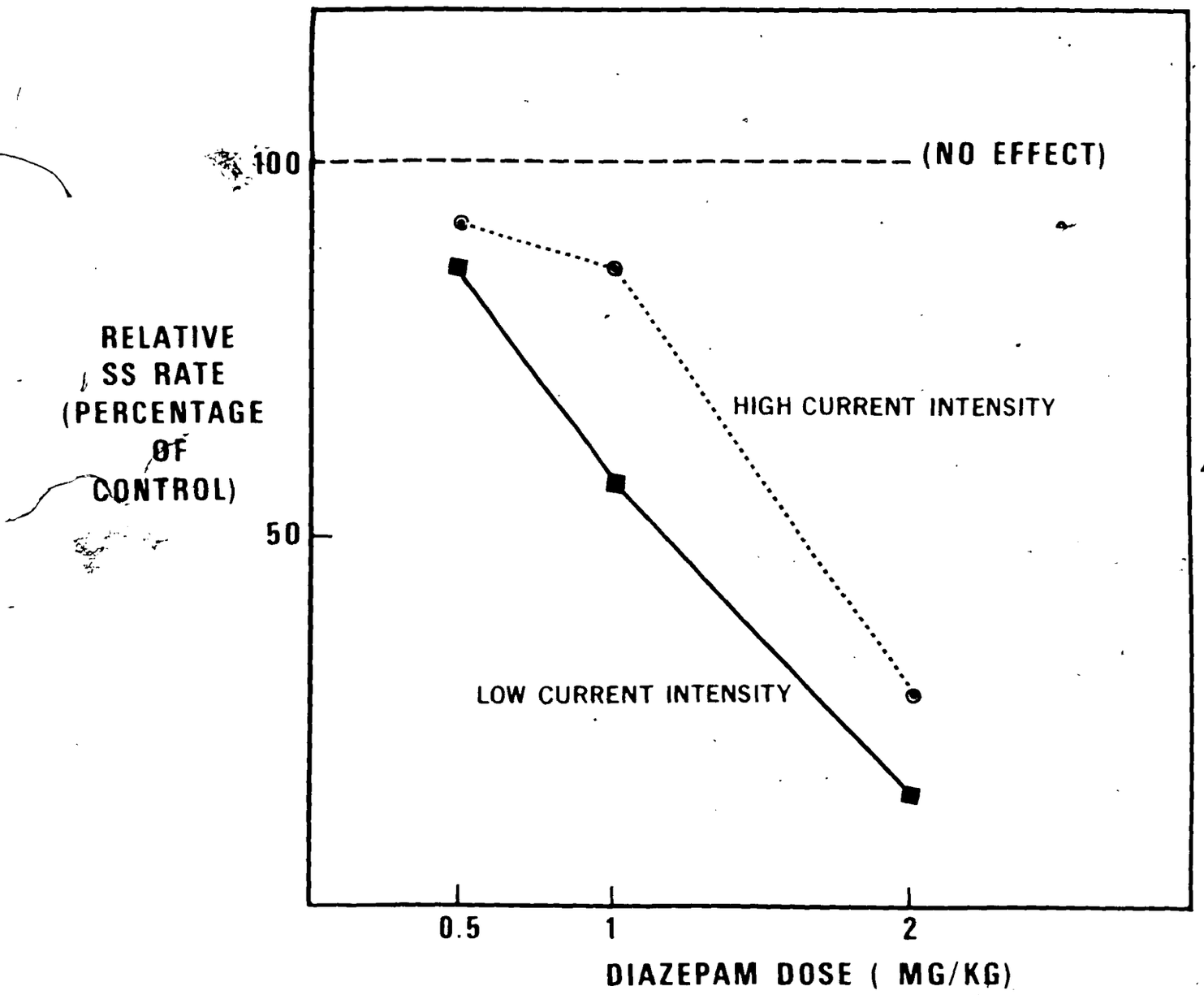

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effects of diazepam and did not encourage them to press the lever.

EEG recordings and convulsive activity

Sample records of hippocampal EEG activity recorded through the stimulating electrode in undrugged animals showed that local epileptiform afterdischarges were evoked only by the first stimulation of the testing session on most days. Subsequent stimulations (during a 10-20 min self-stimulation session) rarely elicited seizure activity. Two animals that received 0.5 sec of hippocampal stimulation five minutes before a self-stimulation test showed no epileptiform afterdischarges during self-stimulation. In general, lever pressing rates did not seem to be related to the occasional occurrence of seizure activity. On days when no seizures occurred, lever pressing rates (30-50 responses per 10-min period) and patterns of responding did not differ noticeably from those observed on days when a seizure did occur (especially if one ignores the period of time during and immediately following a convulsion).

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EXPERIMENT 4, Part B

In Exp. 4A, treatment with diazepam produced a dose-dependent suppression of self-stimulation behavior. Since diazepam has well-known tranquillizing properties and the drugged animals appeared to be relaxed and inactive at the highest dose, the possibility remains that the drug could have suppressive effects on motor activity which would be confounded with any changes in the reward value of the stimulation. Motor and other performance effects of diazepam could be ruled out if it were found that suppression of self-stimulation were specific to the hippocampal locus; that is, if suppression did not occur with stimulation of other brain reward sites. Therefore, two groups of hypothalamic self-stimulators (preoptic and lateral hypothalamus) were also tested with diazepam. This drug has been shown to increase self-stimulation rates with electrodes in the hypothalamus (Olds, 1966, 1976; Olds & Gardner, 1976) but it seemed advisable to replicate this latter finding in the same laboratory and under the same conditions as the hippocampal experiment.

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METHOD

Preoptic Hypothalamus. Six adult male rats with electrodes aimed at the preoptic area of the hypothalamus (coordinates: horizontal- 0.0 mm; lateral - 2.0 mm; vertical - 8.0 mm) were tested daily until stable self-stimulation rates were observed. 2 mg/kg of undiluted Valium injection was injected intraperitoneally 5 min before testing. The current intensity was 30μA for all animals. Lever presses in a Skinner box were recorded after 15 minutes. The following day a lower dose of 1 mg/kg was injected and the same animals were similarly tested. No attempt was made to control for carry-over effects on this second drug test. The drug data were compared with average self-stimulation rates for five days of baserate recording.

Lateral Hypothalamus. Four adult male rats with electrodes aimed at the lateral hypothalamus (coordinates: horizontal - -0.8 mm; lateral - 1.75 mm; vertical - 8.6 mm) were also tested daily until stable SS rates were obtained. Each animal then received 1, 2, and 3 mg/kg of undiluted Valium injection and an equal

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volume of vehicle, with the four treatments administered in counterbalanced order. Each treatment was repeated on each of three successive days with at least four days between treatments. Intraperitoneal injections were made five min before testing. The current intensity was individually set for each subject at a level (20-40μA) which yielded self-stimulation rates of approximately 400-600 lever presses per 15 min. The numbers of lever presses were recorded after 15 and 30 minutes of self-stimulation, and were averaged across the three treatment days.

RESULTS AND CONCLUSIONS

The mean self-stimulation rates during the first 15 min period, for both hypothalamic groups are presented in Table 10 and are also expressed as a percentage of control (vehicle or baserate) self-stimulation rates in Fig. 7 along with the results of Exp. 4A for comparison. Self-stimulation rates almost doubled in the case of the preoptic placement ($p < .05$, at each dose, sign test - Siegel, 1956) and also

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TABLE 10

Mean number of lever presses (± S.E.M.) made in 15 min by two groups of rats - one with electrodes in the preoptic hypothalamus and one with electrodes in the lateral hypothalamus. The drug data are presented in Fig. 7 as a percentage of control (0 mg/kg) response rates.

DIAZEPAM DOSE (mg/kg)	PREOPTIC HYPOTHALAMUS (n=6) 15 min	LATERAL HYPOTHALAMUS (n=4) first 15 min	second 15 min
0	585 ±109	530 ±108	498 ± 78
1	970 ± 51	820 ±108	776 ±110
2	1025 ± 55	846 ±107	855 ±143
3	--	709 ± 74	857 ±158

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Fig. 7 Effect of diazepam on two hypothalamic self-stimulation placements. Within each group, the data constitute repeated measures. Figure 6 (hippocampal) is reproduced for comparison.

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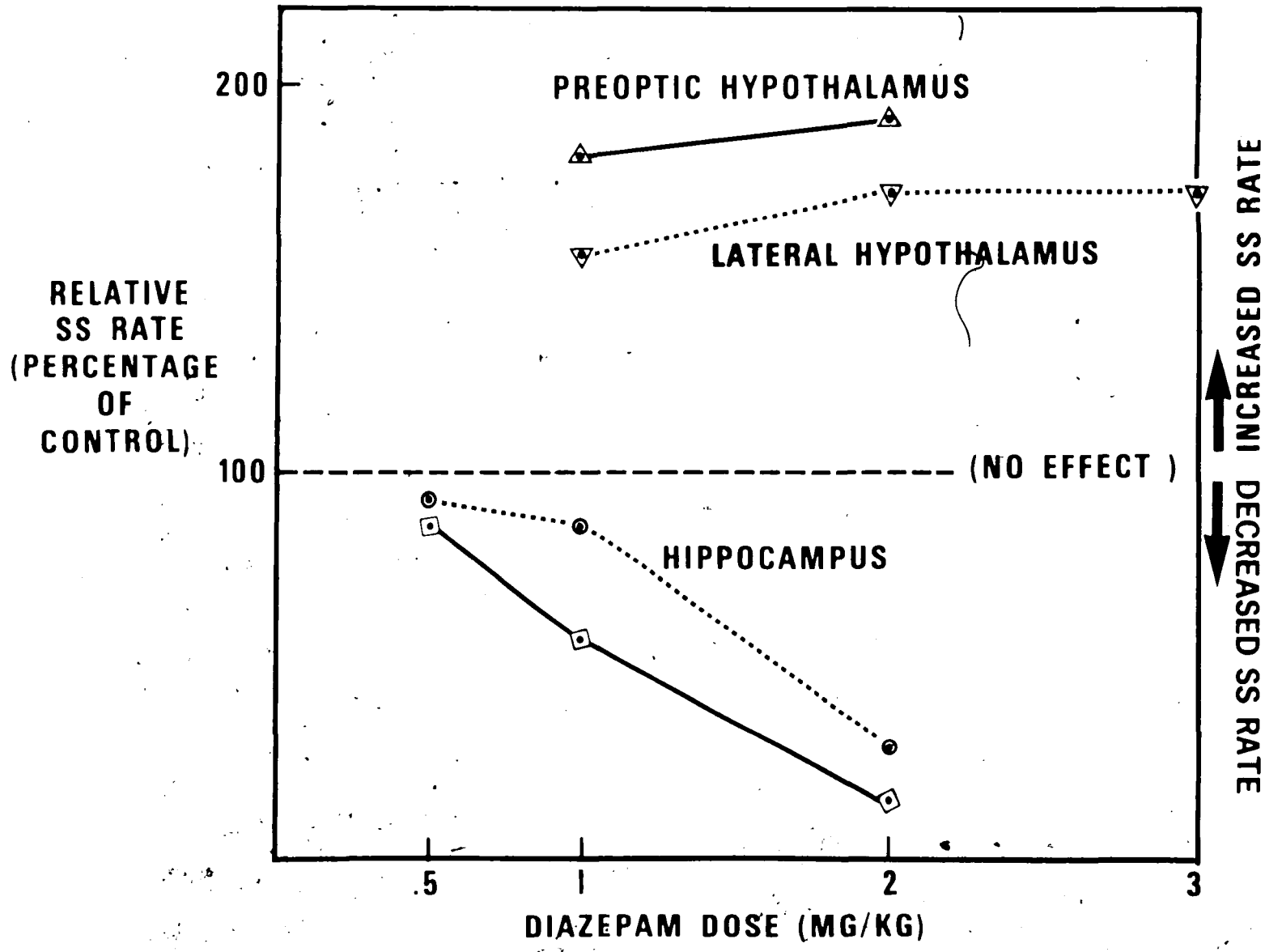

increased, though somewhat less, with lateral hypothalamic stimulation ($p<.05$, at each dose). Similar results were obtained during the second 15-min period (Table 10). The differences between the two hypothalamic placements were not significant.

At the highest doses, animals appeared to be sedated but were immediately aroused and began to press the level when they were given two or three priming stimulations at the beginning of the session.

DISCUSSION: EXPERIMENT 4

The drastic suppression of hippocampal self-stimulation with 2mg/kg of diazepam is obviously not due to any ataxic or sedative effects of the drug since hypothalamic animals were able to increase their lever pressing rates under the effects of even 3 mg/kg of diazepam. This latter finding is consistent with other reports of an increase in hypothalamic self-stimulation rate with similar and even higher doses of diazepam (Olds, 1966, 1976; Olds & Gardner, 1976). The possibility that the suppression of hippocampal self-stimulation was due to motor-blocking effects of

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diazepam seems particularly unlikely when one considers that huge, yet nontoxic, doses of diazepam as high as 60 mg/kg and 120 mg/kg did not result in a significant suppression of hypothalamic self-stimulation rates (Olds, 1976).

The hypothalamic stimulation appeared to arouse the animal from a sedated state (at 2 and 3 mg/kg of diazepam) whereas no such priming effect was seen in the hippocampal self-stimulators, especially at the highest dose (2 mg/kg) of diazepam. In view of this difference between the electrode placements, an argument may still be made that hippocampal stimulation lacks some arousal component present in hypothalamic stimulation which allows the latter to overcome drug-induced sedation.

A quite different interpretation of Exp. 4A may be advanced based on suggestions that self-stimulation of anterior limbic brain structures may be dependent on abnormal seizure activity (Bruner, 1966; Newman & Feldman, 1964; Porter, Conrad & Brady, 1959). Since diazepam has well-known anticonvulsant effects (Browne & Penry, 1973; Hernandez-Peon et al., 1964; Woodbury & Fingl, 1975), it may be suggested that the drug suppresses self-stimulation because it removes the seizure activity responsible for maintaining the

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behavior. However, this interpretation is not consistent with the results of the EEG sampling which showed a dissociation of self-stimulation behavior and EEG seizure activity. In addition, in Exp. 4A, diazepam did not completely block local afterdischarges at a dose which produced almost total suppression of self-stimulation. Therefore, on the basis of the present results, one cannot conclude that the suppression of hippocampal self-stimulation is causally related to suppression of seizure activity.

It appears that diazepam suppresses the ability of hippocampal stimulation to serve as a reward. The fact that diazepam does not disrupt hypothalamic self-stimulation shows that this drug does not block brain stimulation reward in general, regardless of the location of the stimulating electrode, and shows that it does not block motor or other circuits necessary to perform the response of lever pressing. In disrupting hippocampal self-stimulation, therefore, diazepam must be acting by blocking activity in the hippocampal circuits that are directly stimulated by the electrode.

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EXPERIMENT 5

The results of Exp. 4 confirm that diazepam strongly suppresses activity in hippocampal circuits, and disrupts the reinforcement shown in Exp. 1 to be produced by hippocampal stimulation. In addition, Exp. 3 showed facilitation of retention of passive avoidance learning by hippocampal stimulation. If the hippocampus is indeed involved in the retention of avoidance learning, diazepam, which suppresses hippocampal activity, should also prevent the learning of an avoidance response.

Soubrie, Simon & Boissier (1976) found that diazepam disrupts the formation of a conditioned emotional (fear) response with rats in the open field. Since one-trial passive avoidance learning is somewhat similar to a conditioned emotional response paradigm, the Soubrie et al. study was used as a guide in determining an effective dose of diazepam and an optimal injection-test interval. The dose selected for the present experiment (5 mg/kg) was higher than those used to suppress hippocampal self-stimulation in Exp. 4A.

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In the latter experiment, the object was to use the smallest possible dose of diazepam since suppression of self-stimulation by a high dose might be attributable to ataxic side effects; in the present experiment, however, it was important to use a dose higher than the minimum effective dose since the learning involved (passive avoidance) occurs in one trial and any small variation in absorption, metabolism or in individual response to the drug might make a critical difference at a threshold drug level.

Another consideration was that the anxiolitic, fear-reducing effects of diazepam might prevent any aversive consequences of footshock and thus effectively remove the reinforcer from the learning paradigm. This latter effect, rather than interference with memory processes, might then account for any lack of learning. Accordingly, in the following experiment measures of the animal's reactivity to footshock were made during the training session - even though other reports indicate that diazepam does not interfere with the aversiveness of electric shock (Soubrie et al., 1976), has no analgesic properties (Dundee & Haslett, 1970; Foreman, 1974), and even increases responsiveness to

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environmental stimuli at doses that produce mild sedation (Hoffman-LaRoche, 1974; Randall, Heise, Schallek, Bagdon, Banziger, Boris, Moe & Abrams, 1961). A second test with diazepam was also given because of the possibility that learning may be state dependent (Overton, 1978).

METHOD

Procedure. Sixteen rats were divided randomly into two equal groups (n=8): one group received 5 mg/kg of diazepam intraperitoneally (commercially prepared Valium injection) and the other group received an equivalent volume of the vehicle (40% propylene glycol and 10% ethyl alcohol in distilled water). Thirty minutes after the injection each rat was placed in the brightly lit half of a passive avoidance training box as already described in Exp. 3. The central partition was raised about 10 cm and the latency of the rat's entry into the dark chamber was measured with a stopwatch. As soon as the animal entered the dark side, the door was closed and three 1-sec periods of 2.5 mA

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scrambled shock were administered through the floor bars. The three shocks were separated by two 15-sec periods during which the animal's movement was observed through the transparent red Plexiglas top in order to measure reactivity to shock. The floor bars had been marked with a black felt-tip marker so that the compartment was clearly divided into three equal areas; the number of times the rat moved his body (more than just the head) across each dividing line was counted and summed over the two 15-sec periods. In addition, the rat's reaction to the shock was rated by E as 0 (no reaction), 1 (some excited movement, but no vocalization), 2 (moderate reaction), or 3 (frantic running around, loud and sustained vocalization). When the third 1-sec shock terminated, the central partition was again raised, and the rat's latency to escape from the shock compartment was measured up to a maximum of 60 sec. The rat was then removed from the bright side of the box to which it had escaped and replaced in its home cage. One rat that remained in the shock compartment for 60 sec was pushed out to the bright side and then removed. Three days were allowed for recovery from any effects of the drug and then each rat was placed once again, at the same time of day,

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in the bright side of the testing box. The partition was raised and the latency to enter the dark compartment was measured up to a maximum of 20 min. As soon as it entered the dark side, the partition was lowered and the rat was immediately removed to its home cage. Twenty-four hours later, all rats in both groups received an i.p. injection of 5 mg/kg of Valium 30 min before being placed, for a third time, in the bright compartment of the testing box. The partition was raised and the latency to enter the dark chamber was measured up to a maximum of ten min.

RESULTS AND CONCLUSIONS

Each rat's latency to enter the dark chamber on the training day (Day 1) and the testing day three days later (Day 2) is shown in Table 11. It is clear from these data that animals that received a control injection stayed out of the previously preferred dark compartment significantly longer than animals treated with diazepam at the time of training. Table 12 presents three measures of the animals' reactivity to shock: locomotion immediately after two shocks,

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TABLE 11

One-trial passive avoidance training. Latency (in sec) to enter the dark (shock) compartment on Day 1 (before footshock) and on Day 2 (3 days after shock and injection) for both diazepam-treated and vehicle-injected animals. Maximum score is 1200 sec (20 min).

TREATMENT	S No.	DAY 1 (TRAINING)	DAY 2 (TEST)
	21	2	1200
	23	3	1200
	41	3	1200
CONTROL	45	2	1200
VEHICLE	67	1	1200
INJECTION	72	25	1200
(n=8)	78	2	540
	79	2	1200
	22	2	4
	66	10	22
	68	2	7
DIAZEPAM	69	1	66
(5 mg/kg)	70	2	1
INJECTION	74	1	11
(n=8)	75	7	20
	77	1	4

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TABLE 12

Three measures of the animals' reactivity to footshock on Day 1 of the passive avoidance training.

REACTIONS TO FOOTSHOCK	VEHICLE CONTROL		DIAZEPAM
1. LOCOMOTION DURING 15-MIN PERIOD IMMEDIATELY AFTER SHOCK:			
MEAN NO. OF CROSSINGS ±S.E.M.	4.75 ± 1.04	(n.s.)	6.25 ± 1.06
2. LATENCY TO ESCAPE FROM SHOCK COMPARTMENT (IN SEC):			
MEDIAN (SEMI-INTERQUARTILE RANGE)	1.25 (8)		2.0 (3.4)
3. EXPERIMENTER'S RATING (0-3):			
MEAN RATING (RANGE)	2.5 (1-3)		1.75 (1-3)

n.s. - $p > .05$, Mann-Whitney U test.

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the experimenter's rating of strength of reaction, and latency to escape from the shock compartment. These data indicate that the rats given 5 mg/kg of diazepam were able to react to shock and escape from it about as strongly as the control animals. The retest under diazepam (Day 3) did not result in evidence of any substantial avoidance of the dark chamber (Table 13) since latencies were not significantly different ($p>.05$, Mann-Whitney U test) from those on Day 2. Most of the control animals avoided entering dark chamber on this second test (Day 3) even when under the presumably anxiety-reducing effects of diazepam. Thus there is no evidence that the diazepam-treated experimental group learned to avoid in a state-dependent way; on the contrary, it appears that diazepam prevented the learning and retention of an inhibitory avoidance response.

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TABLE 13

Latency (in sec) to enter dark (shock) compartment when passive avoidance was retested on Day 3 (four days after footshock). All animals received diazepam (5 mg/kg) 30 min before testing. Maximum score is 600 sec (10 min). Day 2 latencies (Table 11) are also shown (MAX = 20 min).

TREATMENT ON DAY 1	S No.	DAY 2 (NO DRUG)	DAY 3 (DIAZEPAM)
CONTROL VEHICLE INJECTION (n=8)	21	MAX	600
	23	MAX	15
	41	MAX	600
	45	MAX	600
	67	MAX	325
	72	MAX	600
	78	540	58
	79	MAX	600
DIAZEPAM (n=8)	22	4	6
	66	22	62
	68	7	3
	69	66	57
	70	1	1
	74	11	28
	75	20	3
	77	4	2

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DISCUSSION: EXPERIMENT 5

The anterograde amnesia seen in the diazepam-treated animals is in accordance with the many reports of anterograde amnesia in human clinical diazepam trials and with the report by Soubrie et al. (1976) of disruption of a conditioned emotional response in rats. After Exp. 5 was completed, Jensen, Martinez, Vasquez and McGaugh (1979) reported very similar results showing an amnestic effect of diazepam in mice. However, Vasquez, Martinez, Jensen and McGaugh (1977) reported that propylene glycol, the vehicle used to dissolve diazepam, by itself had dose-dependent anterograde amnestic effects in mice at concentrations of 20, 40 and 60%. This result is puzzling since in Exp. 5 no amnesia was observed in the control animals that received a vehicle solution of 40% propylene glycol and 10% ethanol. It is not clear whether the use of mice rather than rats or the absence of ethanol in the propylene glycol solution (present in commercially-prepared Valium injection) could account for the discrepancy in results.

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GENERAL DISCUSSION

Two main conclusions can be drawn from the present series of experiments: (a) electrical stimulation of the hippocampus is positively reinforcing (rewarding) and (b) diazepam can suppress the rewarding effect of hippocampal stimulation and can prevent learning altogether in a passive avoidance situation. Hippocampal stimulation served as a reward in spatial discrimination learning and its effects were similar to food reward, although hippocampal stimulation may also have had disruptive side-effects. These disruptive effects, though mild, became evident when stimulation was delivered immediately after each lever press response and at the same time as a conventional reward (dropping a food pellet into the food cup) was presented. Perhaps because the stimulation intervened in the natural sequence of response and consumption of food reward, it did not add to the reinforcement and even interfered slightly with learning; however, the stimulation disrupted performance somewhat, and this factor may have reduced learning. The results of the first two experiments agree reasonably well with other findings reported

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in the literature, as do the results of the diazepam experiments. Diazepam suppressed hippocampal self-stimulation but not hypothalamic self-stimulation. Thus, the suppression could not be attributed to perceptual or motor deficits or other performance problems. The results of the third experiment, however, were unexpected. Instead of disrupting learning by preventing memory consolidation as reported in the literature, posttrial hippocampal stimulation facilitated the learning of a one-trial passive avoidance task. The discrepancy with the reported effects of posttrial hippocampal stimulation merits special discussion.

As already noted, posttrial stimulation of the lateral hypothalamus has been reported to facilitate the learning and memory of a variety of simple appetitive and avoidance tasks (Berman & Kesner, 1976; Destrade & Soumireu-Mourat, 1977; Huston & Mueller, 1978; Major & White, 1978; Mondadori, et al., 1976; Mueller et al., 1977; White & Coulombe, 1979) whereas posttrial hippocampal stimulation has been reported to disrupt the learning of similar tasks. Besides the obvious difference in electrode location, there is a less evident difference between the two types of

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studies: hypothalamic stimulation experiments ususally employ animals that have already demonstrated self-stimulation whereas hippocampal stimulation experiments never include tests for self-stimulation before the main experiment. This difference in procedure may be due to some experimenters' belief that hippocampal stimulation is not rewarding (e.g., Destrade & Jaffard, 1977) and, therefore, that it is not necessary to conduct self-stimulation tests. Whatever the reason for the procedural difference, the observations of facilitation seem to occur in animals that have received a considerable amount of prior stimulation while the observations of amnesia seem to be made in naive animals. In Exp. 3 it was necessary to establish for each animal whether or not the hippocampal stimulation was rewarding by conducting self-stimulation tests. However, repeated stimulation of limbic system structures can produce enduring neurophysiological changes (e.g., Douglas & Goddard, 1975; Racine et al., 1975) and there is also evidence that the reinforcing consequences of hippocampal stimulation are altered by prior stimulation: Campbell et al. (1978) suggested that hippocampal reward develops only after neurophysiological changes are produced by stimulation experience. Perhaps the facilitation of

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passive avoidance observed here depends on the development of the rewardingness of the stimulation confirmed during self-stimulation training. It is possible that animals that have had no previous stimulation experience would not show facilitation of learning. One study showed that if the posttrial hippocampal stimulation that produced amnesia after a single aversive conditioning trial was administered after each of a number of repeated trials, amnesia was no longer observed (Kesner & McDonough, 1970; Kesner & Wilburn, 1974); what we do not know, of course, is whether the stimulation would also have lost its amnestic properties if it had been administered several times noncontingently.

Another difference making comparison difficult is that most "amnesia" experiments used bilateral stimulation of hippocampal cell field CA1, whereas I used unilateral stimulation of field CA3 and adjacent fimbria. However, Sideroff et al. (1974) reported retrograde amnesia with only five 0.25 sec pulses of unilateral stimulation of CA3 at intensities that were below seizure threshold. It is therefore difficult to reconcile the different results solely on the basis of electrode location or the unilateral or bilateral

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nature of the stimulation. Another explanation, in terms of strength of reinforcement, of the difference between Sideroff et al. (1974) and the present experiment will be discussed further on.

Re-analysis of experiments that used posttrial stimulation in light of the present findings.

In addition to the studies already mentioned in the general introduction and in the introduction to Exp. 2 showing a facilitatory, rather than amnestic, effect of dorsal hippocampal stimulation on learning, the evidence that posttrial stimulation of the hippocampus proper (CA1 to CA4) produces amnesia is, at best, controversial. Many experimenters have reported failures to produce amnesia with dorsal hippocampal stimulation following single trial learning of passive avoidance (Gold & McGaugh, 1973; McGaugh & Gold, 1976; Zornetzer, Chronister & Ross, 1973), active avoidance (Hirano, 1966), one-trial conditioned suppression (Hirano, 1965; Wyers, Peeke, Williston & Herz, 1968), and discrimination or maze learning (Hirano, 1965, 1966).

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Furthermore, Gustafson, Lidsky and Schwartzbaum (1975) failed to produce amnesia for a conditioned suppression of licking by posttrial application of seizure-eliciting stimulation of the dorsal hippocampal in a series of six experiments. Kapp, Kaufman and Repole (1974) were also unable to disrupt the learning of a passive avoidance with posttrial dorsal hippocampal stimulation in a series of six experiments. They were only able to produce amnesia in a seventh experiment if the stimulation was very intense and prolonged (90 sec); no amnesia was observed with only five sec of intense stimulation. A number of investigators using posttrial dorsal hippocampal stimulation have reported amnesia in only some animals (50% or fewer) or only under some conditions and not under others (Kapp et al., 1978; Kesner & Doty, 1968--2 additional failures, mentioned on p. 64-65, are usually overlooked in reviews; Koranyi & Endroczi, 1965; Lidsky & Slotnick, 1971; Shinkman & Kaufman, 1970, 1972). Two reports of amnesia with posttrial stimulation identify the electrode location only as "dorsal hippocampus" (this term may include dentate gyrus or subiculum): McDonough and Kesner (1971) studied conditioned suppression of feeding in cats, and Brunner, et al. (1970) used step-down passive avoidance in rats.

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The former experiment included no control group; the latter was an unusual passive avoidance experiment in that very light footshock was used (0.5 mA for 0.5 sec) and the learning shown by the control animals was very weak (median step-down latency of the control group, 24 hr later, was a mere 27 sec). Only two reports have indicated clear amnesia produced by posttrial stimulation of the dorsal hippocampus proper: Sideroff et al. (1974), using conditioned suppression of drinking, and Vardaris and Schwartz (1971) using simple, step-through, passive avoidance.

In contrast, there appears to be consistent evidence that posttrial bilateral stimulation of the dentate gyrus produces complete amnesia for one-trial passive avoidance learning (Barcik, 1969--electrode location given in Barcik, 1970; Kapp et al., 1978; Lidsky & Slotnick, 1970; Zornetzer et al., 1973; Zornetzer, Boast & Hamrick, 1974); one-trial conditioned suppression training (Barcik, 1970--electrode location derived from atlas used and coordinates given; Haycock, Deadwyler, Sideroff & McGaugh, 1973; Kesner & Conner, 1972, reported again in 1974; Sideroff et al., 1974) and one-trial appetitive learning

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(Berman & Kesner, 1976).

Sources of variability in experimental results of hippocampal stimulation.

While bilateral stimulation of the dentate gyrus appears always to produce amnesia, there is clearly confusion and contradiction in the reports of the effects of posttrial stimulation of the hippocampus proper. Two lines of recent evidence may help to explain some of the apparently contradictory effects. First, Kapp, Gallagher, Holmquist and Theall (1978) have recently shown that one-trial passive avoidance learning involves two different and separable types of association, viz., response-contingent instrumental learning and noncontingent classical fear conditioning. The type of association formed depends on the strength of the reinforcer (footshock), among other factors. Kapp et al. (1978) showed, furthermore, that bilateral posttrial stimulation of the dorsal hippocampal formation (most electrodes in dentate gyrus) disrupts response-contingent learning but not classical fear

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conditioning. Now, either type of learning will lead to good passive avoidance performance (especially if the footshock intensity is low and the testing session short). Furthermore, since the type of association formed depends on the magnitude of the reinforcer (footshock) and apparently on the learning of response contingency of reinforcement by the animal, it follows that seemingly minor changes in experimental procedure (e.g., strength of footshock) could change the outcome of an experiment from amnesia to retention, or perhaps even to facilitation of learning. These observations might help to clarify some of the apparent contradictions in results obtained with posttrial stimulation. For example, Gold, Hankins, Edwards, Chester & McGaugh (1975) found that the very same posttrial amygdaloid stimulation treatment disrupted passive avoidance learning if the footshock intensity was high and facilitated the same learning task if the footshock intensity was low. In Exp. 3, I used a 2mA footshock whereas Sideroff et al. (1974), who reported amnesia, used a stronger 5mA footshock.

The second line of evidence involves the suggestion made by a number of experimenters (Destrade & Jaffard, 1978; Gold et al., 1975; Zornetzer, 1978) that stimu-

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lation of the hippocampus or other brain structures (e.g., amygdala, lateral hypothalamus) does not act directly on the memory trace while it is in a labile phase but rather exerts a modulatory influence on circuits more directly involved in learning processes and memory formation; that is, activation of hippocampal circuits may act to increase or decrease ongoing activity in other circuits whose function it is to set up and maintain the memory trace. Such an assumption would explain many apparently discrepant results, for the specific results of facilitation or disruption of learning would depend on the specific conditions of the experiment and the experimental treatment (e.g., the type, locus and timing of hippocampal stimulation).

Results of the kind reported by Gold et al. (1975) may also suggest that the physiological state of the animal (e.g., stress, arousal) is an important factor in determining the specific effects of brain stimulation on memory. In this regard, it is interesting to note the similarity to facilitation of learning and memory by alterations of hormonal activity produced by such treatments as adrenalectomy and administration of ACTH (see reviews by Bohus, 1973; De Wied, van Delft, Gispen, Weijnen & van Wimersma Greidamus, 1972; Weiss,

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McEwen, Silva & Kalkut, 1970). It is possible that stimulation of the hippocampus (or other structures) produces neurohumoral changes that interact with the neural substrates of the animal's physiological and motivational state. With amygdaloid stimulation, McIntyre (1976) found that retrograde amnesia for passive avoidance learning produced by an amygdala-kindled convulsion (which would also have involved the hippocampus) could be prevented by adrenalectomy. Evidence was also reviewed in the introduction which suggests a close link between the hippocampus and the pituitary-adrenal system response to stress.

To make a comparison with another area of research, the nonspecific hypothesis of the action of brain stimulation on learning and memory outlined here is analogous to the explanation of so-called chemical transfer of learning from the brain of a trained animal to the brain of a naive animal in terms of nonspecific (perhaps, hormonal) effects (see Byrne, 1970; Chapouthier, 1973). The nonspecific nature of this latter explanation is necessitated by evidence such as the finding that transfer of homogenized liver, as well as brain, from the trained to the naive animals leads to the same apparent "transfer" of memory (Frank, Stein & Rosen, 1970). In this case it is clear that

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memories are not formed or stored in the liver. In the case of hippocampal stimulation, we do not have clear-cut evidence to indicate whether stimulation of the hippocampus or disruption of hippocampal activity (e.g., by diazepam) affects memory processes directly or merely modulates ongoing memory formation processes by nonspecific arousal or stress factors.

Although at present there is not sufficient evidence to decide between a direct and a nonspecific hypothesis of hippocampal involvement in learning, the results of the present investigation do indicate (a) that hippocampal stimulation can serve as a reward (Exp. 1), (b) that, depending on the type of learning and timing of the stimulation, hippocampal stimulation can disrupt (Exp. 2) or facilitate (Exp. 3) long-term memory, (c) that diazepam, a drug which suppresses hippocampal activity, suppresses the ability of the hippocampal stimulation to serve as a reward (Exp. 4) and (d) that diazepam disrupts retention of passive avoidance conditioning (Exp. 5). All of these results, taken together, suggest an important role of the hippocampus in reinforcement in the broad sense; that is, they suggest that the activity of hippocampal circuits is sufficient and may even be necessary for the neural representation of the association between stimuli

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and responses (in conditioning paradigms) to be strengthened and stored for a relatively long time.

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