An Investigation into the Neuropsychology of Learning and Memory

by

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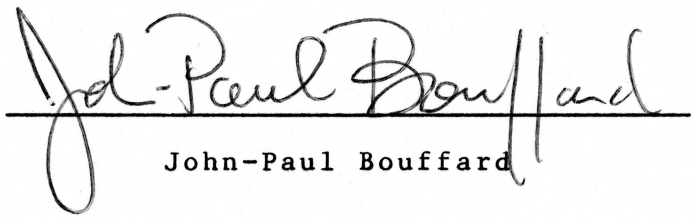
On my honor, I have received no unacknowledged aid on this project.



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Part One

At the heart of psychology is a basic dilemma: We live in a world of time and space, yet the mind is an entity for which discussion in terms of time and space is elusive, to say the least. Psychologists are left, then, to study behavior, from which they can make inferences about the mind. One such behavior whose properties in time and space have been explored in great detail in the last century is remembering. The theoretical construct we have made based on this behavior is called memory.

The science of experimental psychology is only slightly more than a century old, so the empirical study of memory is likewise quite young. The study of the neuropsychology of memory is younger still: Most contemporary psychologists studying the physiological basis of learning and memory would probably agree that meaningful study in their field is about three decades old. Certainly the current study of the neuropsychology of learning and memory bears evidence of influence prior to 1950, however, and so we are reminded of Herman Ebbinghaus's (ironically, the first experimental psychologist to study memory) statement about psychology: It has a short past, but a long history.

The first section of this paper will examine the major psychological and philosophical roots of modern research in the neuropsychology of learning and memory. I will attempt, at the end of this section, to establish the historical assumptions inherent in this field of study. My senior thesis research project, directed at studying the neuropsychology of learning and memory, will follow this section, and will be written up in the

standard journal article format. Specific information relevant to the experimental portion of this project will be discussed in the introduction section of the experiment write up, as is customary.

Historical Perspective

1. Philosophical ideas

The primary body of philosophical thought that has given rise to discussion of memory is the study of theories of knowledge, or epistemology. The following is a simplified overview of notable philosophical ideas about memory that have risen out of epistemology.

Plato described memory as an association of ideas. "What a man recollects," he wrote, "he must have known at some time" (Plato, quoted in Sahakian, 1981). Thoughts about or sensations of one fact cause us to think of or sense another. That two ideas could be so linked caused Plato to wonder whether they were equivalent on some higher level. He stated, ". . . there is such a thing as equality, not of one piece of wood or stone with another, but that, over and above this, there is absolute equality . . . " (Plato, quoted in Sahakian, 1981).

Aristotle spoke more directly about memory than did Plato. In Parva Naturalia, he placed memory in the context of an interaction of time with what we now call cognition. He said that we have memory of the past, perception of the present, and expectation of the future. Memory is a property of time, and all

creatures with a sense of time have memory. (This statement, in addition to being intuitively valid, is interesting in light of the apparent emphasis on verbal memory in the contemporary study of human memory.) Aristotle specified that we do not remember objects, but we remember impressions of objects. "Memory is analogous to a picture within us," he said; ". . . we contemplate and perceive this picture in actual memory" (Aristotle, quoted in Sahakian, 1981).

The memory process posited by Aristotle is what was subsequently called association. Recollection is effected "when one suggestion succeeds another, in natural order" (Aristotle, quoted in Sahakian, 1981). By the "method of sequences," a given stimulus elicits recollection of some event "X," which in turn elicits recollection of "X-1," and so on. Aristotle wrote:

> [When we recollect], we awaken antecedent proceses and continue this until we call up that particular experience, after which the desired one is wont to appear. (quoted in Sahakian, 1981)

The degree of difficulty in memory is a function of how far the starting point is from the target point in a given sequence. The searching process in the method of sequences is a process of awakening images.

Coincident with the birth of modern science in the 17th century are the writings of Descartes, considered to be the first modern philosopher (Brennan, 1982). Descartes's famous statement, cogito ergo sum, or, "I think, therefore, I am," reflects his belief that conscious experience is the starting point of all knowledge. The only reality we can be sure of is conscious experience. Descartes also believed, however, that we

are not equipped with imperfect senses, and we therefore know, through sensory experience, an accurate representation of the physical world. Thus, the world consists of two realities: the concrete, physical reality of the external world, and the spiritual, non-physical reality of the conscious mind. Cartesian dualism, as it is commonly known, states that the nature of man is a combination of these two realities--man has both a physical, bodily self, and a non-physical, spiritual self.

The final three philosophical positions which appear to be relevant to the study of learning and memory can all be thought of as derivatives of Descartes' original formulations. These three positions are British empiricism, French sensationalism, and Kantian rationalism.

British empiricists such as Locke, Berkeley, and Hume believed that all knowledge is derived from experience. Humans are born with a mind that is like a blank tablet (Locke's tabula rasa). At birth, humans know nothing, and derive all of their knowledge from experience, through various associative processes. Memory, within such a framework, would also be an associative process, but need not be a chain-type, linear association process such as Aristotle suggested. John Stuart Mill, a later empiricist whom Brennan refers to as an Associationist (1982), suggested that the association of two ideas could give rise to a learned element that is qualitatively different from any of the ideas from which it arose. Mill called this idea "mental chemistry" (Mill, quoted in Sahakian, 1981).

British empiricism can be taken to an extreme, as Hume did, such that external reality is called into question (i.e., if all

knowledge is determined from subjective experience, then how can we be sure of what is external). The empiricist position is generally not so harsh, however. British empiricism holds that there are two realities, but ascribed more importance to physical reality and its effect on knowledge than did Cartesian dualism.

French sensationalism can be thought of as a radical form of empiricism. French sensationalists such as La Mettrie and Le Condillac seem to use the empiricist theme to make some conclusions about the nature of man. The notion that all knowledge could be explained on the basis of association of sensory experience might cause one to conclude that a person is nothing more than a complex machine (La Mettrie, quoted in Sahakian, 1981). Whereas British empiricism preserves some distinction between man and physical reality, the French sensationalist position states that man is simply a complex subset of physical reality. The notion of a non-physical "soul," or what we might call the mind, is rejected by the sensationalists.

This philosophical position is interesting in the context of a study of the neural basis of memory. The notion that we might learn about memory by studying the brain seems to imply a sort of French sensationalist bias to this sort of research. At the least, we can be certain that the study of the neuropsychology of learning and memory is decidedly non-dualistic. Inherent in the methodology of this field is the fundamental assumption that what we call mind, and body are both part of the same living substance.[1]

Kant's theory of knowledge, known as rationalism, reacted against the associationist notions of British empiricism. Kant used the term a priori to describe certain aspects of human knowledge. Kant believed that people have certain inborn principles of knowledge, such as an inborn knowledge of or sense of time (Kant, quoted in Sahakian, 1981). Rationalism would hold that memory is not simply a matter of associations, linear or otherwise. Memory would be a product of both experience and inborn predispositions to think of things in certain ways. The obvious influence of this philosophical position on experimental psychology is the gestalt school. Gestaltist ideas provide a compelling case warning investigators in the field of learning and memory not to think of memory solely in terms of conditioned associations. The recent trend in animal neuropsychology of devising complex memory tasks that provide information beyond the level of simple S-R associations perhaps indirectly reflects influence from the Gestalt school and rationalism.

Current research in the neuropsychology of learning and memory shows some evidence of influence from each of the philosophical positions described above, although its major philosophical underpinnings appear to come from the French sensationalist position. Perhaps neuroscience does not make the claim that it can actually "build a man" as the sensationalists did, but the implicit assumption that the mind is "in the brain," and therefore made of the same sort of "stuff" as the physical world is unmistakable in neuroscience. Although dualism and physiological psychology are not incompatible (i.e., study of the brain is still interesting to the dualist, since the brain is the

site of interaction with the non-physical mind and the physical body), the two appear incongruous at the least. Although the French sensationalist position, taken to the extreme, seems inadequate (people, not brains, have memories) a mild interpretation of the position might fit with current research in the neuropsychology of learning and memory: A memory, or any sort of knowledge, is only significant in the context of a behavioral field, consisting of the person and his external environment. The crucial part of the person that physiological psychologists choose to study in solving this puzzle is the brain.

2. Experimental psychology

The first systematic research on memory in experimental psychology was performed by Herman Ebbinghaus in the late 19th century. Ebbinghaus collected an unbelievably large amount of data from a small sample size (N=1, himself) on the retention of strings of nonsense syllables (Ebbinghaus, quoted in Sahakian, 1981).

Experimental psychology was caught up in the behaviorist movement for much of the early part of the 20th century, so most of the study on memory during that time discussed memory in terms of simple S-R associations. Later behaviorists such as Hull theorized that complex behaviors such as memory could not be understood on the basis of such simple associations. This prompted Hull to devise a theory that allowed for a "black box" of intervening variables between stimulus and response. Still, no attempt was made to study the brain as a variable in this

black box, in the study of memory.

The first psychologist to perform significant research investigating the role of the brain in learning and memory was Karl Lashley. In a paper entitled "In search of the engram," (Lashley, 1950/1960), Lashley discussed such questions as whether memory was a "thing in a place" or a "process in a population." His experimentation was not unlike that of contemporary neuroscience; Lashley investigated the physiological basis of memory by lesion studies on rats. Although Lashley's conclusions from those early experiments are in tension with current trends in the neuropsychology of learning and memory (Lashley concluded that the notion of localization of function in the brain was non-existent, or at least impossible to prove), he was indeed a "giant," setting trends that persist in this sort of research today.

Perhaps the most significant event in the past four decades influencing the course of research in the neuropsychology of learning and memory is the clinical case of H.M.. Scoville and Milner reported in 1957 that bilateral resection of the medial temporal lobe, including the hippocampal formation (an operation performed to treat epilepsy in the patient), of a patient now known as H.M. resulted in profound anterograde amnesia. In the decades since that paper was published there has been an astounding amount of research investigating the role of certain limbic system structures, especially the hippocamppal formation, in learning and memory.

A large part of the animal research in this area has been

devoted to developing theories of hippocampal function. Although early attempts to mimic H.M.'s brain damage in animals "were in tension with the available human data" (Rawlins, 1985), methodological advances in neuroscience have enabled psychologists to perform experiments that make a strong case for the role of the hippocampal formation in learning and memory. The following is an overview of the major theories of hippocampal function.

In The Hippocampus as a Cognitive Map, O'Keefe and Nadel argue that the hippocampus is a neuronal representation of the the spatial world, and that it provides the organism with crucial information needed to navigate in the world (O'Keefe and Nadel, 1979).

One can navigate in the environment through elementary stategies known as taxon strategies, or through complex, "map-like" means called cognitive mapping. As an example of a taxon strategy, consider the different ways of giving someone directions to Roanoke airport. In making use of taxon strategies, one would instruct someone to "turn left on main street, exit off the left side of route 81, and make a right at the bottom of the ramp." Although a person could effectively navigate from Lexington to Roanoke by such a strategy, the strategy is elementary in that it does not navigate by means of analyzing the direct spatial relationship between Lexington and Roanoke. The path is broken down into subroutines with simple instructions that do not require information about the relative location of the beginning and endpoints. If one were to navigate to Roanoke by "going about 55 miles southwest," one would be

using cognitive mapping. In this strategy, any number of different subroutines might be used in the actual traveling; the traveler can use any of them because he has information about the relative locations of the starting point and destination.

O'Keefe and Nadel's thesis stated that a large part of the behavioral data on humans and animals with hippocampal damage could be explained by positing that the hippocampus is the organism's cognitive map. Among the behavioral data that O'Keefe and Nadel cite to support their thesis are experiments where single unit recording indicates that certain cells in hippocampus fire only when the organism is in a specific place in the environment (see Gray, 1982). Subsequent experiments have shown that animals with selective lesion of hippocampus proper can still perform well in complex place tasks (Jarrard, in press [b]), and theoretical opposition to this theory reminds O'Keefe and Nadel that the fact that part of the brain has access to a certain type of information does not mean that the function of that brain region is to process such information (Gray, 1982).

David Olton of Johns Hopkins has also devised a theory of hippocampal function. As a result of his experiments in the late 1970's, Olton concluded that the hippocampus was the site of working memory in the brain. By "working memory," Olton means that information that is necessary for a short period of time, or a single trial in a behavioral test. Olton found that rats with lesions to fimbria-fornix showed a profound working memory deficit in a radial maze task (Olton, 1979). As an example of a working memory error in such a task, consider a radial maze task

in which four of eight arms are baited. A working memory error would occur in a trial if an animal entered an arm it had already explored. Olton observed that rats with lesions to fimbria-fornix made significantly more working memory errors (in this case, entering correct or baited arms they had already entered) than did normal animals (Olton, 1979). Olton's theory is interesting in that it is analogous to the much-discussed human memory dichotomy, short term and long term memory.

One of the fundamental flaws in Olton's theory is that it is based on erroneous anatomical assumptions. Subsequent studies have shown that animals with lesions to hippocampus proper perform as well as controls on radial maze tasks (Jarrard, in press [b]); Olton's theory was originally based on fimbria-fornix lesions, which are not equivalent to lesions of hippocampus proper. Although Olton's terminology is still an important part of research in the field, his theory does not appear empirically convincing today. Olton himself has stated, "I'd like to do away with all dichotomies of memory" (Olton, personal communication).

Although damage to hippocampus proper does not seem to result in profound memory experiments on a wide variety of complex tasks, Mort Mishkin found that damage to hippocampus and amygdala together do result in an impairment (Mishkin, 1984). This observation and others have led Mishkin to propose that there are two parallel circuits in the midbrain involved in memory. The first is made up of the hippocampus and anterior thalamic nuclei, and the second consists of amygdala and dorsomedial thalamus. When both of these circuits, involved in stimulus recognition and association, are interrupted, "both

alternative pathways for storing stimulus representations are destroyed, [and] there is a profound impairment in recognizing the stimulus itself, and, consequently, acquiring any mnemonic association with it" (Mishkin, 1984).

Perhaps the most complex and interesting theory of hippocampal function is the work of Jeffry Gray. Gray's theory describes the septo-hippocampal system (the hippocampal formation and its major connections with the septum) as a behavioral inhibition system (1982). After extensive review of both behavioral and anatomical data, Gray asserted that the subiculum (an associated area to hippocampus proper, and the origin of much of hippocampal output to neocortex) functions as a "comparator" in the septo-hippocampal system. The subiculum compares predicted events (originating from a "generator of predictions") with actual events occuring in the world. Information about the world is input (from entorhinal cortex) into CA1, which begins a loop through Papez circuit (retruning to the hippocampal formation via cingulate cortex), thereby generating a prediction. When predicted events match actual events, the septo-hippocampal system acts only in a "checking" mode. When actual events do not match the system's predictions, the septo-hippocampal system takes over control of behavior.

Observation of data from experiments in the study of both anxiety (and related psychoactive drugs) and memory, Gray concluded that the function of the septo-hippocampal system was to inhibit response and increase attention of an organism when expected events do not match actual events. According to this

theory, then, damage to hippocampus need not result in a memory impairment, but may result in an inability to inhibit a conditioned response. Gray's theory seems quite compatible with much of the behavioral data on selective lesions to subunits of the hippocampus, in which it is found that although damage to hippocampus alone does not result in an impairment on a memory task, damage to hippocampus plus subiculum does result in an impairment (Jarrard, in press [b]). Further, it accounts for the peculiar tendency for hippocampal animals to exhibit response perseveration (i.e., shuttling back and forth between two alleys of a radial maze, ad absurdium).

The most recent theory of hippocampal function comes from Nick Rawlins at the University of Oxford. Rawlins's theory states that the hippocampus acts as a "high capacity, intermediate term memory store" (Rawlins, in press). In his theory, he states that information is stored in the hippocampus in parallel with a more limited, short-term memory store. The behavioral effects of lesioning the hippocampus are due to the loss of this intermediate system, or as Rawlins states, "[memory tasks] become insoluble when the capacity of the short-term store has been exhausted" (Rawlins, in press).

Research using human subjects in the study of the neuropsychology of learning and memory has been primarily directed towards developing theories of human amnesia. Initial studies of the patient H.M. prompted the early suggestion that human amnesia was due to an impairment in consolidation. In the classical short-term/long-term human memory model, consolidation is the process by which information is taken from the short-term

store and etched into the permanent, long-term store. This theory was based in part on the observation that H.M. could retain verbal information for up to 15 seconds without rehearsal, indicating normal short-term memory function. Subsequent experiments showed, however, that amnesics can often retain information for much longer periods of time if retrieval cues are provided in the testing phase of the experiment (Warrington and Weiskrantz, 1970).

The second major theory of human amnesia states, as the above example suggests, that amnesics do, in fact have a functioning long term memory, and an operative means of consolidation, but that they are impaired in retrieving information from long term storage. As Weiskrantz states, "It is surprising how provacative it has been to suggest that the amnesic patient's difficulty may be one of retrieval rather than storage" (Weiskrantz, unpublished manuscript). One of the experiments illustrating the retrieval deficit was performed by Weiskrantz and Warrington (1970). In this study, Weiskrantz and Warrington showed that amnesics could remember word lists over long time intervals as well as controls if retrieval cues were provided during testing (1970). "Aut" is an example of a cue used for the word "automobile."

More recently, Weiskrantz has modified his original postion on the retrieval deficit theory. The amnesic's impairment is not a result of a retrieval deficit, but is a result of the loss of a "cognitive mediational system" (Weiskrantz, unpublished manuscript). This idea states that amnesics can only learn

memory tasks if the associations required to master the task are unambiguous. In support of this notion Weiskrantz cites experiments in which normal subjects can improve their performance on paired-associate learning if imagery is used as a mnemonic aid. Amnesics do not benefit from this technique, perhaps due to the abstract reasoning required to make use of the technique (unpublished manuscript).

Two closely related theories of human amnesia are reviewed by Hirst (1982). The first of these theories, the encoding deficit theory, states that memory deficits in amnesic patients are due to an inablilty to process verbal information on a deep semantic level. Normal humans, for example, will remember a word list better if they are instructed to attend to the semantic context of the words in the lists than if they are told to attend to some trivial aspect of the words, such as the number of "t's" in each word. Amnesics, unable to process information on such a deep semantic level, show only limited improvement under conditions such as these (Cermak and Reale, 1978).

The second of these related theories is the context theory. This theory states that although amnesics may be able to encode certain classes of information, they cannot properly encode the context in which the information was learned. Amnesics do not benefit from contextual cues about the learning environment (i.e., place and time of learning, etc.) to the same extent that normal humans do (Hirst, 1982). In support of this theory, Hirst and Volpe found that amnesics could perform as well as controls on a recognition task, but performed worse than controls when asked to recall the temporal order in which the test items were

presented (Hirst, 1982).

The final theory of human amnesia to be discussed was developed by Mort Mishkin. Similar to his theory of hippocampal funciton, Mishkin states that there are two parallel systems in the human brain that can be involved in learning and memory. The first, called a memory system, is a fast-acting system that functions in stimulus recognition and response-reward association. The second system, called a habit system, acts more slowly and requires many repititions of associated events for a memory trace to be created. The two systems are qualitatively different, but, as Mishkin states, "their product is not" (Mishkin, 1984). Mishkin concludes that learning is a product of both memory and habit, and that the impairments of human amnesics on certain memory tasks is a natural consequence of the normal operation of the habit system, isolated from the memory system.

3. Summary

Although the most significant events in the study of the neuropsychology of learning and memory have occured in the last four decades, the course of the field's development does not appear to be unlike that of other fields. As in the study of psychoactive drugs, for example, the initial impetus for investigation into the role of the hippocampus in learning and memory was coincidental--obviously, Scoville and Milner did not set out to cause a memory impairment in H.M.. Further, much of the present course of investigation in this field is determined by advances in technique. In fact, the empirical portion of this thesis would not be possible without advances in lesion

techniques and behavioral testing that are perhaps slightly more than a decade old.

The remainder of this thesis will be the write up of the experiment conducted this winter. Although the methodology used most closely resembles those studies aimed at developing theories of hippocampal function, I have attempted throughout to emphasize the significant relationship this project has for theorizing about human pathological memory disorders. Irrespective of whatever clinical applications animal research such as this might have, it is often helpful to remind ourselves that the psychologist's "search for truth" is directed at understanding humans, not animals.

Footnotes

1. The language used in this statement is derived from a conversation with H.E. King. The content of that conversation helped significantly in structuring the historical perspective.

References

Brennan, J.F. (1982). History and Systems of Psychology. (pp. 50-72) New Jersey : Prentice-Hall

Cermak, L.S., & Reale, L. (1978). Depth of processing and retention of words by alcoholic Korsakoff patients. Journal of Experimental Psychology: Human Learning and Memory, 4, 165-174.

Gray, J. (1982). Precis of The Neuropsychology of Anxiety: An enquiry into the function of the Septo-Hippocampal System. Behavioral and Brain Sciences, 5, 469-506.

Hirst, W. (1982). The amnesic syndrome: Descriptions and explanations. Psychological Bulletin, 91, 435-460.

Jarrard, L.E. (in press [b]). Selective hippocampal lesions and behavior: Implications for current research and theorizing. In R.L. Isaacson & K. Pribram (Eds.), The Hippocampus. New York : Plenum Press.

Lashley, K. (1950). In search of the engram. In F.A. Beach, D.O. Hebb, C.T. Morgan, & H.W. Nissen (Eds.), The Neuropsychology of Lashley (pp. 478-505). New York : McGraw-Hill.

Mishkin, M., Malamut, B., & Bachevalier (1984). Memories and habits: Two neural systems. In G. Lynch, J.L. McGaugh, & N.M. Weinberger (Eds.), Neurobiology of Learning and Memory (pp. 65-77). New York : Guilford Press.

O'Keefe, J., & Nadel, L. (1979). Precis of The Hippocampus as a Cognitive Map. Behavioral and Brain Sciences, 2, 487-533.

Olton, D., Becker, J.T., & Handelmann, G.E. (1979). Hippocampus, space, and memory. Behavioral and Brain Sciences, 2, 313-365.

Sahakian, W.S., Ed. (1981). History of Psychology (pp. 3-14; 20-25; 31-81; 107-114) Illinois : F.E. Peacock Publishers.

Scoville, W.B., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. Journal of Neurology, Neurosurgery, and Psychiatry, 20, 11.

Weiskrantz, L., & Warrington, E.K. (1970). Verbal learning and retention by amnesic patients using partial information. Psychonomic Science, 20, 210-211.

ADDITIONAL SOURCES CONSULTED

Bartlett, F.C. (1967). Remembering, (pp. 1-13). Cambridge : Cambridge University Press.

Crowder, R.G. (1976). Principles of Learning and Memory, (pp. 273-314). New Jersey : Lawrence Earlbaum Associates.

Isaacson, R.L. (1982). The Limbic System, 2nd Ed., (pp. v-vi). New York : Plenum Press.

Jarrard, L.E. (1975). Role of interference in retention by rats with hippocampal lesions. Journal of Comparative and Physiological Psychology, 89, 400-408.

Jarrard, L.E., & Elmes, D.G. (1982). Role of retroactive interference in the spatial memory of normal rats and rats with hippocampal lesions. Journal of Comparative and Physiological Psychology, 96, 699-711.

Jarrard, L.E. (1985, in press [a]). Is the hippocampus really involved in memory? In B. Will & P. Schmitt (Eds.), Brain Plasticity, Learning, and Memory. New York : Plenum Press.

King, H.E. (1972). Sensory retaining and the problem of human memory. In M. Hammer, K. Salzinger, & S. Sutton (Eds.), Psychopathology, (pp. 243-259). John Wiley and Sons.

Melton, A.W. (1967). Repitition and retrieval from memory. Science, 158, 532.

Morris, R. (1984). Modeling amnesia and the study of memory in animals. Trends in Neuroscience.

Roitblat, H.L. (1982). The meaning of representation in animal memory. Behavioral and Brain Sciences, 5, 353-406.

Squire, L.R., & Cohen, N.J. (1984). Human memory and amnesia. In G. Lynch, J.L. McGaugh, & N.M. Weinberger (Eds.), Neurbiology of Learning and Memory, (pp. 3-64). New York : Guilford Press.

Weiskrantz, L. (1985). On issues and theories of the human amnesic syndrome. Manuscript submitted for publication.

Part Two

Radial Maze Acquisition in Rats With Lesions to Selected Hippocampal Cell Fields: Effects of Massed vs. Distributed Practice

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Running head: HIPPOCAMPUS AND ACQUISITION

Abstract

The effects of ibotenate lesions to hippocampus proper and to subiculum/entorhinal cortex were studied using a radial maze acquisition task. Subjects were also tested for differences in performance between massed and distributed practice for the radial maze task. Hippocampal animals performed significantly worse than controls on nearly all aspects of the radial maze task, but subiculum/entorhinal cortex lesioned animals did not differ significantly from controls on any dependent measure. The primary impairment for hippocampal animals was on working memory. Distributed practice effects were minimal, but facilitated hippocampals' performance on working memory, and all groups' performance on reference memory. The data are discussed in terms of the theories of hippocampal function proposed by Olton (1979), Rawlins (in press), and Gray (1982), and seem to fit best with the former's working memory theory.

Radial Maze Acquisition in Rats With Lesions to Selected Hippocampal Cell Fields: Effects of Massed vs. Distributed Practice

A substantial amount of current research in neuroscience suggests that a true understanding of the learning and memory impairments associated with hippocampal damage will require thorough investigation of the functions of discrete subregions of the hippocampal formation. This notion is supported by significant findings in both human and animal research.

One of the subregions of the hippocampal formation that seems to be crucial to understanding hippocampal function is the subiculum. It has been shown that while animals with neurotoxin lesions to hippocampus proper do not show memory impairments on complex behavioral tasks, animals with combined damage to hippocampus and dorsal subiculum do show a considerable impairment on such tasks (Jarrard et al, 1984). Further, Gray's theory of the function of the septo-hippocampal system (1982) states that the subiculum is in an ideal anatomical location to function as the "comparator" of predicted vs. actual events occuring in the environment, and is thus a crucial part of what Gray calls the "behavioral inhibition system" (Gray, 1982). In the human literature, analysis of brains of patients diagnosed as having Alzheimer's disease reveals profound damage to subiculum and the deeper layers of entorhinal cortex, a lesion which isolates the hippocampus from its major inputs to and outputs

from neocortex (Van Hoesen et al, 1984).

The refinement of lesioning techniques using ibotenic acid makes it possible to selectively lesion subregions of the hippocampal formation. Given the potential importance of subiculum as revealed in the animal literature, and the potential clinical importance of this area in the study of Alzheimer's disease, it seemed useful to perform a behavioral study on rats with combined damage to subiculum and deep layers of entorhinal cortex. To better correlate these results with various theories of hippocampal function, a second group of animals with neurotoxin damage to hippocampus proper will be studied.

In order to recover additional information on the nature of any memory impairments observed, the animals will be tested on the effects of massed vs. distributed practice on the classical radial maze task. Elmes et al (1979) reported that normal rats show improvement in reference memory in a radial maze task under distributed practice (the so-called "spacing effect" or "lag effect"). One of the explanations proposed for the spacing effect is that distributed practice affords the learner increased contextual information (temporal, spatial, etc.) about the specific items to be remembered (Murdock, 1974). For example, if trials are distributed over a large time interval (distributed practice), important information from those trials is encoded in a larger temporal context than if the trials occur consecutively in time (massed practice). Increased contextual information improves recall.

Given the suggested role of a deficit in encoding of contextual information in humans with pathological memory disorders (Hirst, 1982), investigation of possible context-encoding deficits in animals with lesions to selected regions of the hippocampal formation would appear to be fruitful. We hypothesized that animals with combined damage to subiculum and the deep layers of entorhinal cortex would be unable to profit from the context effects of the distributed practice variable, and would therefore show no spacing effect. Such effects, if they are to occur, should be observed in a "context-loaded" task such as that used by Elmes (1979). A radial maze task is used to study the spacing effect due to the important distinction such a task makes between working and reference memory errors, and the potential importance of this distinction in theorizing about hippocampal function (Olton, 1979).

Method

Subjects

Ss were 17 male Sprague Dawley rats. Throughout the experiment, all rats were maintained at 85% of their free feeding weight. The animals were housed in individual cages and were kept on a 12:12 hour day night cycle. All behavioral testing occurred during the daylight phase of the cycle.

Apparatus

The radial maze used had an octagonal center platform about which the eight arms extended. Each of the arms was fitted with

plexiglass sides and a food cup at the end. Noyes Pellets, 45 grams each, were used as reinforcement in the correct arms.

Design

A 3X2 mixed design was used, with massed vs. distributed practice as the within subjects variable. The 17 animals were divided into three groups for testing. Six rats served in the subiculum-entorhinal cortex lesion group, five rats served in the hippocampal lesion group, and six rats served as controls. Two of the six control animals were operated controls.

Each rat received 11 trials on eight maze problems; each problem required the rats to find food reinforcement in four of the eight arms of the radial maze. For each rat, the trials in one-half of the problems were administered under distributed practice, while the trials in the other one-half were administered under massed practice. Block randomization was used to determine both the order of problems each rat would receive during the experiment, and the level of practice (massed or distributed) used for each problem.

Surgical and Anatomical Techniques

All animals were anesthetized with intraperitoneal injections chloropent (1.0-1.4cc). All animals were then placed in a Kopf stereotaxic apparatus and subjected to the lesioning procedure.

1. Subiculum/Entorhinal Cortex combined lesion: Animals

were placed in the stereotaxic with the DV coordinate of bregma 1.0 mm dorsal to the DV coordinate of lambda. The lesion was effected by injecting .10 microliters of ibotenic acid at seven sites bilaterally. Relative to bregma, the coordinates were as follows: At AP= -5.5, two injections (ML= +/-2.2, DV= -2.5), at AP= -6.7, four injections (ML= +/-3.0, DV= -2.5 : AND : ML= +/-4.9, DV= -7.0), at AP= -7.4, two injections (ML= +/-4.1, DV= -2.7), and at AP= -8.7, six injections (ML= +/-5.2, DV= -3.0, -4.2, and -5.3).

2. Complete Hippocampal lesion: Each animal was placed in the stereotaxic with the DV coordinates of bregma and lambda equal. The lesion was effected by injecting .10 microliters (except as otherwise noted) of ibotenic acid at 11 sites bilaterally. Relative to bregma, the coordinates were as follows: At AP= 2.4, two injections of .05 microliters (ML= +/-2.4, DV= -3.2), at AP= -3.0, four injections (ML= +/- 1.4, DV= -3.0 : AND : ML= +/- 3.0, DV= -3.0), at AP= -4.0, six injections (.05 microliter injections at ML= +/-2.2, DV= -3.3 and -2.3 : AND : ML= +/-3.7, DV= -3.0), at AP= -5.0, two injections (ML= +/-4.1, DV= -7.0), and at AP= -5.6, eight injections (ML= +/- 3.8, DV= -3.8 : AND : .05 microliter injections at ML= +/- 4.9, DV= -4.0, -4.8, and -5.9).

3. Operated controls: These animals were subjected to the same operating procedures as the lesioned animals with the exception of the injections of ibotenic acid.

For all injections, the neurotoxin was injected slowly over a two minute period, and the cannula was left in place for one minute at the most ventral coordinates to prevent spreading of the neurotoxin up the needle track. All animals were given a two week post-operative recovery period.

Following behavioral testing, all lesioned animals were sacrificed and perfused with physiological saline and formalin. The brains were removed, embedded in egg yolk, and cut horizontally on a microtome into 40 micron sections for staining. A cresyl violet stain was used to determine cell loss due to the lesion.

Procedure

Both pretraining and actual testing was carried out postoperatively. In the first two days of pretraining, each rat was placed in the center of the maze and allowed to explore for five minutes. Several food pellets were scattered about the center platform of the maze. In the next three days of pretraining, the Ss behavior was shaped by placing the food reinforcement in the arms of the maze, and increasing the distance from the center platform each day. So, on the third day of pretraining, the reinforcement was placed at the entrance to each arm, on the fourth day the reinforcement was placed half way down each arm, and on the fifth day of pretraining the reinforcement was placed at the end of each arm. In each of these days the rats were allowed to explore the maze for five minutes.

In the last three days of pretraining, reinforcement was placed in four of the eight arms, and the rats were immediately removed from the maze after obtaining all four food rewards.

In actual testing each rat received 11 trials on eight different radial maze problems. A problem is defined as a set of four of the eight arms in the radial maze. The trials for each problem were administered over three days. On the first two days, each rat received five trials, and on the last day each rat received one trial. The trials on each of days one and two were separated by an intertrial interval of 45 seconds for the massed practice condition, and an intertrial interval of 10 minutes for the distributed practice condition. Twenty-four hours after the last trial on day two, each rat received one trial (test trial). The effects of the massed-distributed variable are thus unconfounded by the length of the retention interval. The time from the last trial on day one and the first trial on day two was the same for all rats, with 30 minutes. After the third day in a particular problem, each rat received a new problem. By the end of the experiment, each rat had received the same eight problems. The assignment of practice condition to problems was discussed under design.

For each trial in the massed practice condition, each rat was placed in the maze and allowed to search for all four rewards, after which he was returned to the home cage. The appropriate arms were then rebaited, and the rat was quickly replaced into the maze. This continued for each of the five

trials on a given day. For each trial in the distributed practice condition, each rat was placed in the maze and allowed to search for the rewards as described above, but after obtaining all rewards was returned to the home cage for ten minutes. During the ten minute intertrial interval, other animals were run. The distributed practice animals were rotated through this cycle until each had received five trials.

The rats were allowed a maximum of five minutes to obtain all rewards, and were allowed to enter and reenter arms freely to obtain the rewards. The arms entered and the order in which they were entered was recorded, along with the total time of testing for each trial.

Results

Histological

Subiculum/Entorhinal lesion - Analysis of cresyl violet-stained sections demonstrates profound loss of cells in dorsal subiculum (>90%), while sparing hippocampus proper at the most dorsal location. At more ventral locations, there was similar loss to subicular cells, plus loss to cells in the deep layers of entorhinal cortex. There was some thinning of dentate gyrus and some CA1 cells in the ventral third of two animals.

Complete hippocampal lesion - Dorsal hippocampus was effectively eliminated in all animals, with some loss to dorsal subiculum in two animals. At the more ventral coordinates,

approximately 40% of dentate gyrus was spared on all but one animal. A small percentage of CA1 and/or CA3 cells (<30%) were spared at the most ventral third of three animals. The complete hippocampal lesioned animals with damage to dorsal subiculum appeared to show the most profound behavioral impairments.

Behavioral

Dependent variables and statistics - S(A)xBxC mixed ANOVA's were used to determine behavioral effects for all but one dependent variable. To determine effects over time (learning to learn), an S(A)xB ANOVA was used with lesion group as the between Ss variable, and with problem (the particular maze problem, designated by the numbers 1-8) as the within subjects variable. The dependent variable in this analysis was total number of a particular type of error made, summed for the eleven trials in each problem.

To determine the effects of lesion and practice conditions and important interactions, S(A)xBxC mixed ANOVA's were used with lesion group as the between Ss variable, with practice condition (massed vs. distributed) as the first within subjects variable, and with day of testing (first, second, or third, within a problem) as the second within subjects variable. The different dependent variables (types of errors) were averaged per trial for a given test day (i.e., avg. error/trial, day 1; avg. error/trial, day 2, etc.).

Five principal dependent variables were used. The first DV

used in analysis was total errors (TOTER). The next DV, reference memory total errors (RMTOTER), refers to the number of entries into non-baited arms (not including repeat entries into baited arms that were already visited on that trial). Working memory correct errors (WMCER) refers to the number of repeat entries into baited arms in which the reward had already been obtained. Working memory total errors (WMTOTER) refers to the number of repeat entries into any arm (baited or non-baited; in either case a repeat entry can be considered an error in working memory). The final DV, called reference memory only errors (RMONLER), refers to the number of first visits to non-baited arms. Subsequent visits to non-baited arms could be construed as working memory errors, and are separated from true reference memory errors in this DV. On a four out of eight task, there is a maximum of four RMONLER possible on a given trial. Four the DV's listed above, ANOVA's were run using gross number of errors/trial/problem, and also using the proportion of total errors that a given type of error constituted (i.e., RMTOT/TOTER, etc.).

The reason for analyzing so many DV's is simple. The working memory/ reference memory distinction has been a crucial part of much theorizing about the physiological substrates of learning and memory. In the limited baiting, radial maze task, however, not all errors fall neatly into the working-reference memory dichotomy. For example, consider an eight-arm maze task in which arms #1-4 are baited. Assume the animal enters arm #1,

then arm #5. Entering arm five is clearly a reference memory error in this case. If the animal subsequently reenters arm #5, does this constitute a working memory error or a reference memory error? It has elements of both, since the animal's reference memory should have instructed him that the arm has never been baited, and the animal's working memory should have instructed him that he had already entered that arm on that trial. In order to account for such subtelties as this, errors were analyzed in the multiple ways described above.

Significant results of these analyses are summarized below.

Controls vs. Operated controls - The performance of controls and operated controls did not differ on any dependent variable. Their data were pooled for subsequent analysis.

Learning to learn - Figure 1 illustrates learning over problems for each of the lesion groups. There was a main effect of time (learning to learn; $F=2.91$, $p<.01$, eta=.41), but no significant lesion X time interaction.

INSERT FIGURE 1 ABOUT HERE

When total errors were summed across problems for days 1, 2, and 3 of the problem, there was a main effect of time, illustrating substantial improvement within a problem ($F=6.29$, $p<.01$, eta=.56).

Effects of lesion - There was a main effect of lesion on all DV's mentioned above. In every case, hippocampal animals

differed from both controls and subiculum/entorhinal animals, while the subiculum/entorhinal animals never differed from controls. Table 1 shows the effects of lesion on total errors ($F=15.5$, $p<.001$, eta=.83), reference memory total errors ($F=22.5$, $p<.001$, eta=.87), and working memory correct errors ($F=9.14$, $p<.001$, eta=.75), respectively.

INSERT TABLE 1 ABOUT HERE

When percent scores were analyzed for working memory correct errors, the ANOVA revealed that hippocampals made a larger proportion of working memory correct errors with respect to total errors than did subiculum/entorhinal animals ($p<.05$), but did not differ significantly from controls.

Lesion X time interactions - There was substantial improvement within a problem for the proportion of working memory correct errors to total errors for the subiculum/entorhinal group, while hippocampals showed the opposite effect (for the interaction, $F=11.47$, $p<.001$, eta=.79). There was no effect of test day on performance for controls on this dependent variable. For gross number of working memory correct errors, hippocampals made significantly more working memory correct errors across days within a problem, while there was no such effect for either of the other groups (for the interaction, $F=5.46$, $p<.01$, eta=.53). These results are illustrated in figures 2 and 3.

INSERT FIGURES 2 AND 3 ABOUT HERE

Effects of practice condition - Overall effects of massed vs. distributed practice were minimal. There was a main effect of practice condition for the proportion of working memory total errors to total errors, and a significant interaction of practice condition with lesion group on this dependent variable. Hippocampal animals made significantly fewer working memory total errors proportional to total errors under distributed practice than under massed practice, but there was no such effect for either of the other two lesion groups (for the interaction, $F=4.56$, $p<.03$, eta=.62). In other words, working memory improved for hippocampals under distributed practice. This effect is illustrated in figure 4.

INSERT FIGURE 4 ABOUT HERE

Although there were no other main effects of practice condition, there was a significant interaction of practice condition X time (day of testing within a problem). For the gross number of working memory total errors, there was an effect of practice condition at day 2 only (for the interaction, $F=4.87$, $p<.02$, eta=.51). All animal groups made fewer working memory total errors under distributed practice than under massed practice on the second day of a problem. This effect is illustrated in figure 5. This and similar interactions indicated that the data from day one of a problem (in which the animal had to begin

making new discriminations) and from day three of a problem (in which the animal recieved only one trial) may have been problematic, obscuring certain interesting results.

INSERT FIGURE 5 ABOUT HERE

Note that there was an effect of distributed practice on reference memory total errors proportional to total errors on test trial (third day) performance for all animal groups ($F=9.6$, $p<.01$, eta=.50) These results are identical to those reported by Elmes et al (1979). Conclusions based on this result, however, must be tempered in light of the variability of day 3 performance mentioned above. These results are illustrated in figure 6.

INSERT FIGURE 6 ABOUT HERE

Summary of behavioral results - There is a profound effect of the hippocampal lesion, with those animals showing impaired performance relative to the other groups on all dependent measures. Subiculum/entorhinal lesioned animals did not differ from control animals on any dependent measure. Further, there is a consistent working memory impairment in hippocampal animals that does not seem to improve within a problem as performance did for the other two groups. Overall, performance improved both across problems and within a problem. Practice effects were minimal but included an effect of practice on working memory for hippocampal animals, and a questionable effect of practice on reference memory for all groups. The overall effects of practice

may have been obscured by high variability in the scores from days 1 and day 3.

Discussion

Many of the effects observed in this experiment are in tension with existing theories of hippocampal function, and seem to contradict some current data on hippocampal function. There are no easy comparisons to make between this experiment and others investigating hippocampal function. This is not surprising, however, given the fact that we used a task variable (massed vs. distributed practice) and a lesion (subiculum plus entorhinal cortex) that have yet to be tried in a study such as this. Although potentially important effects may have been masked by methodological pitfalls, the data seem to correlate best with Olton's working memory hypothesis, and contradict the theories proposed by Rawlins and Gray. With respect to the human literature on Alzheimer's disease, the significance of the data in this experiment is unclear.

The main effect of the hippocampal lesion on overall performance and especially working memory contradicts recent data on hippocampal lesioned animals in memory tasks. In the study by Jarrard, hippocampal animals did not show impairments on the radial maze place task, similar to the one used in the present experiment (Jarrard et al, 1984). Note, however, that this effect is seen for a retention task, in which training on the task occurred preoperatively. Since all training occurred

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postoperatively in this experiment (acquisition), direct comparison with the Jarrard (1984) study is not possible. The differential effect of hippocampal damage between acquisition and retention suggests that perhaps hippocampal damage changes the animal's facility for laying down new memories, while those memories already stored in long term memory are left intact and functional (reminiscent of H.M.'s impairment).

The consistent working memory impairment in hippocampal animals correlates with Olton's working memory theory. Although overall performance improved within a problem for all animals, hippocampal animals did not show a working memory improvement within a problem (in fact, the impairment grew within a problem). This suggests that for an acquisition paradigm, hippocampus proper is crucial to working memory performance.

While hippocampals' performance supports Olton's theory, it is clearly in tension with Rawlins's intermediate term memory theory of hippocampal function. Consider the effect of distributed practice on working memory in hippocampal animals. At an intertrial interval of 10 minutes (distributed practice), hippocampal animals showed a working memory facilitation, compared to their performance at an intertrial interval of 45 seconds (massed practice). If intermediate memory is destroyed by the hippocampal lesion, one would expect that, as Rawlins states, "the task [will become] insoluble when the capacity of the short term store has been exhausted" (Rawlins, in press). At an intertrial interval of 10 minutes, then, short term storage

should be exhausted, and the animal's performance should be impaired. In fact, the opposite is observed, as the spacing effect for hippocampals on working memory illustrates.

Other effects of the practice condition are called into question by certain methodological considerations. Effects of the practice variable usually differed across days, for example, with effects on third day performance most variable. One would not expect a large spacing effect on the first day of acquisition, since new associations were being made and old ones extinguished; since each animal recieved only one trial on the third day, any spacing effect may have been obscured by an "exploratory" first trial (on the first trial of any day within the paradigm used, the animal "does not know" whether the same arms will be baited as on the previous day). These observations indicate that the best data to use to look for practice effects are data from day two. In fact, working memory improved for all animals on day two, but, as mentioned above, this effect was significant for all days for hippocampals only. Further, note that given the considerations mentioned above on appropriate data for analysis of practice effects, the meaning of the effect of distributed practice on reference memory (for test trial performance--replicating the effect seen by Elmes, 1979) is unclear.

A possible pitfall in interpreting the practice effects from the present study is a floor effect on the overall difficulty of the task used. Effects of massed and distributed

practice were subtle when they occurred, and it may be the case that such effects are only demonstrable when the task is very difficult. Substantial learning both within and across problems for controls and subiculum/entorhinal animals indicates that the task was not exceedingly difficult. Lesion effects show, however, that the task was difficult for the hippocampals relative to the other groups. This increased difficulty for hippocampal animals may have accounted for the spacing effect observed for working memory at all three days of a problem. Perhaps the acquisition impairment induced by the hippocampal lesion forced those animals to process the information at a deeper mnemonic level than the other groups, and attend to such features as enriched contextual cues provided by the distributed practice condition. For the other two groups, the task may have been simple enough that attending to salient features of the practice variable were unnecessary for solving the task. In this case, the floor effect may have caused controls and subiculum/entorhinal animals to "take the easy way out." Note that this explanation is the opposite of the initial hypothesis about the interaction between practice condition and lesion. Such explanations are purely speculative however, and require further data collection in order to be confirmed.

Clearly the most surprising result of the experiment was the total absence of effect on memory from subiculum/entorhinal lesion. Given the histological confirmation of the extent of the

lesion for the subiculum/entorhinal group, it appears that this area of the hippocampal formation is not crucial to acquisition in the radial maze place task.

These data clearly conflict with the comparator theory advanced by Gray (1982). If the comparator of predicted events vs. actual events is eliminated, the animal should have no means of inhibiting response. Yet animals in which the comaprator is removed show substantial improvement within a problem for overall performance. Further, the fact that hippocampal animals do show an impairment also seems anomalous. In Gray's theory, the hippocampus functions as a portion of a loop which generates predictions about the world (Gray, 1982). Intuitively, it would seem that damage to a comparing system (subic.) would impair performance more than damage to a predicticting system. With damage to a predicting system, one would expect an animal to respond at random at least--and random response is not such a bad strategy in a radial maze task such as the one used in the present study. With damage to a comparing system, however, one would expect an animal to respond according to stored regularities which it has no means of changing. Thus, crucial discriminations needed for learning of this sort should be impossible. It should be pointed out that Gray mentions that the comparator function of the septohippocampal system does not function in the acquisition of new memories, but only in response to old ones (Gray, 1982). Although we are unable to evaluate the significance of this provision on claims such as the one leveled

above, Gray's theory still seems to be in tension with the data from both the hippocampal animals and the subiculum/entorhinal animals collected in the present experiment.

The data collected on the subiculum/entorhinal animals does not invite significant comparison with the human study in which the brains of patients with Alzheimer's disease showed significant loss of cells in subiculum/entorhinal cortex. One might conclude from the present study that the memory effects observed in Alzheimer's disease are not associated with damage to a hippocampal formation cell field, but are instead associated with damage to nucleus basalis (the latter condition was reported by Coyle et al, 1983). The lack of evidence for <u>any</u> functional impairment due to the "Alzheimer's lesion" in the present experiment, however, seems to raise the question of cross-species differences between rats and humans. Again, such claims are speculative.

The analysis of lesion and practice condition effects, discussed in terms of relevant theories of hippocampal function, seems to lead to the following conclusions: 1) The subiculum and deep layers of the entorhinal cortex are not crucial physiological substrates in discrimination learning in a radial maze acquisition task. 2) The performance of animals with lesions to hippocampus proper on this task supports the working memory theory proposed by Olton, and conflicts with predictions about performance generated from the theories of Rawlins and Gray. 3) Due to methodological considerations, the effects of

massed vs. distributed practice and their interactions across lesion groups are not clear, but seem to occur most significantly for working memory.

Some of the methodological problems might be overcome if the present study were replicated using a more difficult behavioral task. If massed-distributed effects are there, they should show up if the task becomes more difficult. It would also seem appropriate to try the massed-distributed variable on a retention task. Given the profound differences in hippocampal performance between retention and acquisition on radial maze tasks, it could prove interesting to look for differences between acquisition and retention in animals with lesions to subiculum plus the deeper layers of the entorhinal cortex.

References

Coyle, J.T., Price, D.L., & DeLong, M.R. (1983). Alzheimer's disease: A disorder of cortical cholinergic innervation. Science, 219, 1184-1190.

Elmes, D.G. Willhite, J.C., & Bauer, G.B. (1979). Reference memory effects of distributed practice on radial maze learning in rats. Bulletin of the Psychonomic Society, 14, 109-111.

Gray, J. (1982). Precis of The Neuropsychology of Anxiety: An enquiry into the function of the Septo-Hippocampal System. Behavioral and Brain Sciences, 5, 469-506.

Hirst, W. (1982). The amnesic syndrome: Descriptions and explanations. Psychological Bulletin, 91, 435-460.

Jarrard, L.E., Okaichi, H., Steward, O., & Goldschmidt, R.B. (1984). On the role of hippocampal connections in the performance of place and cue tasks: Comparisons with damage to hippocampus. Behavioral Neuroscience, 98, 946-954.

Murdock, B.B. (1974). Human Memory: Theory and Data (pp. 241-244). Maryland: Lawrence Earlbaum Associates.

Olton, D., Becker, J.T., & Handelmann, G.E. (1979). Hippocampus, space, and memory. Behavioral and Brain Sciences, 2, 313-365.

Rawlins, J.N.P. (in press). Associations across time: The hippocampus as a temporary memory store. Behavioral and Brain Sciences.

Van Hoesen, G.W., Hyman, B.T., Damasio, A.R., & Barnes, C.L. (1984). Alzheimer's disease: Cell-specific pathology isolates the hippocampal formation. Science, 225, 1168-1170.

Author Notes

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Table 1

Mean Errors Per Trial for Total Errors, RM TOT Errors, and WMC Errors for Each Lesion Group

LESION GROUP	TOTAL ERRORS	RM TOT ERRORS	WMC ERRORS
Hippocampal	6.3	4.4	1.9
Subic + Entor	3.1	2.7	.4
Control	3.0	2.5	.5

Figure Captions

Figure 1. Total errors as a function of maze problem for each lesion group.

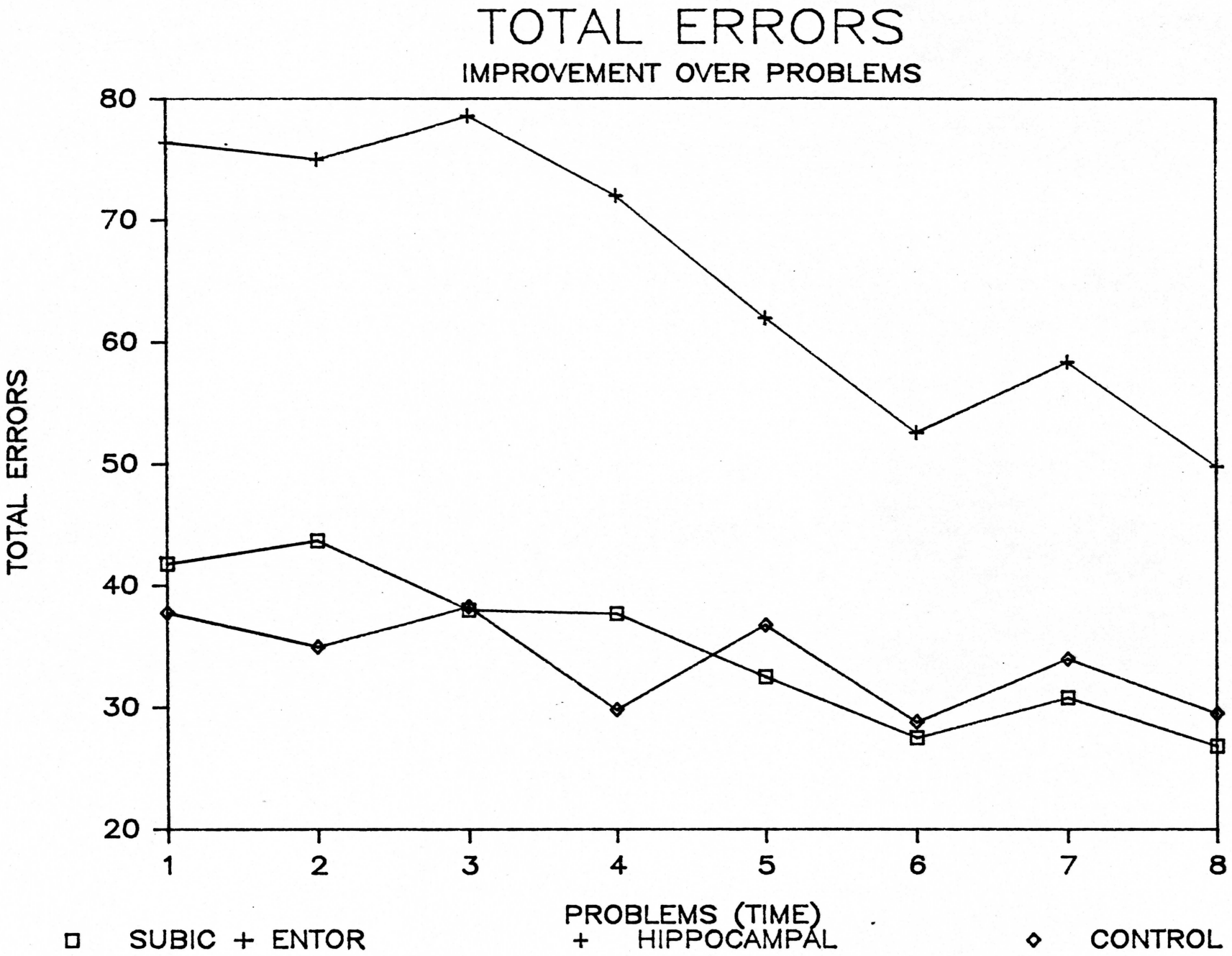
Figure 2. Proportion of WMC errors to Total errors within a problem.

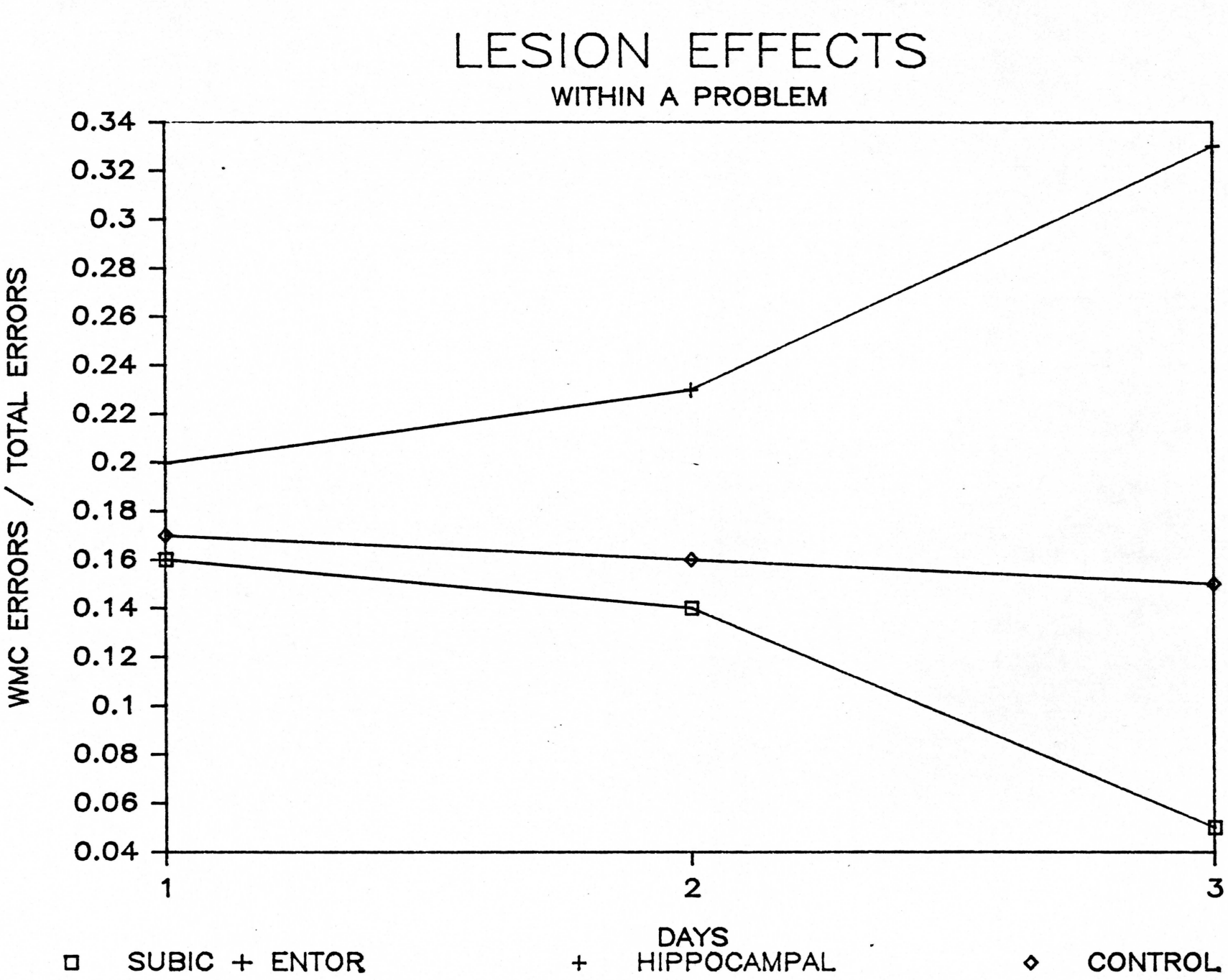
Figure 3. WMC errors within a problem, showing differences in lesion groups.

Figure 4. Spacing effect for hippocampal rats on proportion of WMTOT errors to Total errors.

Figure 5. Spacing effect for all animal groups on day 2 performance for WMTOT errors.

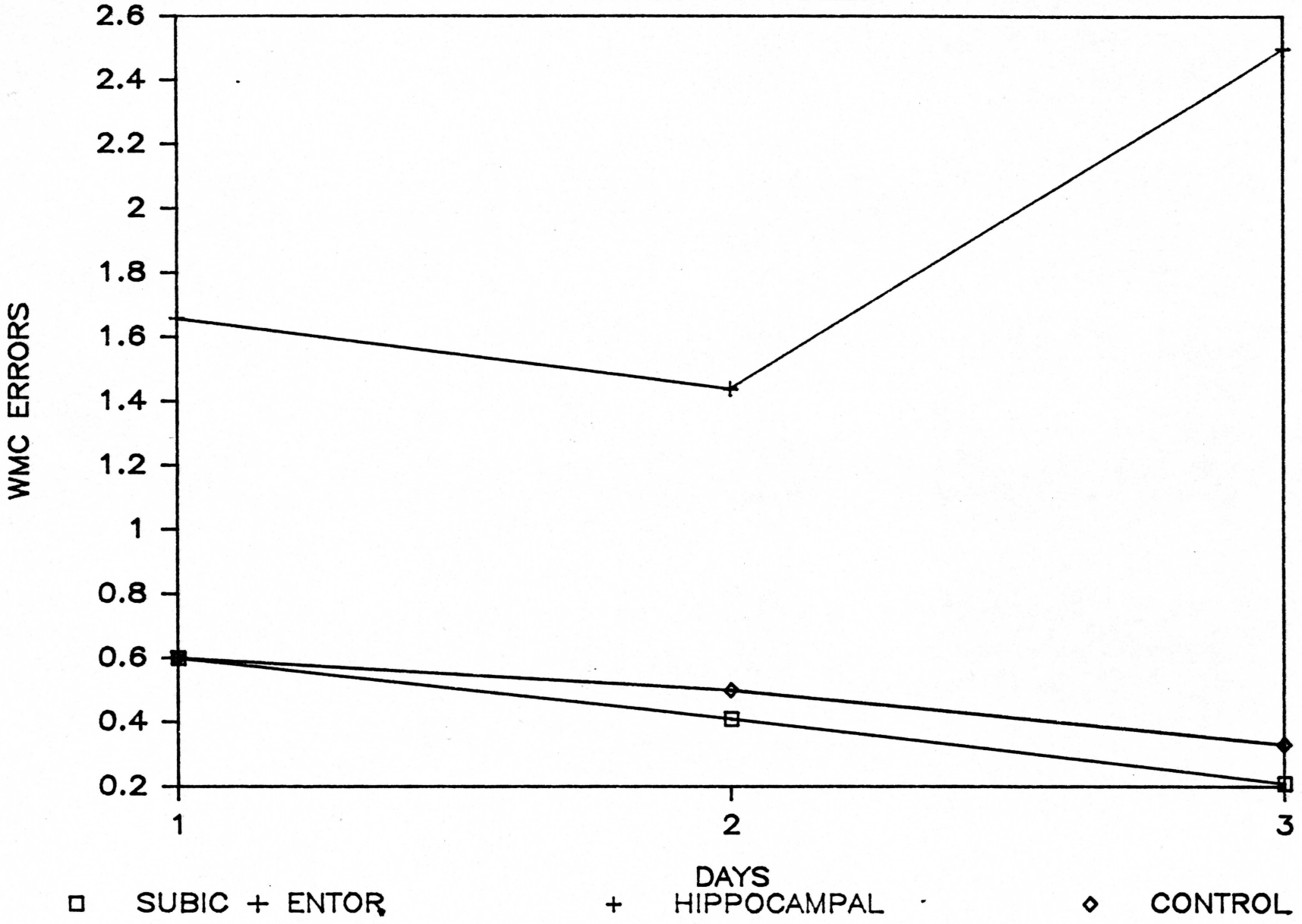
Figure 6. Spacing effect for all animal groups on day 3 performance for proportion of RMTOT errors to Total errors.


TOTAL ERRORS
IMPROVEMENT OVER PROBLEMS
TOTAL ERRORS
80
70
60
50
40
30
20
1
2
3
4
5
6
7
8
PROBLEMS (TIME)
SUBIC + ENTOR
HIPPOCAMPAL
CONTROL


LESION EFFECTS
WITHIN A PROBLEM
WMC ERRORS / TOTAL ERRORS
0.34
0.32
0.3
0.28
0.26
0.24
0.22
0.2
0.18
0.16
0.14
0.12
0.1
0.08
0.06
0.04
1
2
3
DAYS
SUBIC + ENTOR
HIPPOCAMPAL
CONTROL

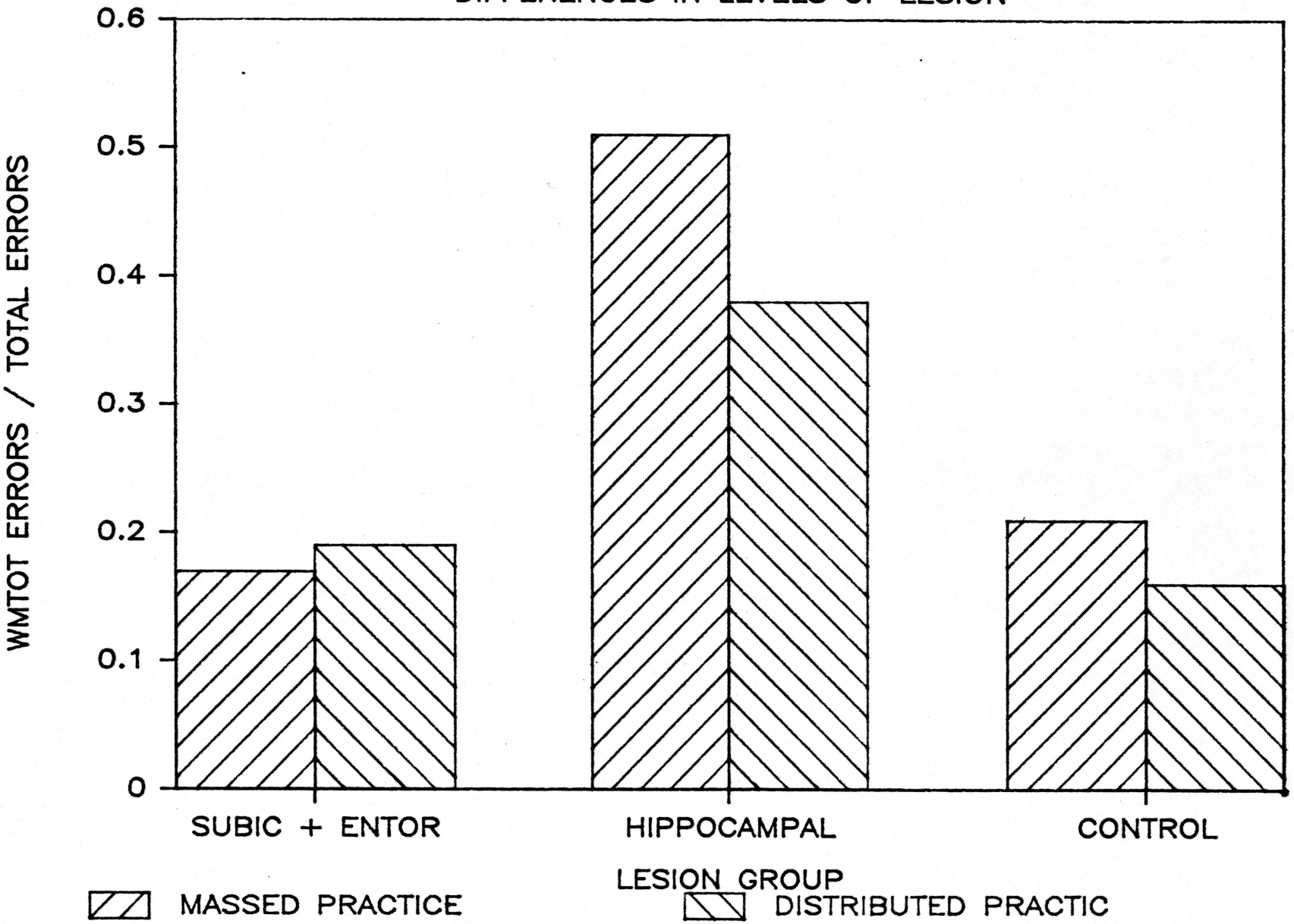
LESION EFFECTS

WITHIN A PROBLEM



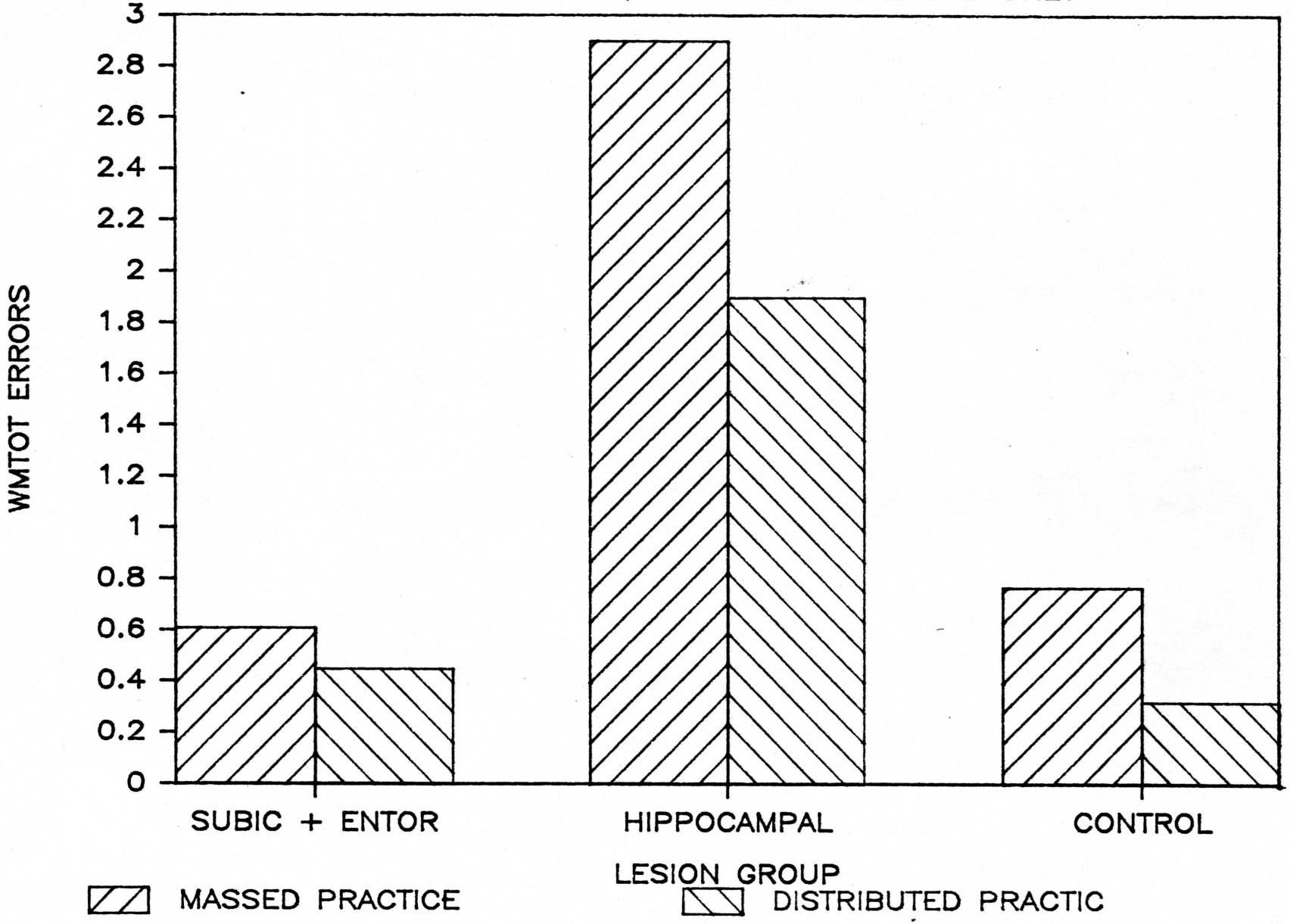
PRACTICE EFFECTS

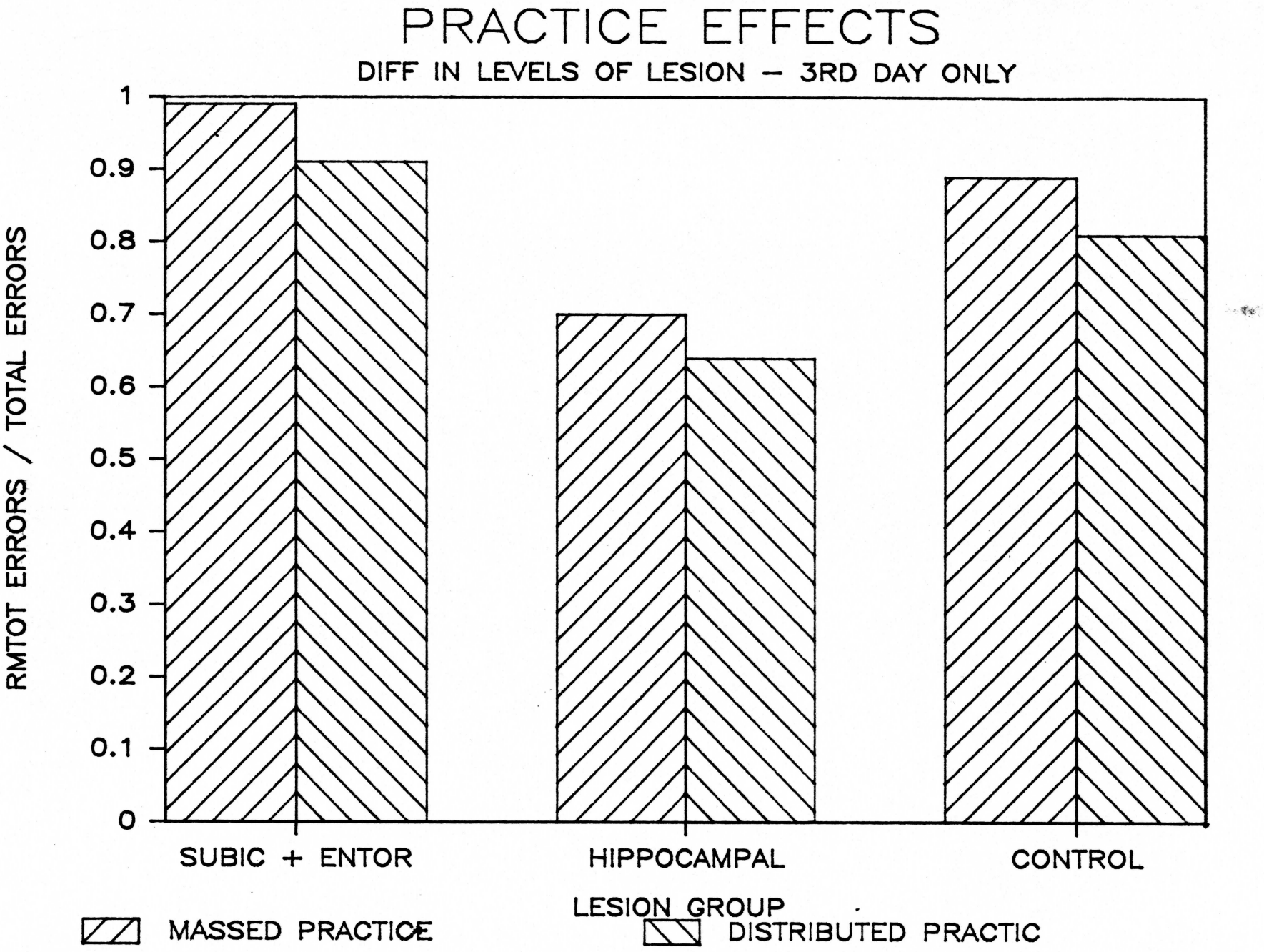
DIFFERENCES IN LEVELS OF LESION



PRACTICE EFFECTS

DIFF IN LEVELS OF LESION – 2ND DAY ONLY




PRACTICE EFFECTS
DIFF IN LEVELS OF LESION – 3RD DAY ONLY
RMTOT ERRORS / TOTAL ERRORS
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
SUBIC + ENTOR
HIPPOCAMPAL
CONTROL
LESION GROUP
MASSED PRACTICE
DISTRIBUTED PRACTIC