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The effects of thalamic, frontal cortical and hippocampal formation lesions on a delayed nonmatching to sample task

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The effects of thalamic, frontal cortical and hippocampal
formation lesions on a delayed nonmatching to sample task

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University of New Hampshire, 1994

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THE EFFECTS OF THALAMIC, FRONTAL CORTICAL AND
HIPPOCAMPAL FORMATION LESIONS ON A DELAYED
NONMATCHING TO SAMPLE TASK

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DISSERTATION

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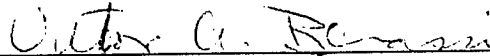
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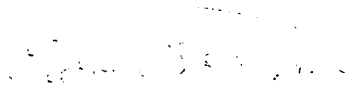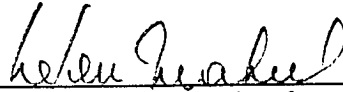
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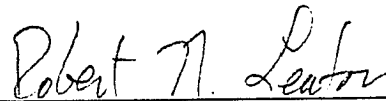
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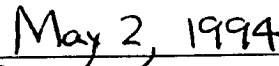
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DEDICATION

I dedicate this dissertation to those closest to me. To my parents and family Cecile, James, Jane and Bradley for establishing the possibilities while supporting my own path. To my dear brother Kevin who understood my point of view for many years and always guided me toward higher things. To my loving husband, Alan whose patience and understanding have made this dissertation possible. Your value of this project, particularly when I felt lost in the late hours, was in many moments solely what carried me closer to its completion. In doing this, you helped me to find my voice. Finally, to my son Winston, a look in your beautiful eyes and I know that one of the most significant gifts I can offer is further understanding of our world.

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ABSTRACT

THE EFFECTS OF THALAMIC, FRONTAL CORTICAL, AND HIPPOCAMPAL LESIONS ON THE DELAYED NONMATCHING TO SAMPLE TASK

By

Heather Leslie Young
University of New Hampshire, May 1994

Two areas of the brain have been implicated in global amnesia: the medial temporal lobe and the midline diencephalon (Squire and Zola-Morgan; Victor, Adams, and Collins, 1989). A third area of the brain, the prefrontal cortex, has more recently been included as a memory related area (Fuster, 1989).

The purpose of the study reported here was to further examine the neurological basis of the delayed nonmatching to sample place cue task (DNMTS-PC) deficit by comparing lesions in each of the three major areas attributed to memory processes. Patterns of impairments on the DNMTS-PC were further understood by manipulating retention and inter-trial intervals and by extensive pretreatment training. The effects of radio frequency lesions of the L-IML were compared to lesions in the MW and the dentate nucleus of the hippocampal formation (HP). DNMTS was measured with three retention intervals within session (0.4, 1.6, 6.4 s). Inter-trial interval was varied between sessions (0.8, 3.2, 12.8 s).

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L-IML, MW, and HP groups were significantly impaired on the initial 1008 trials. HP animals recovered their performance within the first 432 trials of post-surgical training. Following recovery of performance HP animals were not significantly impaired for the duration of post-surgical training. L-IML and MW animals continued to be impaired across different inter-trial interval manipulations.

L-IML lesions result in substantial impairment on the DNMTS-PC task. MW lesions also produced substantial impairment on the DNMTS-PC task. Although the effects of the L-IML lesion on the DNMTS-PC task can be accounted for by the MW lesion, when compared across studies MW lesions produced more selective impairments on working memory tasks than did L-IML lesions.

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INTRODUCTION

For nearly one-hundred years, it has been known that damage to certain areas of the brain can result in profound polysensory amnesia characterized by a nearly complete anterograde amnesia and a variable degree of pretraumatic retrograde amnesia (Amaral, 1987). The medial temporal lobe and diencephalon have been implicated (McKee & Squire, 1992; Squire & Zola-Morgan, 1991). A third area of the brain, prefrontal cortex, has more recently been included as a memory related area (Squire, 1987). Differences in the underlying neuropathology of medial temporal lobe amnesia and diencephalic amnesia have been well documented (McKee and Squire, 1992). The medial temporal lobe, diencephalon and possibly the prefrontal cortex may make different contributions to normal memory. Alternatively, the areas may each provide the necessary components to a larger functional memory system in which amnesia results from damage to any part of the system. The following literature review investigates the anatomical and functional role of each of these areas of the brain as they relate to memory processes.

Overview of Memory Related Structures and Pathways

Medial temporal lobe

The memory related structures of the medial temporal lobe include the hippocampal formation and the amygdaloid complex. The hippocampal formation

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consists of the dentate gyrus, hippocampus proper, subicular complex, and the entorhinal cortex. These structures have a more primitive laminar structure than the neocortex and are classified as allocortex. The structures which fall under the grouping of the hippocampal formation, although similar in their laminar structure as compared to surrounding cortical regions, are somewhat arbitrary. It is likely that these structures are grouped together because they are "functionally interconnected by a series of powerful associational projections" (Amaral, 1987).

The structures of the hippocampal formation can be further described. The nomenclature of the subdivisions of the hippocampus varies greatly in the anatomical literature. These variations within the hippocampal formation are largely based on species. The hippocampal formation in humans is much larger than in other primates or rodents (Stephan, 1983). Amaral (1987) divides the hippocampus proper into two major fields, CA3 (cornu ammonis) and CA1[1], and includes a narrow CA2 region which borders CA3 and CA1. The subicular complex consists of three subdivisions: the subiculum proper, presubiculum, and parasubiculum. The entorhinal cortex also varies considerably in terms of number of fields across species.

The hippocampal circuit begins with the major input of axons received from the II and III layers of the entorhinal cortex. These fibers travel through the subiculum and terminate on dendrites of the granule cells of the molecular layer of the dentate gyrus. Granule cells of the dentate produce axons which

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[1]Amaral (1987) further elaborates that CA3 and CA1 are regio inferior and regio superior according to Ramon y Cajal's nomenclature based on Golgi preparations of the mouse and rabbit.

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terminate on CA3 pyramidal cells. CA3 pyramidal cells project to CA1. The CA1 field, in turn, projects to the subicular complex. Completing the circuit, the cells of the subicular complex project to the entorhinal cortex. The hippocampal circuit is referred to as the trisynaptic circuit (Amaral, 1987).

There are several cortical afferent projections to the hippocampal formation. The entorhinal cortex receives input from all major fields of the temporal lobe except the superior temporal gyrus (Van Hoesen, Pandya, and Butters 1975). The entorhinal cortex also receives input from orbitofrontal cortex and medial prefrontal cortex (Leichnetz and Astruc, 1975, 1976). The entorhinal cortex has been found to receive the major cortical input to the hippocampal formation. Apart from entorhinal cortical inputs, the subicular complex has been found to also receive direct cortical input (Van Hoesen et al., 1975). Amaral (1987) concludes that the cortical input to the hippocampal formation consists of sensory information from primarily polysensory association areas of the cortex.

The two major subcortical afferent projections to the hippocampal formation are the septal projections and the mammillary projections. The septal projections terminate in all areas of the hippocampal formation. The mammillary projections arise from supramammillary nuclei, project through the fimbria and terminate most heavily in the dentate gyrus. Other subcortical projections to the hippocampal formation include the amygdala, anterior nucleus of the thalamus, and brain stem (Hamilton, 1976). Amaral (1987) reports that in

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addition to the anterior nucleus of the thalamus, there are reciprocal midline thalamic nuclei connections with the hippocampal formation.

Hippocampal formation efferents include the fimbria/fornix, hippocampal commissures, septal nuclei, and anterior nucleus of the thalamus. The fibers of the fimbria/fornix travel from the hippocampus proper to the medial mammillary nucleus and the anterior nucleus of the thalamus (Hamilton, 1976). The entorhinal cortex and the subicular complex also project extensively to cortical areas (Swanson and Kohler, 1986 and Rosene and Van Hoesen, 1977). The subicular complex has been found to project to the parahippocampal gyrus, among other cortical locations. The parahippocampal gyrus, in turn, projects to many association areas within the primate brain (Van Hoesen, 1982). Amaral (1987) suggests that the parahippocampal gyrus provides a significant cortical input of polymodal sensory information. It may also act as a relay through the hippocampal formation and greatly influence cortical activity.

The second memory related structure thought to have a role in the medial temporal lobe amnesia is the amygdaloid complex. The subcortical complex sits between the inferomedial aspect of cortex and the lateral border of the hypothalamus. The nuclei of the amygdaloid complex include the lateral nucleus, central nucleus, medial nucleus, basal nucleus, cortical nucleus, accessory basal nucleus, and several nuclei that contain small, darkly stained neurons called the intercalated cell masses (Hamilton, 1976).

Intrinsic connections of the amygdaloid complex are not very well

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understood. Amaral (1987) summarizes the intrinsic circuitry as generally following a dorsomedial direction. The central nucleus receives the largest projection from the lateral, basal, and accessory basal nuclei. This projection is thought to be important because most of the neocortical projections to the amygdaloid complex terminate in these nuclei. The subdivisions are organized largely for independent action. This view is substantiated by the observation that the amygdaloid subdivisions frequently have antagonistic roles in eliciting of species-specific behaviors (Kaada, 1972).

The amygdaloid complex projects to the striatum but does not receive input from the striatum. The amygdaloid complex has extensive reciprocal projections throughout the brain. Reciprocal projections from the brain stem include the nucleus of the solitary tract, parabrachial nucleus, and the dorsal motor nucleus of the vagus medulla (Hopkins and Holstege, 1978). The raphe nuclei projects reciprocally to the amygdaloid complex. There are several projections between the hypothalamus and the amygdaloid complex, but not all of these projections are reciprocal. In the thalamus there are reciprocal connections between the mediodorsal nucleus, midline and intralaminar nuclei of the thalamus and the amygdaloid complex (Jones 1985). In the basal forebrain, there are reciprocal connections between the amygdaloid complex and the stria terminalis, substantia innominata, and nucleus of Meynert. The amygdaloid complex also has reciprocal connections with the hippocampal formation.

The amygdaloid complex projects to cortical areas than it receives from

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cortical areas. Cortical projections arise from the piriform cortex, perirhinal

cortex, the prelimbic and infralimbic areas of medial frontal lobe and the

orbitalfrontal regions. The temporal lobe provides extensive projections to the

amygdaloid complex including the temporal pole, anterior superior gyrus, rostral

inferotemporal cortex, and the parahippocampal gyrus. The information

regarding amygdaloid efferents is limited. Nevertheless, It has been established

that the frontal, temporal, insular, and occipital cortices receive direct input from

the amygdaloid complex (Amaral, 1987).

The organization of the hippocampus and amygdala differ in several

important ways. The intrinsic circuitry of the hippocampal formation is designed

for unidirectional serial processing, whereas the amygdaloid complex is organized

for more independent action. The amygdaloid complex is widely connected to

unimodal and polymodal information. The hippocampal formation primarily

receives information from polysensory association cortex.

Diencephalon

Two structures in the diencephalon that are frequently tied to memory

related processes are the mediodorsal nucleus of the thalamus (MDn) and the

mammillary bodies. The MDn is located in the middle third of the thalamus and

lies dorsal and medial to the internal medullary lamina of the thalamus (IML).

MDn receives input from several areas and projects to frontal association cortex.

There are significant differences in the MDn across phyla. The MDn differs

cytoarchitectonically between primates and non-primates (Markowitsch, 1982). In

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the primate, MDn is subdivided into a medial magnocellular area, a more lateral component called the parvocellular area, and a paralamellar area which is lateral and situated between the parvocellular area and the IML (Fuster, 1989). The parvocellular area is the largest region of the primate MDn (Amaral, 1987). In the rat, borders within the MDn are less well defined. Although a parvocellular area is not present and the presence of a paralamellar segment is questioned in the rat, there are distinct regions of lateral and medial areas (Markowitsch, 1982). These non-primate lateral and medial areas correspond to the magnocellular and parvocellular areas of the primate.

The most significant afferent from the MDn is to the prefrontal cortex (PFC). MDn afferents define the PFC (Markowitsch, 1982; Fuster, 1989). Given this intimate connection with PFC, it is important to note that the PFC increases in size and complexity, along with the MDn, with more advanced phyla (Fuster, 1989). This suggests that the role of MDn may differ substantially across phyla. Amaral (1987) describes the MDn frontal efferents: the magnocellular area projects to the medial and orbital surface, the parvocellular area projects to the dorsolateral area, and the paralamellar area projects to the frontal eye fields. The major inputs from MDn to frontal cortex are mostly reciprocal (Markowitsch, 1982). The projections are largely to cortical layers III and IV. The cortical projections to MDn originate in layer VI as with other cortical projections to specific thalamic nuclei. MDn also receives projections from the primary olfactory cortex, cortex of the temporal pole, inferotemporal cortex, superior temporal

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cortex, perirhinal cortex, entorhinal cortex, subiculum, parahippocampal gyrus, and the amygdaloid complex.

The subcortical connections are numerous. Amaral (1987) describes projections from the basal forebrain including the substantia innominata and basal nucleus of Meynert, hypothalamus, olfactory tubercle, reticular nucleus of the thalamus, ventral tegmental area, superior colliculus and several inputs from the brain stem.

Markowitsch (1982) raises an important issue when considering the MDn as a memory related structure. Specifically, he states that "one cannot rule out the possibility that passing fibers rather than the neurons of MDn itself carry the main burden for memory functions." Markowitsch includes the habenulointerpeduncular tract, IML, and the mammillothalamic tract as adjacent fibers passing through the area of MDn. The habenulointerpeduncular tract has not been found to have a role in memory related processes (Markowitsch, 1982). The mammillothalamic tract which projects from the mammillary bodies to the anterior nucleus of the thalamus will be considered within the context of the mammillary complex.

The IML is a system of myelinated axons which traverse the thalamus. The cell masses within the IML include the central medial, paracentral, and the central lateral nuclei. The posterior end of the IML includes the centre médian and parafascicular nuclei. The intralamina nuclei are classified as nonspecific nuclei (Kelly, 1985). Jones (1985) describes the intralamina nuclei as projecting

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heavily to the striatum and rather diffusely to many areas of cortex. The projections of the nonspecific nuclei terminate within layer I and VI and synapse with dendrites of layer III and V pyramidal cells. The cortical afferents to the nonspecific nuclei receive afferents from layer V. Jones (1985) note precise reciprocal projections between nonspecific thalamic nuclei and the areas of cortex that they innervate. The subcortical afferents to the IML arise from the basal ganglia, cerebellum, brain stem, and the spinal cord.

The mammillary bodies have also received consideration as memory related structures within the diencephalon. The mammillary complex is located in the posterior base of the hypothalamus. The mammillary complex includes the lateral mammillary nucleus and the medial mammillary nucleus which can be further subdivided (Hamilton, 1985). In non-primates, the medial nucleus is fused across the midline. In higher primates and humans, the medial nucleus is separate and bilateral. The mammillary complex is thought to be less differentiated in primates than it is in rodents. The patterns of connectivity are similar, however (Amaral, 1987). One difference in the intrinsic circuitry is that the dendrites of the medial mammillary nucleus are confined to the nucleus, whereas some of the dendrites of the lateral mammillary nucleus leave the nucleus.

Afferent projections of the mammillary complex originate in the hippocampal formation, by way of the post commissural fornix, and the dorsal and ventral tegmental nuclei of the midbrain. Of the fornix fibers, the medial mammillary nuclei receives input from the presubiculum, subiculum proper and

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entorhinal cortex. The lateral mammillary complex receives input from the presubiculum (Swanson and Cowan, 1977). Irle and Markowitsch (1982) suggest the possibility of cortical input to the mammillary complex from the cingulate and prefrontal cortex. In addition, they suggest various subcortical afferents including septal nuclei and MDn.

Both the medial mammillary nucleus and the lateral mammillary nucleus project via the mammillothalamic tract to the anteriormedial nucleus of the thalamus and to the tegmentum via the mammillotegmental tract. It should be noted that the mammillothalamic tract provides a significant link in the Papez circuit. There is also a lesser projection from both nuclei through the medial forebrain bundle to the septal nuclei. It has been suggested that cells of the lateral mammillary nucleus project to cortex near the principal sulcus and to the amygdaloid complex (Amaral, 1987).

The MDn and mammillary complex are repeatedly cited as memory related structures. These structures are not known to be connected, if at all. The importance of these structures for memory will be reviewed below.

Prefrontal cortex

Whether the PFC is found to have a direct contribution to memory or whether its role is more limited to temporal integration it is a significant area with regard to polysensory amnesia. The PFC is a large polymodal association area which lies anterior to the precentral and premotor areas (Brodmann's areas 4 and 6). PFC in humans includes Brodmann's area 8, 9, 10, 11, 44, 45, 46, and 47

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(Goldman-Rakic, 1987) and consists of granular cortex. By hodological criteria, the PFC is defined as the area of the cerebral cortex which receives projections from MDn (Leonard, 1972). This definition applies to all mammals. The PFC varies considerably across species. It occupies proportionally greater areas of cerebral cortex with phylogenetic development. Using Fuster's definition, PFC in the rat is comprised of two discontinuous areas of projection of MDn, a medial area in the medial surface of the hemisphere, and an orbital area in the lower and lateral aspect of the hemisphere. A definite granule layer IV is absent in either of the two rodent PFC areas.

The significant subcortical connections have been reported above. Cortical connections with PFC include projections from basically all areas of the association cortex. The olfactory cortex projects directly to PFC. Thus all types of sensory information converge in the PFC. PFC projects to the temporal cortex and limbic cortex including superior temporal gyrus, superior temporal sulcus, temporal polar cortex and cingulate gyrus. There are projections to sensory cortex from PFC to inferior parietal lobule (Damasio and Anderson, 1993).

Review of Human and Nonhuman Animal Studies

Medial Temporal Lobe Amnesia

The most noteable case of medial temporal lobe damage resulting in global amnesia was first reported in 1953 when patient H.M. underwent a bilateral medial temporal lobectomy (Corkin, 1984). Approximately 8 cm of hippocampal

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tissue was removed, including the prepiriform gyrus, uncus, amygdala, hippocampus and the parahippocampal gyrus. An extensive amount of empirical and theoretical work has been based on this original case. Penfield and Milner, (1958) report two cases in which both patients developed severe amnesia following a left medial temporal lobectomy. It has been concluded that a positive correlation exists between the severity of the memory deficit and the extent of the damage to medial temporal lobe (Milner, 1974).

Human Studies

Patient H.M. exhibits a pure amnesic syndrome. His IQ was normal postsurgically. The gap between IQ and memory quotient (MQ) was 30 points. This gap, albeit a rough measure, was highly suggestive of memory deficits in the presence of otherwise intact intellectual capacities. He has maintained a normal IQ for 30 years. His performance on the Wisconsin Card Sorting Test is normal. He did not perseverate his responses. H.M. exhibited some spatial ability deficits such as impairment on the hidden figures test and visual locomotor test. He was able to draw a map of the Clincial Research Center where he was tested and various homes in which he has resided (Corkin, 1984). The extent of H.M.'s surgery has prompted researchers to question whether the hippocampus is the critical structure responsible for medial temporal lobe amnesia. Horel (1978) suggested that the surgical procedure used in H.M. and subsequent attempts at an animal model of medial temporal lobe amnesia undoubtedly damaged the temporal stem. Thus he argued that the temporal stem was as the critical

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substrate for medial temporal amnesia. Animal findings (Zola-Morgan, Squire and Mishkin, 1982) and an interesting human case involving an ischemic episode have invalidated the temporal stem argument.

Patient R.B. suffered from an ischemic episode which resulted in brain damage including two unilateral lesions, one in globus pallidus and another in sensorimotor cortex, and bilateral lesions of the hippocampus proper. These bilateral lesions were restricted to area CA1. This lesion was considered significant enough to completely disrupt the unidirectional flow of information in the trisynaptic circuit of the hippocampal formation (Squire, 1991; Squire, 1987). R.B. maintained a normal IQ but suffered a severe memory impairment as indicated by a 20 point gap between IQ and MQ. R.B. did not exhibit any frontal deficits or language impairments. This case was important because the lesion was limited to CA1 in the presence of a significant amnesic syndrome.

More recently, patients with medial temporal damage resulting from anoxia or ischemia were found to be impaired on tasks designed for monkeys. Patients were impaired on a delayed nonmatching-to-sample for trial unique objects (DNMTS-TUO), object-reward association, 8-pr concurrent discrimination learning, and object discrimination (Squire, Zola-Morgan and Chen, 1988).

The rate at which information is forgotten is one aspect of the amnesic condition. H.M. exhibited an abnormally fast rate of forgetting when assessed by Huppert and Piercy (1978, 1979). H.M.'s increased rate of forgetting was compared with several Korsakoff patients' rate of forgetting which were found to

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be normal. These observations resulted in the conclusion that medial temporal lobe damage increases the rate of forgetting, whereas diencephalic damage as seen in Korsakoff patients does not result in fast forgetting. A more recent study of temporal decay in long-term memory reported equivalent rates of forgetting for both medial temporal lobe and Korsakoff patients (McKee and Squire, 1992). The evidence that medial temporal lobe damage results in increased rates of forgetting is not conclusive. Additional research is required to fully understand this component of the amnesic syndrome.

Primate Studies

Substantial primate research has been conducted in the development of an animal model of medial temporal lobe amnesia. Utilizing the DNMTS-TUO task, several researchers have reported significant memory deficits in monkeys with lesions of the hippocampal formation(Mishkin, 1978; Mahut, Zola-Morgan and Moss, 1982; Murray & Mishkin, 1984; Zola-Morgan & Squire, 1986). In addition to impairment on the DNMTS-TUO several studies have founf medial temporal lobe monkeys to be impaired on other tasks including, object discrimination, 8-pair object discrimination (Zola-Morgan and Squire, 1985), object reward association (Phillips and Mishkin, 1984). Monkeys with hippocampal lesions were not impaired on the pattern discrimination or motor skill learning task (Zola-Morgan and Squire, 1984).

Deficits attributed to areas associated with amensia can be understood in terms of the working and reference memory subdivisions. The working memory

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and reference memory subdivisions capture systematic differences in many of the tasks described in this review. Working memory consists of a memory buffer where information is maintained while it is being processed (Baddeley, 1986). Reference memory consists of memory for a specific rule or strategy once it has been acquired. Humans and other animals suffering from global memory deficits have impaired working memory, although they retain a capacity for reference memory. Lesions to the medial temporal lobe can result in two types of working memory deficits on the DNMTS task. These deficits can be catergorized as delay dependent and delay independnent working memory deficits. The DNMTS task involves presentation of a sample stimulus, and then removal of the sample stimulus. A delay occurs and then presentation of two stimuli occurs, one of which was the original sample stimuli. A response to stimuli which was not the original sample stimuli is rewarded. The demands placed on working memory in the DNMTS task are to remember the sample stimuli during the delay. Thus, the stimulus information in a working memory task is useful for one trial but not subsequent trials (Honig, 1978). The delay dependent impairment is characterized by rapid forgetting. Delay independent impairment is characterized by poor performance across all delays. In a reference memory task, stimulus response contingencies are consistent across several trials. The strategy for responding on a reference memory task is the same on every trial. The ability of medial temporal lobe monkeys to perform pattern discrimination and motor skill tasks suggests that their reference memory is intact.

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The challenge has been to determine what anatomical damage is responsible for the working memory deficits. Much of the primate literature has focused on determining the relative contributions of lesions of the hippocampus and the amygdala. Lesions of the hippocampus that included the dentate gyrus, subicular cortex, the parahippocampal gyrus, and the posterior entorhinal cortex produced significant impairment working memory tasks. Lesions of the hippocampus and amygdala however, produced larger impairments on working memory tasks (Mishkin, 1978; Mahut, Zola-Morgan and Moss, 1982; Zola-Morgan and Squire, 1986).

The effects of lesions restricted to hippocampus has been somewhat variable. Some studies have reported moderate deficits on the DNMTS task resulting from the hippocampal lesion (Mishkin, 1978; Murray and Mishkin, 1984), whereas other studies have reported more severe hippocampal impairments on the DNMTS task (Zola-Morgan and Squire, 1986; Mahut, Zola-Morgan and Moss, 1982). Squire, (1987) offers an interesting argument regarding this disparity. Those studies which exhibited less severe impairments included preoperative training. He suggests that preoperative training enhances the animals' ability to perform the DNMTS task by enhancing the basic principles involved in the task. Animals may actually employ strategies as a result of preoperative training, such as maintaining sample information in working memory. Maintenance of sample information in working memory would enhance for short retention interval trials, but would not affect longer delays according to Squire

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(1987).

Although the hippocampus lesion does produce significant deficits on the DNMTS task, it is the combined hippocampal and amygdala lesion which results in the most severe memory impairment. The combined hippocampal and amygdala lesion tends to include extensive damage to the rhinal cortex (entorhinal, prorhinal, and perirhinal cortex). Lesion studies which included rhinal cortical removal along with the hippocampectomy have not report additional impairments than those found in the hippocampectomy alone (Mishkin, 1978). Lesions of the amygdala that included rhinal cortex removal resulted in substantially more impairment on the DNMTS task (Murray and Mishkin, 1986). The effect of amygdala and rhinal cortex removal is as severe as the combined effect of the hippocampal and amygdala lesion. Murray and Mishkin (1986) conclude that removal of the rhinal cortex is equivalent to removal of the entire hippocampal formation because the rhinal cortical lesion, particularly the entorhinal, disconnects the hippocampus from its neocortical input. In addition, monkeys with combined amygdaloid and hippocampal ablations that spare rhinal cortex exhibit less impairment than monkeys that have had amygdaloid and hippocampal ablations that do not spare the rhinal cortex (Murray, Bachevalier and Mishkin, 1985). More recently, Gaffan and Murray (1992) report that monkeys with rhinal cortex lesions failed to learn a delayed matching to sample (DMTS) task although they performed normally on a 24-hr concurrent learning task.

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Friedman and Goldman-Rakic, (1988) used a different approach to investigate the role of medial temporal structures in working memory tasks. Using the 2-deoxyglucose method of functional mapping they have examined the metabolic rate of the dentate gyrus and hippocampal subfields in monkeys trained to perform working memory tasks and control tasks which did not rely on working memory. The working memory tasks included a delayed spatial response task, a delayed spatial alternation task, and a delayed object alternation task. Control tasks consisted of an associative memory problem, visual pattern discrimination and a sensory-motor task. The metabolic rate increased 18 to 24% in the dentate gyrus, CA1 and CA3 of the hippocampal formation of monkeys performing delayed response tasks. No significant increase was recorded in the 7 amygdaloid nuclei examined. This study further supports a significant role of the trisynaptic path in completion of working memory tasks.

Review of studies examining the effects of lesions in the medial temporal lobe of nonhuman primates indicates that medial temporal lobe lesions consistently produce impairment on delayed conditional discrimination tasks. The extent of impairment resulting from medial temporal lobe lesions has varied across several studies. Destruction of the hippocampus, the hippocampus and amygdala, and the rhinal cortex have each resulted in impairment on the DNMTS task.

Rodent Studies

Rats with hippocampal lesions have been impaired on several tasks,

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including the Morris water maze (Sutherland and McDonald, 1990), odor discrimination (Eichenbaum, Fagen, and Cohen, 1986), spatial alternation (Aggleton, Hunt and Rawlins, 1986), nonspatial alternation (Aggleton, Blindt, and Rawlins, 1989), and the radial arm maze (Becker, Walker, and Olton, 1980; Olton, Becker, and Handelmann, 1979). In contrast to the monkey literature, rats with amygdala lesions were not impaired. In addition, the inclusion of amygdala lesions to the hippocampal lesions did not increase impairments (Sutherland and McDonald, 1990; Eichenbaum, Fagen, and Cohen, 1986; Aggleton, Hunt and Rawlins, 1986). One exception to these findings is reported by Aggleton, Blindt, and Rawlins (1989) where conjoint lesions of the hippocampal formation and amygdala impaired performance on an object recognition task. Individual lesions of the hippocampal formation or the amygdala did not impair performance.

A major direction of the rodent hippocampal research has been the study of performance on spatial tasks (O'Keefe and Nadel, 1978). Rats have been consistently impaired on tasks with spatial components (Black, Nadel, and O'Keefe, 1977; O'Keefe and Black, 1974; O'Keefe and Nadel, 1978). Single unit recordings of free moving rats have also contributed to this literature. Neurons within the hippocampus referred to as 'place cells' have firing rates that are a function of the absolute space occupied by the animal. As an animal moves to a particular location in his environment, different hippocampal complex-spike cells are activated maximally (Eichenbaum and Cohen, 1988). The lesion and single unit recording research have culminated into a comprehensive proposal regarding

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the function of the hippocampus. The basic theory is that the hippocampus forms and stores a map of the animal's environment (O'Keefe and Nadel, 1978). The spatial mapping theory has generated a great deal of controversy regarding the role of the hippocampus. It is clear from the human and primate literature that damage to the medial temporal lobe results in more than a spatial impairment. H.M. was impaired on spatial tasks such as learning mazes, but he was also impaired on nonspatial tasks such as object recognition. Monkeys with hippocampal and amygdala damage have been impaired on delayed response tasks which require memory for spatial location and on DNMTS which require memory for objects and temporal order (Zola-Morgan and Squire, 1985).

By independently manipulating the spatial and memory demands of the radial arm maze, Olton, Becker, and Handelmann, (1979) investigated the functional role of the hippocampal formation in rats. Animals with hippocampal formation lesions or lesions of the fimbria/fornix were impaired on both the spatial version and nonspatial version of the radial arm maze. Rats with hippocampal formation or fimbria/fornix lesions were not impaired on the reference memory version of the task. By controlling for the spatial demands of the radial arm maze task, this study demonstrated that rats with hippocampal formation or fimbria/fornix lesions were also impaired on the nonspatial components of the radial arm maze. This study is significant because it demonstrates that the functional role of the hippocampal formation of the rat is not limited to the mapping and storage of spatial information.

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The functional role of the hippocampus may vary across species. The functional role of the rodent hippocampus may largely be related to the mapping and storing of spatial information. However, the research findings suggest that processing of spatial information is not the primary role of the rodent hippocampus. Review of the literature also suggests that human and nonhuman primates with damage to the hippocampal formation, hippocampal formation and amygdala, or rhinal cortex exhibit spatial and nonspatial impairments on delayed conditional discrimination tasks.

Diencephalic Amnesia

Korsakoff's disease, which results in global memory impairments, is the most frequent cause of diencephalon amnesia (Victor, Adams and Collins, 1989). Korsakoff first reported a comprehensive description of global amnesia in 1887. The primary etiological factor in Korsakoff's disease is thiamine deficiency (Malamud and Skillicorn, 1956). Korsakoff's disease is the chronic phase of the Wernicke-Korsakoff syndrome. The acute phase referred to as Wernicke encephalopathy is a nervous system disorder with abrupt onset. It is characterized by nystagmus, abducens and conjugate gaze palsies, unsteadiness in gait and a confusional state (Victor et al., 1989). With restitution of nutritional status, the severe neurologic symptoms diminish and the confusional state clears, leaving the amnesic symptoms of Korsakoff's disease. In a study examining 245 patients with Wernicke encephalopathy, 186 survived. Of those 186 surviving patients, 84% developed the symptoms of Korsakoff's disease (Victor et al., 1989). Diencephalic

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amnesia has also been observed in patients with third ventricle tumors (Williams and Pennybacker, 1954), thalamic infarct (von Cramon, Hebel, and Schuri, 1985), and accidental trauma (Squire and Moore, 1979).

Human studies

The pathology underlying Korsakoff's disease varies from patient to patient. Victor, et al., (1989) reported pathology in the cerebral cortex, mammillary bodies, several thalamic nuclei, mesencephalon, pons, and the cerebellum.

Determining the neural substrate of the memory deficits in Korsakoff's disease has been very difficult because of the variability of the lesions from patient to patient. The amnesic symptoms of Korsakoff's disease have been attributed to three different systems: ascending neurochemical systems (Mair et al., 1985; McEntee and Mair, 1990), the mammillary complex, and the MDn (Victor et al., 1989; Markowitsch, 1982). Investigations of the noradrenergic pathways ascending from the locus coeruleus have not provided conclusive evidence for a neurochemical role in Korsakoff's disease. The effect of giving Korsakoff patients adrenergic agonist drugs such as clonidine has not been consistent. Mair and McEntee (1983) report that Korsakoff patients' performances on short term memory and attention were enhanced by clonidine. However, Clonidine failed to enhance cognition in O'Carroll et al., (1992).

Mammillary bodies are frequently damaged in Korsakoff's disease, although the mammillary complex is usually not the sole locus of damage (Squire,

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1987). Victor, et al., (1989) reported that where 5 of their patients had

mammillary body lesions but not medial thalamic lesions, recovered from acute

Wernicke phase without signs of amnesia. In all cases reviewed, medial thalamic

lesions were found to be damaged when amnesia was observed. Although Victor,

et al., strongly argue in favor of the role of the MDn, Mayes, Meudell, Mann and

Pickering (1988) state that these findings could indicate that a medial thalamic

lesion is necessary for amnesia, or that a conjoint mammillary body and medial

thalamic lesion is necessary for amnesia. Mair, Warrington, and Weiskrantz

(1979) report that one of their patients had well established retrograde and

anterograde amnesia, but the lesions were limited to the mammillary complex and

the parataenial nuclei of the thalamus. Mayes et al., (1988) studied two patients

with varying degrees of amnesia. Both patients had extensive cell loss of the

mammillary bodies. In addition, there was a narrow band of gliosis present

bilaterally at the area of the parataenial nuclei. Independently, neither the Mayes

et al., (1988) nor the Mair et al., (1979) study can determine the role of the

mammillary complex in diencephalic amnesia. However, considering these studies

together with the findings of Victor et al. (1989), there is strong evidence against

the mammillary complex and in favor of a thalamic role in diencephalic amnesia.

The most frequently occurring lesion in Korsakoff patients reported

by Victor et al., (1989) is found in the MDn. This very consistent pathological

finding has led many investigators to attach a causative relationship between MDn

lesions and memory impairments. Given the variation of pathology observed in

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Korsakoff's disease, it is not presently possible to conclude that the MDn is responsible for memory deficits. Areas adjacent to the MDn, such as the IML, or medial pulvinar must also be considered. In a study examining thalamic infarction, von Cramon et al., (1985) found that patients with large MDn lesions resulting from paramedian infarction did not suffer from memory deficits. The authors also report that patients with damage to the IML, mammillothalamic tract and minor involvement of MDn did suffer from memory impairments.

While there is a strong argument in favor of a thalamic role in diencephalic amnesia, the variation of Korsakoff pathology makes it very difficult to conclude which area of thalamus is directly involved with memory deficits.

Neuropsychological findings

The pattern of memory impairments in diencephalic amnesia is very consistent across patients. The chronic amnesic state can be characterized by two important features: temporally graded pretraumatic amnesia and anterograde amnesia. In addition to memory impairments, Korsakoff's patients have been found to perform poorly on some attention and perception tasks (Cermak, 1984; Victor et al., 1989; Young, 1991). The mood of Korsakoff's patients can be described as rather placid, and they tend to have flat affect (Talland, 1965; Young, 1991).

Psychometric testing of IQ and MQ of Korsakoff patients results in very significant mean differences between IQ and MQ (Victor et al., 1989; Mann et al., 1988; Talland, 1965,). This gap strongly indicates that while memory processes

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are severely impaired, other cognitive functions are relatively spared. Of the Wechsler Memory Scale subtests, paired associates were most severely impaired and story recall and visual reproduction were severely impaired (Talland 1965; Butters and Cermak, 1976; McEntee, Mair, and Langlais, 1984; Victor et al., 1989). These findings correspond to the observations that Korsakoff patients cannot learn or retain very basic information such as the name of their examiner, date, location, or the time of day (Victor et al., 1989; Young, 1991). Regardless of how many times information is repeated, Korsakoff patients cannot learn the names of persons, objects, or nonsense syllables (Victor et al., 1989). The only types of new information Korsakoff patients have been reported to acquire were very simple motor tasks such as the mirror trace drawing task (Squire, 1987). Retrograde memory has been measured with the familiar faces test (Talland, 1965), famous voices test (Mann et al., 1988), and remote public events test (Mann et al., 1988). Results from retrograde assessment were variable but generally remote memories were better recalled than more recent memories.

Korsakoff patients have been found to be impaired on many tasks which rely on working memory. Performance of Korsakoff patients have been impaired on measures of DNMTS and DMTS tasks designed for monkey studies (Aggleton et al., 1988; Squire et al., 1988; Oscar-Berman and Bonner, 1985). In Squire et al., (1988), impairments were observed at retention intervals as brief as 5 s. Korsakoff patients were also observed to have an increased rate of forgetting as compared with controls.

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The performance on story recall on the Wechsler Memory Scale is evidence of rapid forgetting. Additional evidence is found in the observation that Korsakoff patients forget information very quickly that is repeated frequently, such as an examiner's name or the patient's own location. Cave and Squire, (1992) report that Korsakoff patients were impaired on digit span. These observations conflict with reports that Korsakoff patients had normal performance on digit span (Victor et al., 1989). They also conflict with studies comparing medial temporal lobe and diencephalic amnesics on rate of forgetting (Huppert and Piercy, 1978, 1979; McKee and Squire, 1992) that have been described above. Rate of temporal decay can have a significant impact on amnesia. Increased rates of temporal decay can affect short-term memory, and thus severely impair a person's ability to move information from short-term memory to long-term memory, which directly contributes to anterograde amnesia. Whether or not an increased rate of forgetting is contributing to the memory impairments observed in Korsakoff's disease is unknown.

Korsakoff patients have also been found to be impaired on the Wisconsin Card Sorting Test (Joyce and Robbins, 1991; Mann et al., 1988). This test is traditionally used to assess prefrontal dysfunction. Although it is not typically classified as a working memory task, Goldman-Rakic, (1993) argues that the Wisconsin Card Sporting Test places demands on working memory. In spite of the fact that information regarding color, shape and size is present, no information concerning the correct choice is present. Therefore, one must

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maintain a representation to guide the correct choice in working memory. Alternatively, one could argue that the Wisconsin Card Sorting Test requires the same response strategy across several trials, and therefore it should be classified as a reference memory task.

Joyce and Robbins (1991) compared Korsakoff patients with alcoholic and non-alcoholic controls on the Tower of London task, a spatial working memory task, and the Wisconsin Card Sorting test. The Tower of London task is a planning task which is used to measure prefrontal dysfunction. Korsakoff patients were impaired on the spatial working memory task, Tower of London task and the Wisconsin Card Sorting Test. Joyce and Robbins argue strongly in favor of a disturbance in frontal-lobe function in Korsakoff's disease.

In contrast to the consistent working memory deficits observed, Korsakoff patients have a spared capacity for tasks that place demands on reference memory. Most significant is the Korsakoff patient's ability to utilize semantic memory (Squire, 1987). Korsakoff patients' reference memory has been assessed using a task similar to the serial reversal learning tasks used in animal studies. Korsakoff patients were found to perform to criterion once the initial discrimination was learned on serial reversal learning tasks (Oscar-Berman and Zola-Morgan, 1980).

Primate studies

Aggleton and Mishkin (1983a) reported severe primate memory deficits on the DNMTS-TUO task following medial thalamic lesions. These lesions included

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the anterior nucleus, midline nucleus, mammillothalamic tract and the anterior portion of the MDn. Retrograde degeneration of the mammillary nuclei occurred as a result of the damage to the anterior nucleus and mammillothalamic tract. Aggleton and Mishkin (1983b), studied the effects of smaller bilateral thalamic lesions in a subsequent study which included the anterior portion of the MDn and adjacent midline nuclei. The lesions excluded the anterior nucleus, did not involve degeneration of the mammillary bodies, and produced moderate impairment. Zola-Morgan and Squire (1985) also report significant memory impairment utilizing a DNMTS-TUO task with small bilateral lesions in the posterior portion of the MDn, and no damage to the adjacent midline nuclei. The literature supports the role of MDn as a significant contributor to the neuropathology and behavioral impairment of diencephalic amnesia. However, one should not dismiss concerns raised by Markowitsch, (1982) and Amaral (1987) regarding damage to the nonspecific nuclei of the IML which frequently accompany MDn lesions.

Rodent studies

Pyrithiamine-induced deficiency (PTD) has been used to produce an animal model of diencephalic amnesia. A thiamine-deficient diet in conjunction with daily injections of pyrithiamine will result in lesions in similar areas of the brain as found in Korsakoff's disease. Histological analyses have shown that the PTD treatment produces consistent bilaterally symmetrical lesions in the thalamus and the mammillary bodies. The thalamic lesions were centered on the IML and

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included intralaminar nuclei and portions of the MDn in addition to the paralaminar nonspecific nuclei. Mammillary body lesions were centered on the medial mammillary nuclei.

PTD behavioral performance was directly correlated with the extent of the IML lesion. Behavioral impairment did not result in rodents when portions of the IML were spared (Mair, 1994). PTD animals with near-complete destruction of the IML were impaired on learning several tasks, including: passive and active avoidance (Mair, Anderson, Langlais, and McEntee, 1985), serial reversal learning (Mair, Knoth, and Rabchenuk, 1991), the Morris water maze (Langlais, Mandel, and Mair, 1992), and the radial arm maze (Robinson and Mair, 1992). PTD treated animals were impaired during acquisition of these tasks, but achieved criterion with additional training. PTD animals have been assessed on delayed conditional discrimination tasks based on place cues. The PTD animals performed significantly worse than controls on DNMTS task based on place cues (DNMTS-PC) (Mair, Anderson, Langlais, and McEntee, 1988; Mair, Otto, Knoth, Rabchenuk and Langlais, 1991; Robinson and Mair, 1991) and on the DMTS task based on place cues (Mair, Knoth, Rabchenuk, and Langlais, 1991). Impairments on the conditional delayed discrimination tasks did not improve with additional training.

The pattern of impairment established with the PTD treatment is consistent with that observed in Korsakoff patients. The PTD animals and Korsakoff patients have been found to be consistently able to reach criterion on

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the serial reversal learning task, a task which places demands on reference memory. Both PTD animals and Korsakoff patients were consistently impaired on delayed conditional response tasks which place demands on working memory. PTD animals did not exhibit a rapid temporal decay on the DNMTS-PC task. Given the variation in observations of rapid forgetting in Korsakoff patients, it is not known whether this finding is significant.

The importance of thalamic pathology has been further verified by investigation of radio-frequency lesions. Mair and Lacourse (1992) studied the locus of brain lesions in the PTD treatment. This study included lesions of the midline, L-IML, medial mammillary nuclei, and the combination of midline and medial mammillary nuclei. L-IML animals were found to be impaired on the DNMTS-PC task. Normal performance was observed in animals with lesions of the medial mammillary nuclei and medial mammillary nuclei, combined with midline nuclei lesions. These findings indicated that the limbic-related pathways running through the fornix via the mammillary nuclei to the thalamus were probably not contributing to the DNMTS-PC deficit of L-IML or PTD lesioned animals. Mair and Lacourse (1992) also investigated the effect of fornix lesions at the level of the septum on the DNMTS-PC task. Although fornix lesions produced impairment on the DNMTS-PC task, the extent of this imapirment was not sufficient to account for the DNMTS-PC deficit found in the PTD model. Not only is the extent of hippocampal-related pathways damage much greater in the fornix lesion at the level of the septum than is found in the PTD model, but

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the extent of the DNMTS-PC impairment is much less than the impairment produced by the PTD treatment. On the other hand, the L-IML lesions were found to be quantitatively sufficient to account for deficits incurred by the PTD treatment. A study further examining the role of L-IML lesions in the DNMTS-PC task compared partial vs. complete lesions of the L-IML site. Partial lesions were aimed at detroying either the anterior half of the L-IML or posterior half of the L-IML lesions (Mair et al., 1992). Complete L-IML lesions impaired performance on DNMTS-PC, whereas lesions of the anterior or posterior portion of the L-IML did not. This suggests that L-IML site hits a critical substrate that is necessary for the processing required on DNMTS-PC.

Kivlahan (1992) examined the rate of temporal decay in rats on the DNMTS-PC task with L-IML, MDn and fornix lesions. Animals with the L-IML lesion performed significantly worse than other animals. Using all response data, L-IML animals were found to have faster rates of temporal decay than the MDn, fornix and control animals.

An important methodological consideration, the relationship between RI and ITI with respect to rate of temporal decay, has not been addressed in the animal or human amnesia literature. Frequently, ITI is not manipulated in studies of extensive memory impairments. Other areas of forgetting research have manipulated ITI, and report that as ITI is decreased, performance is impaired in pigeons (Maki, Moe, and Bierly, 1977; Edhouse and White, 1988), monkeys (Jarrad and Moise, 1971), and dolphins (Herman, 1975). The extent to which

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proactive interference accounts for impairment can be investigated by manipulating the ITI. Each of these studies utilized a delayed matching-to-sample task. The relationship between RI and ITI on the DNMTS-PC task has not been systematically studied.

It is not clear which systems that are disrupted by the L-IML leison are contributing to the DNMTS-PC deficit. One possibility is disruption to the thalmocortical connections. The cortical denervation resulting from radio-frequency lesions of the L-IML, has been investigated using Fink-Heimer staining (Zhang, 1992). Complete L-IML lesions were found to disrupt projections to both medial wall (MW) and rhinal sulcus (RS) areas of the prefrontal cortex. Areas of the prefrontal cortex are defined in terms of MDn projection sites. The projections of the MDn which transverse the L-IML are subdivided into specific areas. The lateral segment of the MDn projects preferentially to the MW area in the upper edge and the medial surface of the hemisphere, which is referred to as the medial wall area. The central segment of the MDn projects to the dorsal bank of the rhinal sulcus (Kolb, 1990; Fuster, 1991).

Most recently, Harrison (1992) investigated the role of thalamic projections to the prefrontal cortex on several tasks. This study investigated the performance of animals L-IML, MW and RS on the radial arm maze and a spatial serial reversal task. L-IML animals were impaired on both the radial arm maze and in the acquisition of the serial reversal of learning task. L-IML, MW and RS animals committed more errors during the initial learning of the spatial serial

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reversal but were able to reach criterion. A subsequent experiment examined the effects of lesions of the MW, and RS on the DNMTS-PC task. The MW lesion produced severe impairment on the DNMTS-PC task. Animals with RS lesions exhibited impairments on DNMTS-PC, although this group eventually performed comparably to controls with extensive post-surgical training. This experiment did not include a direct comparison with L-IML lesioned animals. The rate of temporal decay was not examined in this study. The extent to which a MW lesion can sufficiently account for rapid temporal decay as exhibited in the L-IML (Kivlahan, 1992) is also unknown.

The review of the literature provides consistent evidence that thalamic lesions are associated with working memory deficits on delayed conditional response tasks. Examination of specific patterns of impairment such as rate of forgetting, release from proactive interference, or the effect of extensive pre-surgical training on the DNMTS-PC task has not been systematically studied.

Frontal lobe syndrome

Damage to the frontal lobes can result in varying degrees of dysfunction depending on the source of damage and the location affected. Damasio and Anderson (1993) conclude that because of the variety and location of prefrontal lesions, no single frontal lobe syndrome truly exists. Fuster (1989) identifies two broadly defined PFC functional fields. These fields have quantitative differences in terms of behavior. A functional dissociation is thought to exist between the dorsolateral cortex including the sulcus principalis and the ventral cortex which

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includes the inferior convexity and orbital cortex.

<u>Human Studies</u>

Although a specific syndrome is difficult to define, there are consistent neuropsychological findings within functional fields. Personalty changes resulting from changes in higher cognitive processes and social behavior that permit appropriate decision making and planning are the most characteristic of frontal lobe patients.

Frontal lobe patients do not suffer from the same global memory impairments observed in medial temporal lobe or Korsakoff patients. Patients with PFC damage were able to recall prose and paired associates after a delay (Milner, 1967). Patients with focal, unilateral frontal lesions were normal at recalling spatial location of an array of 16 objects (Smith and Milner, 1984). Deficits arose when patients were required to remember the order of contextually similar events or recall any part of a group. Fuster (1989) describes this type of impairment as a disorder of temporal integration. He argues that it is the most distinctive disorder arising from PFC damage. The patient does not have difficulty in executing an old, well-rehearsed routine but cannot develop a new form of behavior based on deliberation and choice (Fuster, 1989). Milner (1982) examined cognitive impairments of patients that underwent unilateral frontal-lobe excisions for the relief of epilepsy. These lesions ranged from posterior dorsolateral frontal cortex to near-complete frontal lobectomies. Patients were impaired on spatial conditional associative learning and nonspatial conditional

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associative learning. This findings supports the idea that PFC patients are impaired in their ability to use external cues to guide behavior. These tasks place demands on the ability to temporally order a sequence of events. Patients were also impaired on a subject-ordered pointing task which examined the subjects' ability to initiate and keep track of their own responses. PFC patients with dorsolateral lesions were typically impaired on the Wisconsin Card Sorting Test. The most common finding in the dorsolateral patient is the tendency to perseverate. These patients could not switch to a new sorting principle. In contrast, patients with orbital frontal lesions have been found to perform normally on the Wisconsin Card Sorting Task (Milner, 1963). Milner (1971) compared PFC and medial temporal lobe patients on a task that required temporal integration. Patients were shown a series of 184 stimuli and intermittently tested on recognition and their ability to determine which of two stimuli had been presented more recently. PFC patients were impaired on judging recency but not on judging familiarity. Medial temporal lobe patients were not impaired on judging recency but impaired on judging familiarity.

Primate studies

The functional fields described by Fuster have been particularly well dissociated in ablation studies of the monkey. Monkeys with PFC lesions in the sulcus principalis and dorsolateral convexity were frequently impaired on the delayed response and delayed alternation (Goldman-Rakic, 1993). Historically, the impairment on the delayed response task and delayed alternation task has not

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been attributed to a memory deficit. More recently, there has been a shift toward defining the impairment of primates on delayed response or delayed alternation tasks as working memory deficits. Presently it is thought that working memory deficits in PFC monkeys on the delayed response and delayed alternation tasks result from the inability to perform integration within the tasks. Goldman-Rakic (1993) argues strongly in favor of a working memory deficit underlying the delayed response and delayed alternation impairments.

Further support for a working memory deficit has come from single unit recordings of monkeys in the PFC. Unit recordings of monkeys have established that neurons of the prefrontal cortex become activated during the delay period of a delayed response task (Fuster, 1980). Goldman-Rakic and colleagues have been utilizing an oculomotor delayed response task. Recordings have found that PFC neurons activated when the stimulus disappeared from view and maintained their activation until execution of the response occurred. She attributes the activation to a working memory process (Goldman-Rakic, 1993).

Monkeys with inferior convexity lesions of PFC suffered impairments on object reversal, object alternation and go-no-go discrimination tasks (Mishkin and Manning, 1978). These lesions also produced severe perservative tendencies. Monkeys with inferior convexity PFC lesions were unimpaired on the DNMTS-TUO, but were impaired on the traditional two object DMTS task. Squire (1987) suggests the discrepancy between performance on these two tasks was a result of whether the task was trial unique object or limited to two objects. DNMTS-TUO

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simply requires recognizing whether the object is familiar. The traditional DMTS

task requires a recency judgement. The demands on temporal discrimination may

contribute to the deficit. Squire also suggests the possibility that the requirements

of the DMTS task contradict the strong desire for the monkey to select the novel

stimuli.

Rodent studies

The functional dissociation between dorsolateral cortex and ventral cortex

of PFC described by Fuster (1989) is maintained in the rodent. The dorsomedial

sector which corresponds to the monkey's dorsolateral cortex is thought to bridge

discontiguities in time. The sulcal sector which corresponds to the monkey's

ventral cortex is thought to be involved in behavioral inhibition (Fuster, 1989).

Kolb and his colleagues compared the performance on the Morris water maze and

radial arm maze of rats with medial frontal lesions and MDn lesions. Animals

with medial frontal lesions were impaired on both the Morris water maze and the

radial arm maze. MDn animals were not impaired on either task. Kolb

concludes that this finding is the first unequivocal evidence of a spatial orientation

deficit following PFC lesions in the rat. Kolb (1990) reports that the spatial

orientation deficits observed as a result of medial PFC lesions are also similar to

deficits in animals with hippocampal lesions. He concludes that the hippocampus

and medial PFC area may form an integrated system for learning and using spatial

representations in the environment. Kolb (1990) reports that rats with medial

PFC lesions but not orbital lesions were impaired on delayed response, delayed

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alternation and DNMTS tasks. Kolb concludes that the deficits of the delay tasks are likely related to working memory processes that hold information "on line" during a temporal interval.

A direct comparison of the three major memory related areas on the DNMTS

Differences in the underlying neuropathology of medial temporal lobe amnesia and diencephalic amnesia have been well documented, although distinct patterns of memory loss have not been thoroughly established (McKee and Squire, 1992). There is consistent evidence that damage to the medial temporal lobe, PFC, and diencephalon results in impairments on working memory tasks, but spares performance on reference memory tasks. The medial temporal lobe and diencephalon may make different contributions to normal working memory. Alternatively, the two areas may each provide the necessary components to a larger functional memory system in which amnesia results from damage to any part of the system. In the latter case, the prefrontal cortex, receiving inputs from both the hippocampal formation and thalamus (which are disrupted by L-IML lesions), may account for deficits on the DNMTS task for medial temporal lobe and diencephalic amnesia. Previous studies have shown that lesions of the hippocampal formation, thalamus, and PFC may play a critical role in performance on delayed conditional discrimination tasks. The L-IML is the most effective lesion in the thalamus studied thus far for producing impairment on the DNMTS-PC task. Lesions of the fornix at the level of the septum do not

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contribute to the impairments on the DNMTS-PC task. Both lesions of the hippocampus proper and the rhinal cortex have resulted in impairments on the DNMTS task. Performance on the DNMTS-PC task of animals with hippocampal lesions or rhinal cortical lesions has not been directly compared to animals with L-IML lesions. Damage to the trisynaptic pathway results in disruption of neocortical connections with the hippocampal formation. The medial wall of PFC is denervated by lesions at either the L-IML or the entorhinal cortex.

This study directly compared the effects of lesions involving the three major memory related areas in the rodent brain on a DNMTS-PC task. The DNMTS-PC is a delayed conditional discrimination task that depends on working memory. The effects of lesions to the hippocampal formation, MW, and the L-IML in the rat brain on performance of DNMTS-PC were compared with control animals' performance. Specific patterns of memory impairments on the DNMTS-PC task resulting from lesions to the hippocampal formation, MW and L-IML were systematically studied. Delay dependent and delay independent performances were measured. The effect of manipulating inter-trial interval was measured. Lesions to the hippocampal formation were targeted specifically for the dentate gyrus, (HP). Lesions of the dentate gyrus are thought to provide significant damage which results in disruption of the trisynaptic path, therefore denervates the entorhinal projection to PFC. Delay dependent effects were examined by manipulating retention intervals within session. Inter-trial interval was manipulated between session. To minimize the effects of procedural

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demands, extensive pre-surgical training was used. Comparison of these lesion groups with the manipulations of RI and ITI provided a extremely thorough and systematic analysis of working memory deficits resulting from damage to the three major memory related areas of the brain.

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METHOD

<u>Subjects</u>

Fifty-four male Long-Evans rats served as subjects for pretraining. The rats were on average 18 weeks old on the first day of pretraining. The animals were housed in individual wire mesh cages in a vivarium on a 12:12 light:dark schedule. The animals were placed on a 23 hour water deprivation schedule 4 days prior to behavioral training, receiving water daily only during training sessions (7 - 10 ml) and an additional 30 minutes after training sessions. Rats were fed lab chow ad libitum throughout the experiment.

<u>Apparatus</u>

Subjects received extensive pretraining on the DNMTS-PC prior to surgery. Behavioral testing took place in three Layfayette 8500 automated chambers measuring 31 cm in length X 21 cm in width X 20 cm in height. Each chamber was controlled by an Omron Sysmac s-6 programmable controller. The chambers were each constructed of stainless steel side panels with a flooring consisting of stainless steel bars measuring 0.4 cm in diameter (spaced 1.7 cm apart). The top and ends of the chamber were constructed of plexiglass. A "start" port was located at one end and two "choice" ports placed 10.5 cm apart were at the opposite end. The top contained a houselight and buzzer. All three ports were constructed of PVC tubing (5.5 cm in diameter and 7.5 cm in length). Each

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port was mounted horizontally (3 cm above the floor), opening into the chamber. Each port contained a 6 watt instrument light. Infrared photocells were positioned vertically in each port to detect nose pokes. Each "choice" port had a drinking spout through which 0.1 ml of tap water was dispensed as a reinforcement following brief activation of a miniature solenoid valve. Licks were recorded by a contact relay switch. The chambers were each placed in individual sound barrier boxes (60 cm in length X 40 cm in width X 47 cm in height) constructed of wood and ventilated by fans.

Treatment

Subjects received water ad libitum three days prior to surgery and throughout the 12 day recovery period.

Prior to surgery, the 36 animals with the best performance were matched for percent correct over the last 150 trials of pretraining. The animals were assigned by block randomization to one of four groups: medial wall (MW), lateral-internal medullary lamina (L-IML), dentate gyrus of the hippocampal formation (HP) and sham operation controls.

Surgery was performed under sterile conditions. The animals were anesthetized with a combined dose of Rompun (6 mg/kg IM) and Ketamine (60 mg/kg IM). The animals were be mounted in a Kopf Stereotaxic Instrument with incisors 3.3 mm below the interaural line. The scalp was then sectioned, retracted, and the periosteum scraped from the skull. The positioning of the head was then verified by measuring the location of Bregma and Lambda.

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Experimental animals had their skulls opened with a dental burr. Radio frequency lesions were made bilaterally. For L-IML treatment, lesions were 1.0 mm off the midline and coordinates measured relative to the inter-aural line (IA). At AP 5.2, lesions were placed at DV 4.8 and 3.6. At 6.2, lesions were placed at DV 5.0 and 3.6. At AP 7.2, lesions were placed at DV 5.0 and 3.6. L-IML lesions were made by heating an electrode to 70° for a period of 30 s. For MW treatment, lesions were made bilaterally, at 0.8 mm and 2.0 mm off the midline. The coordinates for AP were measured relative to Bregma. The coordinates for DV were measured relative to the surface of cerebral cortex. At 0.8 mm off the midline, lesions were made at 1) AP 4.7 / DV 1.0; 2) AP 3.7 / DV 1.0 and DV 2.2; 3) AP 2.7 / DV 1.0 and DV 2.2; 4) AP 1.7 / DV 1.0 and DV 2.2; 5) AP 0.7 / DV 1.0 and 2.2. At 2 mm off the midline, they were placed at 1) AP 4.7 / DV1.0; 2) AP 3.7 / DV 1.0; 3) AP 2.7 / DV 1.0. For HP treatment, lesions were made bilaterally, corrdinates were relative to IA and placed at 1) 0.8 and 1.8 ML, at AP 6.8 / DV 6.5 and AP 5.8 / DV 6.5; 2)+/-1.4 and 2.4 ML, AP 4.8 / DV 6.5; 3)+/- 2.6 and 3.6 and AP 3.8 / DV 6.5. MW and HP lesions were made by heating the electrode to 75° C and maintaining the temperature for 30 s.

After the surgery was completed, body temperature was maintained by wrapping the animals in small blankets for the first 24 hours of recovery in their home cages. The animals were placed on ad lib food and water for the recovery period. Behavioral training began after 12 days of recovery.

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Procedure

Pretraining

All animals received 2 sessions of dipper training in which they were reinforced for licking water spouts on a FI-6 schedule. During dipper training, the choice port in which reinforcement was available was darkened, while the lights remained lit in the start port as well as the choice port in which reinforcement was not available. Animals received reinforcement (0.1 ml of tap water) in one choice port before alternating to the other choice port. The criterion for successful dipper training was to reach 20 reinforcements per side within 20 minutes.

Following dipper training, the animals were shuttle trained. Shuttle training requires the animal to break the photocell beam in the start-end port to initiate choice-end reinforcement. For each shuttle trial, reinforcement was given in one choice port as indicated by the light being turned off. The lights were turned on in the start port and the other choice port. After reinforcement, both choice port lights were turned on and the start port light turns off. During the first set of shuttle training sessions, animals were given 3 reinforcements in one choice port and then the reinforced port was alternated with the other choice port. Upon achieving 45 reinforcements per side on the 3:3 reinforcement schedule, the animals completed the second set of shuttle training sessions, which was the same as above but consisted of a 1:1 reinforcement schedule.

Once dipper and shuttle training were completed, animals began training

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on the DNMTS-PC task (see Figure 1). The DNMTS-PC consisted of a sample run and a choice run for each trial. The trial began with the lights on in both choice ports and off in the start port. The sample trial is initiated with a nose poke at the start port. Lights then turn on in the start port and in one choice port. Animals received reinforcement by drinking in the darkened port. After a RI, the lights turned on in both choice ports and off in the start port. The choice trial was initiated by a nose poke in the darkened start port, after which the start port light turned on and both choice ports were left off. If the animal entered the port reinforced during the sample run, no reinforcement was given. This was considered an incorrect response (matching-to-sample response). The error was indicated by a 2 s buzzer and time-out and the trial was terminated without reinforcement. If the animal entered the port not reinforced on the preceding sample run (this was a correct nonmatching to sample response), reinforcement was given and the correct response recorded. After the trial concluded, an ITI was imposed during which all port lights were turned on. The choice port reinforced in a sample run was varied following an irregular, but balanced sequence.

Animals were trained in daily 48 trial sessions. Initial sessions of DNMTS had a RI of 0.1 s and an ITI of 3.0 s. Further sessions had a RI of 3.0 s and ITI of 6.0 s, followed by a RI 3.0 s and an ITI of 10.0 s. The final step in pretraining was to introduce multiple delays while holding the ITI constant. These sessions began with RIs of 0.7 s, 2.0 s, and 6.0 s, and an ITI of 10.0 s. The final sessions

of pretraining included RIs of 0.4 s, 1.6 s, and 6.4 s, and an ITI of 0.8 s. Each animal in this study received over 4,000 trials of pretraining.

Post-surgical training Following recovery from surgery, animals were returned to the 23 hour water deprivation schedule described above. Initial retraining of the DNMTS task began with RIs at 0.4 s, 1.6 s, and 6.4 s, and an ITI of 0.8 s for 1008 trials. The RIs remained the same for the duration of post-surgical training. After completion of the initial retraining the ITI was increased to 3.2 s for 528 trials. Next, the ITI was increased to 12.8 s 528 trials. The ITI was then returned to 0.8 s for 624 trials. There were a total of 2,688 post-surgical trials.

Histological Analyses

Upon completion of the post-surgical DNMTS-PC training, the animals were sacrificed under deep anaesthesia (100mg/kg Ketamine and 10 mg/kg Rompun). Animals were sacrificed by transcardiac profusion with saline was followed by 10% neutral buffered formalin solution. Brain tissue was removed from the skull and stored in formalin solution. The brain tissue was then frozen and sectioned in the coronal plane every $30 \mu m$, and mounted onto gelatinized slides at $150 \mu m$ intervals. Tissue was then stained with cresyl violet.

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RESULTS

Behavioral Assessment

Analysis of the final six days of preoperative training confirmed that performance was comparable across groups. An analysis (two factor ANOVA) confirmed that there were no significant differences between groups: $F(3, 30) = 1.006$, $p = .4035$.

Initial Retraining

Each surgical group was impaired during the first post-surgical training sessions. The HP animals, however, quickly improved (see Figure 2). Analyses (two factor ANOVA) of groups and blocks of trials of 144 revealed significant differences in performance between groups: $F(3, 30) = 10.660$, $p < .0001$, and across blocks $F(3, 6) = 12.301$, $p < .0001$. A significant effect of a block x group interaction was also found: $F(18, 180) = 1.676$, $p = .0471$. Controls performed at 76% correct on the first post-surgical block of trials and increased their performance to 85% by the end of the initial training period. HP animals performed at 60% correct on the initial block of trials of post-surgical trials, however, they fully recovered to the level of control animals by block 3 (432 trials, see Figure 2). L-IML animals were severely impaired, and performance levels were equal to chance for the inital block of trials. L-IML animals improved moderately, and performed at 65% correct on the final block of 0.8 s ITI trials.

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MW animals were also severely impaired, and performed at near chance levels 54% correct on the inital block. MW animals also improved moderately, and performed at 66% correct on the final block of 0.8 s ITI (see Table 1).

A three factor ANOVA of RI (see Figure 3) revealed significant post-surgical differences across RI: $F(2, 60) = 26.711$, $p < .0001$. A group x RI interaction was not found: $F(6, 60)$, $p = .6633$. Figure 2 depicts animal group performance at each RI. The absence of a group x RI interaction indicates that group forgetting functions were equivalent. Given that all lesion group forgetting functions were equivalent to controls, there was no evidence of rapid forgetting among the lesion groups.

3.2 s Inter-Trial Interval

Analysis of groups (three factor ANOVA) revealed significant post-surgical differences between groups: $F(3, 30) = 8.563$, $p = .0003$. Post hoc (Student-Newman-Keuls) analyses ($\alpha = .05$) confirmed that L-IML animals were significantly different from control and HP animals. MW animals were also significantly different from control and HP animals. No significant differences between L-IML and MW animals were found. This finding further supports that patterns of impairment were different across lesion groups. Analysis of RI (see Figure 4) revealed significant differences: $F(2, 60) = 90.715$, $p < .0001$. A group x RI interaction was not significant: $F(6, 60) = .386$, $p = .8851$. This finding further suggests that all animal groups were forgetting at comparable rates. A significant effect of block was found: $F(3, 9) = 3.985$, $p = .0103$. The interaction

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of group x block was not significant: $F_{(9, 90)} = 1.205$, $p = .3016$. Control animals performed consistently across blocks, with block 1 performance at 87%, and the final block performance at 88% (see Table 2). HP animals improved slightly with inital block performance at 81%, and final block performance at 85%. MW animals improved slightly with initial block performance at 73% and final block performance at 79%. L-IML animals exhibited the greatest improvement with inital block performance at 67% and final block performance at 76%.

12.8 s Inter-Trial Interval

Analysis (three factor ANOVA) of group differences (see Table 3) was not significant on the 12.8 s ITI trials: $F_{(3, 30)} = 2.232$, $p = .10$. Analysis (three factor ANOVA) of RI was significant: $F_{(2, 60)} = 84.053$, $p < .0001$ (see Figure 5). A group x RI interaction was not significant: $F_{(6, 60)} = 1.295$, $p = .2734$. This finding further confirms that all animals were consistently performing at normal rates of forgetting across all ITI manipulations. A significant effect of block was revealed: $F_{(3, 9)} = 3.157$, $p = .0286$. There was not a significant group x block interaction: $F_{(9, 90)} = .746$, $p = .666$.

Return to 0.8 s ITI

An analysis (three factor ANOVA) of group found significant differences between groups: $F_{(3, 30)} = 5.630$, $p = .0035$ (see Table 4). Post hoc (Student, Newman, Keuls) analyses confirmed ($\alpha = .05$) that MW and L-IML animals performed significantly different from control animals. HP animals were not significantly different from controls. Analysis of RI was significant: $F_{(2, 60)} =$

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64.118, p < .0001 (see Figure 6). The group x RI interaction was not significant: $\underline{F}(6, 60)$ = .515, p = .7945. This result, coupled with analyses above, provides very strong evidence that none of the lesions affected rate of decay of DNMTS-PC. A significant effect of block was found: $\underline{F}(3, 9)$ = 3.51, p = .0288. No significant interaction between group x block was found: $\underline{F}(9, 90)$ = 1.64, p= .1158.

Analyses Across all Inter-Trial Intervals

Analysis (four factor ANOVA) across all data revealed significant group differences: $\underline{F}(3, 30)$ = 8.932, p = .0002. Post hoc (α = .05) analyses confirmed that L-IML animals were significantly different from control and HP animals. MW animals were also significantly different from control and HP animals. HP animals were not significantly different from controls. These findings strongly suggest that lesion groups were differentially impaired on the DNMTS-PC task. Significant differences for RI were also found: $\underline{F}(2, 60)$ = 113.046, p < .0001. The group x RI interaction was not significant: $\underline{F}(6, 60)$ = .597, p = .7314. The lack of interaction indicates that the rate of temporal decay was comparable across all lesion groups, i.e. the forgetting functions were equivalent. Comparable rates of forgetting were observed across all animal groups for each ITI manipulation, including the return to 0.8 s ITI.

This four factor ANOVA also found significant differences for ITI: $\underline{F}(3, 90)$ = 49.559, p < .0001, and a significant group x ITI interaction: $\underline{F}(9, 90)$ = 5.005, p < .0001. A significant group x ITI x RI interaction was found: $\underline{F}(18, 180)$

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= 2.211, p = .0045. The manipulations of ITI allowed the role of proactive interference on the DNMTS-PC task to be explored. Typically, ITI has not been manipulated in the animal models of amnesia. Increases in performance were observed as ITI was increased. Three possible explanations exist: a) animals were improving over time with additional post-surgical training; b) animals benefitted from increases in ITI length, perhaps by reducing the effects of proactive inhibition and thus enhancing the animals' ability to make a recency judgement; or c) a combination of both improvement with time and some benefit of ITI may have occurred. To control for the effects of post-treatment recovery, the ITI was returned to the 0.8 s ITI directly following the 12.8 s ITI manipulation. If animals were acquiring a large benefit from an increased ITI duration (12.8 s), it would be expected that performance would drop with the decrease in ITI length (0.8 s). By comparing performance means in Tables 3 and 4, it is quite clear that animals maintained their performance in spite of the decrease in ITI duration. Not only did all animal groups maintain performance with the decrease in ITI duration, but all animal groups exhibited slight improvements. These improvements in the presence of an abrupt decrease in ITI length suggest that animals were not benefitting significantly from increases ITI. A final consideration of ITI was the significant group x ITI x RI interaction. In the presence of equivalent forgetting functions and improvement with further training, this significant interaction does not contribute additional information describing the relative patterns of impairment across groups.

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<u>Lesion Analyses</u>

Figures 7, 8, and 9 show the minimum and maximum lesions for the HP, MW and L-IML groups. Cresyl violet stained brain sections were examined under a light microscope and the lesions were drawn onto templates. Six drawings were made relative to interaural (as designated in the sterotaxic atlas of Paxinos and Watson, 1986) representing the anterior, mid and posterior lesion dimensions for the minimum and maximum animals from each lesion group. HP drawings were made at 6.7, 5.7, and 4.7 relative to IA. MW drawings were made at 12.7, 11.7, and 10.7 relative to the IA. L-IML drawings were made at 7.2, 6.2, 5.2 relative to the IA.

Hippocampal lesions met criterion if substantial damage to the dorsal hippocampus including the dentate gyrus was present and midline cortex was spared. Two HP animals did not show signs of substantial bilateral lesion and thus data from these animals was not included in the analyses.

MW lesions met criterion if substantial damage to frontal area 2, cingulate areas 1 & 3, and the infralimbic area were present. All MW animals met the established lesion criterion.

The criterion for the measurement of L-IML animals consisted of bilateral damage to: AP extending 5.4 to 7.0 (mm relative to IA); DV extending from habenula through the extent of the central medial thalamic nucleus; ML centered .9 to 1.1 mm off the midline. All animals in the L-IML group met the established criterion.

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DISCUSSION

Patterns of Working Memory Deficits

The purpose of this study was to compare the working memory deficits that result from damage to the hippocampus, thalamus, and prefrontal cortex. Working memory was measured by the DNMTS-PC task trained at different retention and inter-trial intervals. By manipulating RI and ITI in the presence of extensive pre-surgical training on the DNMTS-PC task, patterns of impairments could be more clearly defined. Quantitative differences in the patterns of impairments across lesion groups were observed.

Hippocampal Formation

Animals with HP lesions were initially impaired on the DNMTS-PC task. However, performance of these animals returned to pre-surgical levels within 432 trials of post-surgical training and did not differ significantly from control animals throughout the remainder of the study. HP animals exhibited normal rates of forgetting. Regardless of how difficult the task was made via manipulations of RI and ITI, HP animals showed no signs of impairment after their initial recovery. This finding was somewhat surprising given the extensive amount of human, nonhuman primate, and rodent literature that suggests that damage to the hippocampal formation results in working memory impairments (Corkin, 1984;

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Squire, 1991; Squire, Zola-Morgan, and Chen, 1988; Mishkin, 1978; Mahut, Zola-Morgan, and Moss, 1982; Murray and Mishkin, 1984; Sutherland and McDonald, 1990; Eichenbaum, Fagen, and Cohen, 1986; Olton, Becker, and Handelmann, 1979). Interestingly, this finding did replicate previous work conducted in our lab which investigated the role of limbic-related pathways in the DNMTS-PC task. Neither the lesions to the medial mammillary nuclei which disrupts limbic-related pathways via fornix nor lesions of the fornix at the level of the septum produced severe, long-lasting impairments. These findings indicate that damage to the fornix or hippocampal-pathways cannot account for the DNMTS-PC lesion associated with PTD or L-IML.

An important variable in this study was the use of extensive pre-surgical training trials (> 4,000) completed by the animals. Effect of extensive pre-surgical training has not been thoroughly investigated in studies of hippocampal lesions. In Squire's analysis of the disparity of the behavioral effects of HP lesions across several studies, the conclusion is drawn that severity of impairment was related to presence or absence of pre-surgical training. The present study intentionally went beyond the typical number of pre-surgery training trials (<1,000) to explore the effect of such extensive training. Olton et al. (1979) report on the significance of pre-surgical training in a study of the effects of bilateral kainic acid injections into CA3 made before or after training on the radial arm maze had begun. HP animals that received injections prior to training

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failed to learn the task. HP animals that were injected after training were initially impaired, but subsequently recovered their performance. If pre-surgical training eliminates the deficit on the DNMTS-PC task, then hippocampal lesions cannot be taken to impair mnemonic aspects of this task. This would suggest that initial impairments observed were learning deficits and not memory deficits. Different levels of pre-surgical training should be manipulated within a study before failure to produce a long-lasting deficit is conclusively attributed to extensive pretraining.

HP lesions were consistent with lesions found to produce a more long-lasting impairment on the Hebb-Williams maze (Winocur and Moscovitsch, 1990). In a recent study, examining the magnitude of impairment of dorsal vs. ventral hippocampal lesions, it was reported that animals with dorsal hippocampal lesions were consistently more impaired on the Morris water maze task than animals with ventral hippocampal lesions (Moser, Moser, and Andersen, 1993). The dorsal lesions had to be larger than 20% of the total hippocampal volume to result in impairments. The degree of impairment was correlated with the lesion volume. This correlation was not observed in the present study. The positive correlation between impairment and total lesion volume may have resulted because HP animals were performing a spatial task. In the present study, the lesions destroyed a substantial portion of the dentate gyrus and this must be presumed to have affected the trisynaptic pathway. The extent of these lesions suggests that the trisynaptic circuit is not critically important for the DNMTS-PC task. The

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possibility remains, however, that a more extensive lesion might have produced a greater degree of impairment.

The full and rapid recovery of HP performance might be attributed to the specific demands of the DNMTS-PC task. The DNMTS-PC task is trained in an operant chamber, that does not provide a particularly cue rich environment. Both left and right place cues remain in fixed locations for the task, and thus there is no need to integrate new sensory information to differentiate between them. Furthermore, this task places extensive demands on temporal integration. The animals are required to perform a recency judgment for each trial and distinguish the side visited on the preceding sample trial from responses made during earlier trials. This demand almost certainly must place demands on the animal to release from proactive interference. Although HP animals have been found to be impaired on nonspatial working memory tasks (Olton et al., 1979; Aggleton, Blindt, and Rawlins, 1989), HP lesions have been found to contribute significantly more impairment to spatial tasks (Becker, Walker, and Olton, 1980; Sutherland and McDonald, 1990; Aggleton, Hunt, and Rawlins, 1986).

The functional role in memory processes of the hippocampal formation's unidirectional serial processing of polysensory association cortex information is not well understood. The anatomical effect of intrinsic lesions to the dentate gyrus is to significantly disrupt this serial processing within the hippocampal formation. In addition, lesions of the dentate gyrus disrupt connections between

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hippocampal formation and neocortex. Review of the literature suggests that the extent that the HP lesion disrupts cortical connections is directly related to the degree of behavioral impairment. Studies have examined removal of hippocampal formation and the surrounding rhinal cortex. Murray and Mishkin (1986) argue that the effect of removing the rhinal cortex is the equivalent of removing the entire hippocampal formation. (Although this finding is not supported by the observations of patient R.B. who suffered long-lasting memory impairments following bilateral lesions that were restricted to the CA1). The rhinal cortex, specifically the entorhinal cortex, projects extensive neocortical input to the PFC (Swanson and Köhler, 1986). Thus the result of the rhinal cortex lesion is to disconnect the hippocampal formation from its neocortical input. A recent study by Mumby and Pinel (1994) reports that rhinal cortex lesions in the rat resulted in a severe deficit on a DNMTS task. The authors additionally report that bilateral damage to the hippocampus and amygdala cause only mild DNMTS deficits unless there is also damage to the rhinal cortex (Mumby, Wood, and Pinel, 1992). Further examination of the rhinal cortex and its neocortical connections may provide a better understanding of medial temporal lobe amnesia.

Medial Wall and L-IML

The pattern of impairment in the MW and L-IML lesion groups was remarkably similar. Both groups were consistently impaired across the study. Analyses of the final 632 trials revealed that the performance of the MW and L-

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IML animals continued to be significantly different from control animals. The L-IML and MW lesions replicate earlier findings supporting a strong working memory deficit (Mair and Lacourse, 1991; Kivlahan, 1992; Harrison, 1992). Anatomical studies have shown that L-IML lesions disrupt specific and nonspecific thalamic afferents to the MW area. The MW and L-IML groups had not been compared directly in previous studies. The direct comparison in this study supports the conclusion that the effects of the L-IML lesion can be ascribed to its denervation of PFC. Improvement in performance of both the MW and L-IML animals was slightly greater than found in previous studies. This may have been a result of extensive pre and post-surgical training. MW and L-IML animals had rates of forgetting that were equivalent to control animals. Neither group appeared to benefit significantly from increases of ITI. By increasing ITI length, interference should be reduced. This suggests that deficits on the DNMTS-PC task are not a result of proactive interference. This finding is interesting in that Korsakoff patients and certainly frontal lobe patients have been found to be impaired on the Wisconsin Card Sorting task (Joyce and Robbins, 1991; Mann et al., 1988; Milner, 1963).

The DNMTS-PC task requires the temporal integration of information. Information regarding cue location must be maintained during th retention interval to perform a correct response. The DNMTS-PC requires an accurate recency judgment of cue location for a correct response. A correct recency

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judgment depends on the animals' ability to integrate the sample information on a given trial as the most recent cue location. The observation that performance levels L-IML and MW animals did not decrease when ITI decreased from 12.8 s to 0.8 s suggests that ITI did significantly enhance performance on the DNMTS-PC. Maintained performance of L-IML and MW animals suggests that interference does not appear to contribute significantly to the memory deficits observed in MW and L-IML groups. Failure of ITI to have a significant effect on performance may indicate that proactive interference does not have a prominant role in the observed deficits. Alternatively, the ITI manipulation may have not been effective. A longer ITI length may be necessary to have an effect on performance.

The patterns of impairment on the DNMTS-PC task for MW and L-IML are comparable. The two groups, however, have been found to differ in performance on other working memory tasks. MW animals have been found to impaired on DNMTS-PC (Harrison, 1992), DMTS-PC (Stevens, 1993), but not impaired on the radial arm maze, serial reversal learning task (Harrison, 1992) and olfactory continous DMTS. L-IML animals are impaired on radial arm maze, DNMTS-PC, DMTS-PC, and on the acquisition of a serial reversal learning task (Mair and Lacourse, 1991; Harrison, 1992; Kivlahan, 1992). Harrison (1992) reported that rhinal sulcal PFC animals were also impaired on DNMTS-PC, although the size of impairment for this lesion group correlated with the extent of

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encroachment into the MW area. A study of the effects of combined lesions to the MW and rhinal sulcal area has yet to be conducted. It is possible that damage other areas of PFC, in addition to MW, may produce more extensive working memory deficits across tasks. Perhaps a combined PFC lesion will yield less selective working memory impairments like the L-IML and PTD lesions.

The patterns of performance of animals with L-IML lesions is very comparable to patterns of performance of animals with PTD-induced lesions. Both PTD and L-IML animals have been found to be impaired on DNMTS-PC, DMTS-PC, radial arm maze, and serial reversal learning task, although they eventually reached criterion on radial arm maze and serial reversal learning (Mair, Knoth, and Rabchenuk, 1991; Robinson and Mair, 1991; Harrison, 1992; Kivlahan, 1992; Stevens, 1993). The present findings further verify the validity of the PTD model. The behavioral deficits associated with the L-IML lesion more closely resemble impairments observed in animals following PTD treatment than any other lesion attempted thus far. The effects of L-IML lesion on thalamo-cortical pathways have been mapped with the Fink-Heimer staining technique (Zhang and Mair, 1992). L-IML lesions produce signs of degenerating axons throughout cortex in layers I and VI, and is associated with nonspecific nuclei. L-IML lesions were also associated with signs of specific axonal degeneration in the projection areas of MDn in PFC along the medial wall and dorsal to the rhinal sulcal in layer III or IV. The results of the Fink-Heimer studies suggest two possible

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thalamocortical pathways that may contribute to the DNMTS-PC deficit: the deficit may result in destruction of the specific thalamocortical projections from MDN to PFC; or destruction of nonspecific thalamocortical projections from intralaminar and paralaminar nuclei (Mair, 1994). Behavioral effects of the MDn lesion on the DNMTS-PC have been limited when compared to PTD or L-IML animals (Kivlahan, 1992). These observations support the conclusion that impairments associated with the L-IML lesion are not a result of disruption of MDn projections to PFC. This study provides additional evidence that the working memory deficit on the DNMTS-PC task produced by L-IML lesions is a result of destruction to nonspecific nuclei.

Neural Mechanisms in Memory

Amnesia is frequently described as the disruption of functional circuits that reside in the medial temporal lobe and the thalamus. These circuits are thought to receive information from association cortex, and then process and maintain the information for a limited period of time. Following this processing in the medial temporal lobe and the thalamus, the information is returned to association cortex for permanent storage (Squire, 1987; Zola-Morgan and Squire, 1993). It is reasonable to suggest that the processing in the functional circuits of the medial temporal lobe and thalamus do not make the same contributions to working memory. A more detailed understanding of the specific demands of working

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memory tasks is required, however, before it can be concluded that processing in the medial temporal lobe and the thalamus are functionally different.

The L-IML lesion results in widespread nonspecific cortical denervation. L-IML lesions also produce a comparable pattern of impairment comparable to the PTD-induced lesions. It is not presently known how nonspecific cortical denervation results in the working memory deficits observed across several tasks.

The MW lesion produces more selective impairments across working memory tasks. Animals with lesions in the MW are impaired on the DNMTS-PC and DMTS-PC tasks. Both of these tasks place great demands on temporal integration. Fuster (1989) argues strongly that a major functional role of the PFC is to perform temporal integration. The requirement to perform a recency judgment on the DNMTS-PC task places demands on temporal integration. Failure to perform temporal integration results in a working memory deficit on the DNMTS-PC task. The limited behavioral impairment of MW animals on tasks with fewer temporal demands support Fuster's proposal. The contribution of the MW may be restricted to performance of temporal integration. The lesions to the MW result in patterns of impairment across working memory tasks that suggest the PFC's contribution is restricted to the temporal intergration of information. Further examination of lesions to other areas of PFC will be required before this conclusion can be confirmed.

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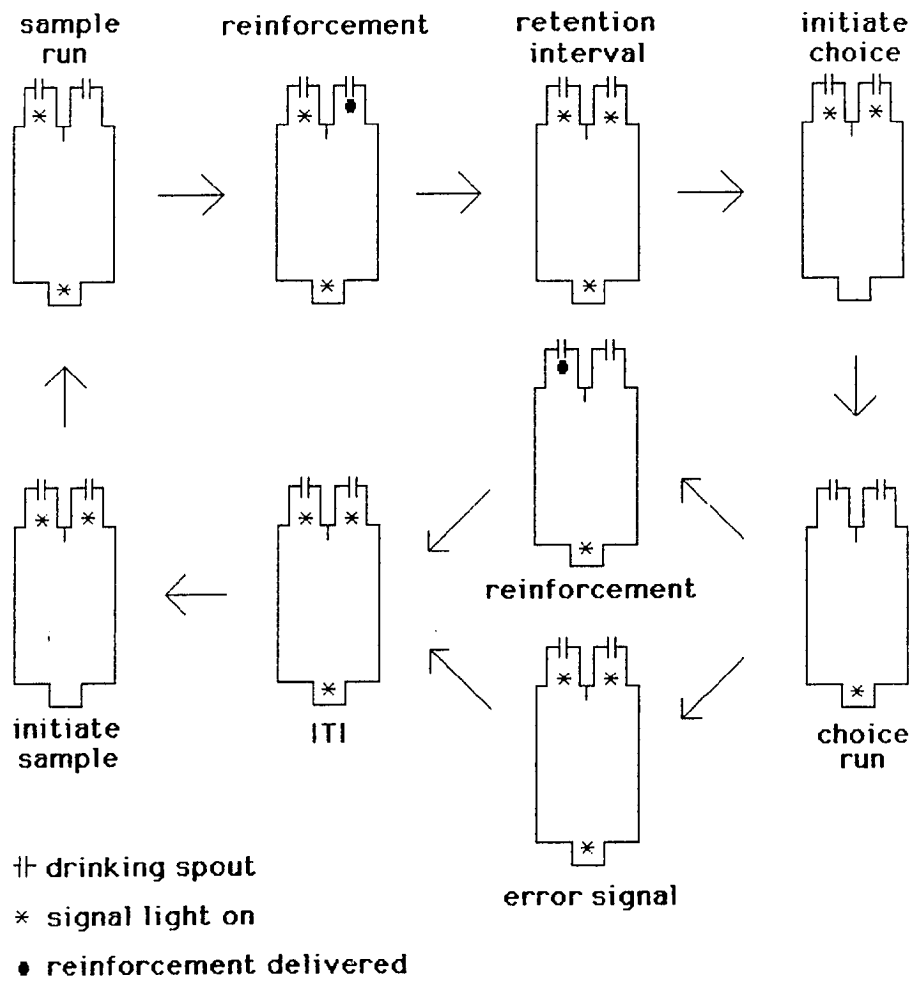
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APPENDIX

Figure 1. Schematic of the DNMTS-PC task*

sample run   reinforcement   retention interval   initiate choice

reinforcement

initiate sample   ITI   error signal   choice run

╫ drinking spout

* signal light on

● reinforcement delivered

*Adapted from Mair (1994).

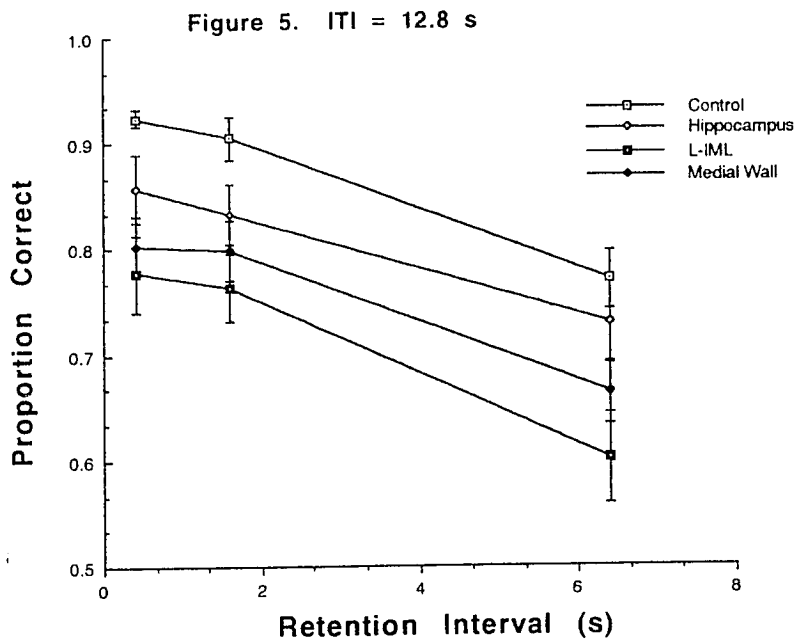Figure 2. Initial Post-Surgical Performance

74
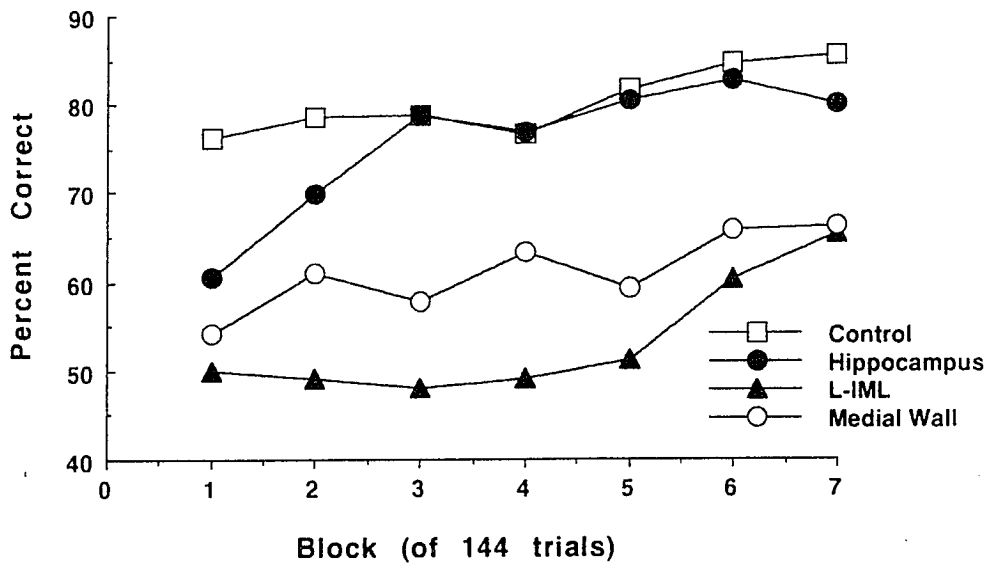
Figure 3. First 1008 Trials: ITI = 0.8 s

75

Figure 4. ITI = 3.2 s

76

Figure 5.   ITI = 12.8 s

77
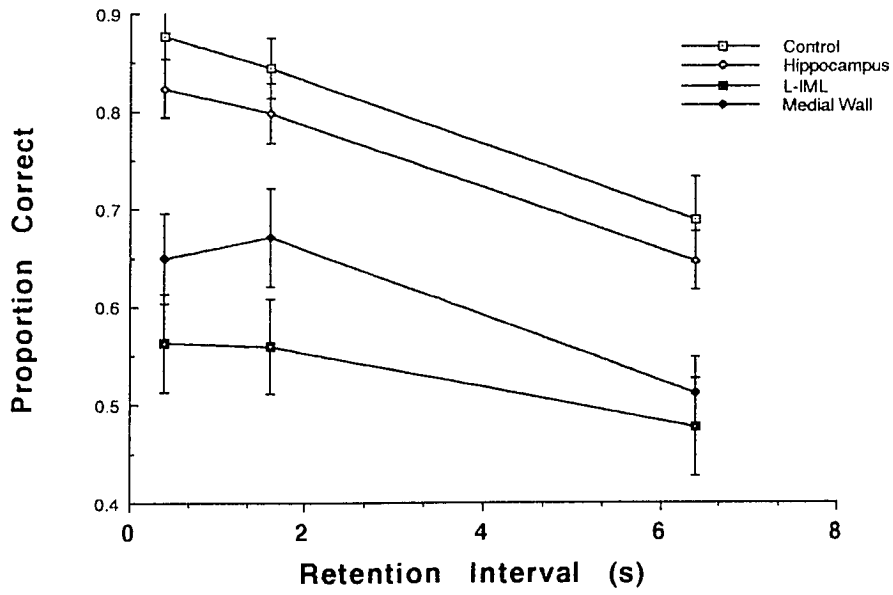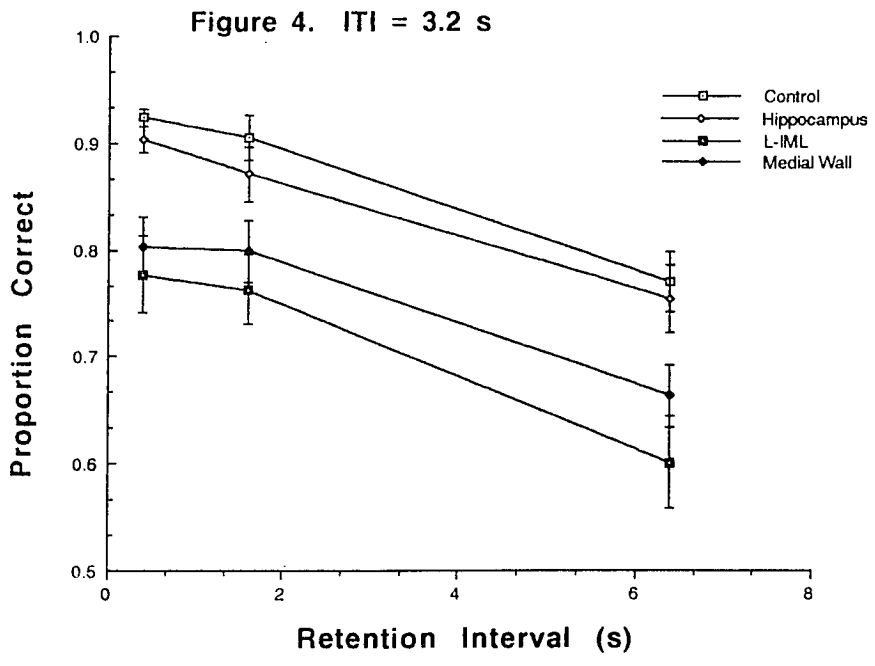
Figure 6. Final 632 Trials: ITI = 0.8 s

78
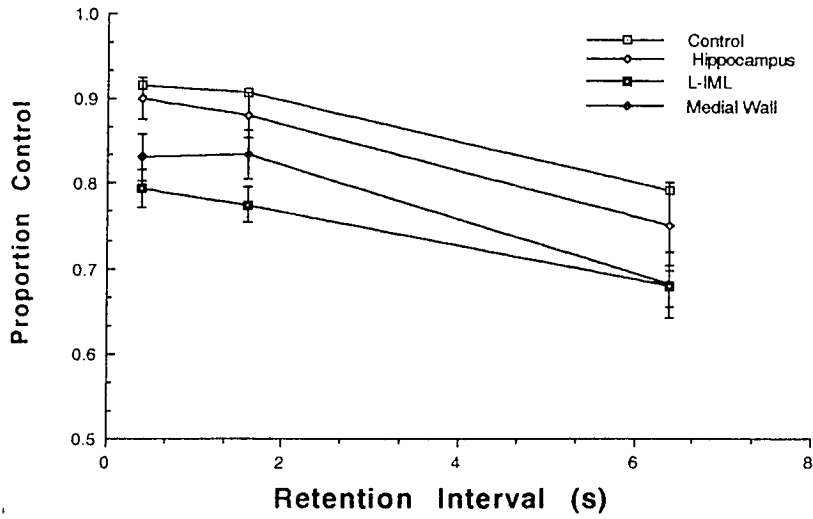
Table 1

0.8 s Inter-Trial Interval - Mean Proportion Correct Across Initial 1008 Trials

Treatment	Mean	Standard Error
Control	.80	.014
Hippocampal	.76	.017
Medial Wall	.61	.018
L-IML	.53	.022

79

Table 2

3.2 s Inter-Trial Interval - Mean Proportion Correct Across 528 Trials

Treatment	Mean	Standard Error
Control	.86	.020
Hippocampal	.84	.023
Medial Wall	.75	.028
L-IML	.71	.037

80

Table 3

12.8 s Inter-Trial Interval - Mean Proportion Correct Across 528 Trials

Treatment	Mean	Standard Error
Control	.83	.012
Hippocampal	.81	.014
Medial Wall	.76	.013
L-IML	.76	.012

81

Table 4

0.8 s Inter-Trial Interval - Mean Proportion Correct Across Final 632 Trials

Treatment	Mean	Standard Error
Control	.87	.010
Hippocampal	.84	.014
Medial Wall	.78	.011
L-IML	.75	.014

82

Figure 7. Minimum and Maximum Drawings of the HP Lesion

6.7

5.7

4.7

83
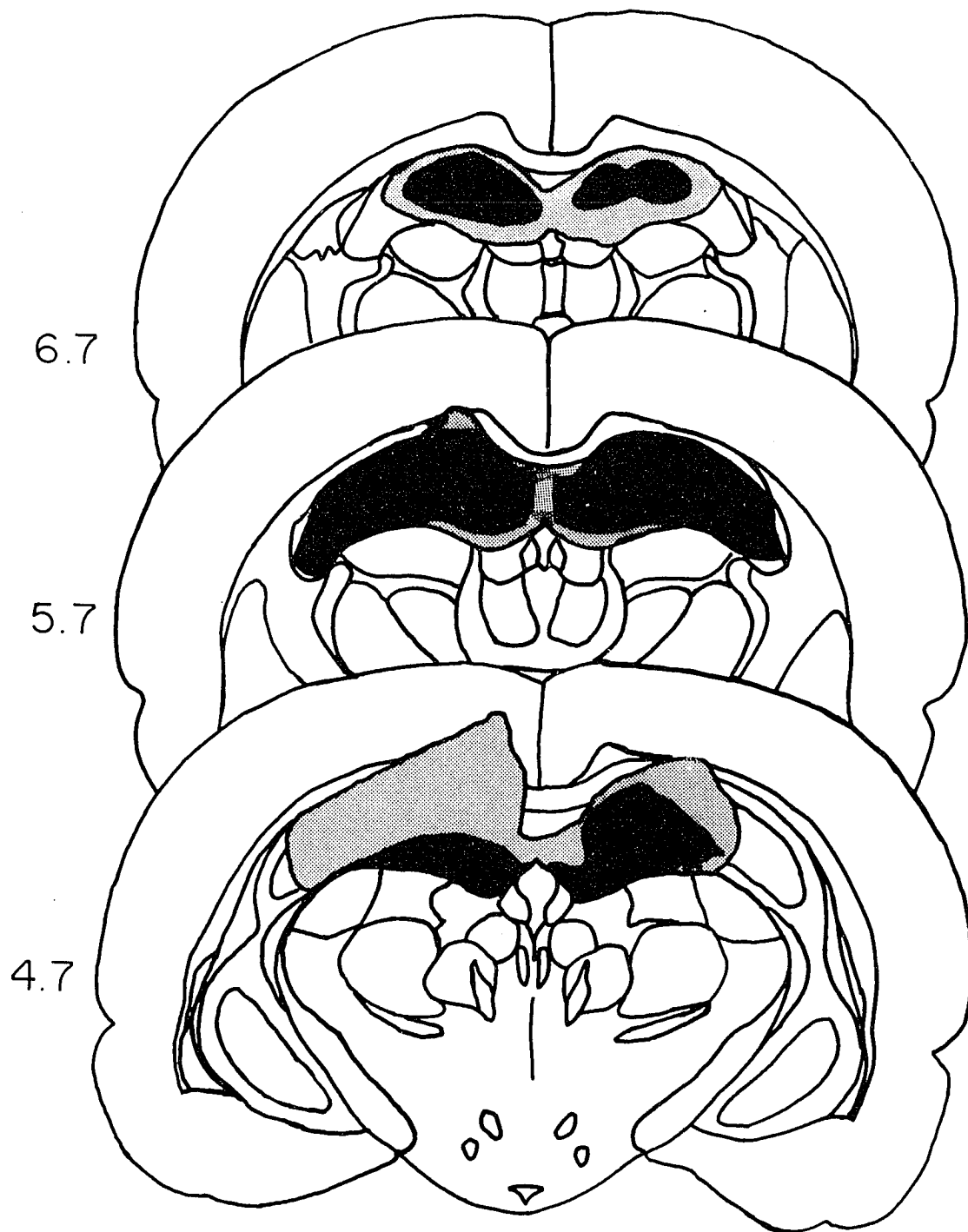
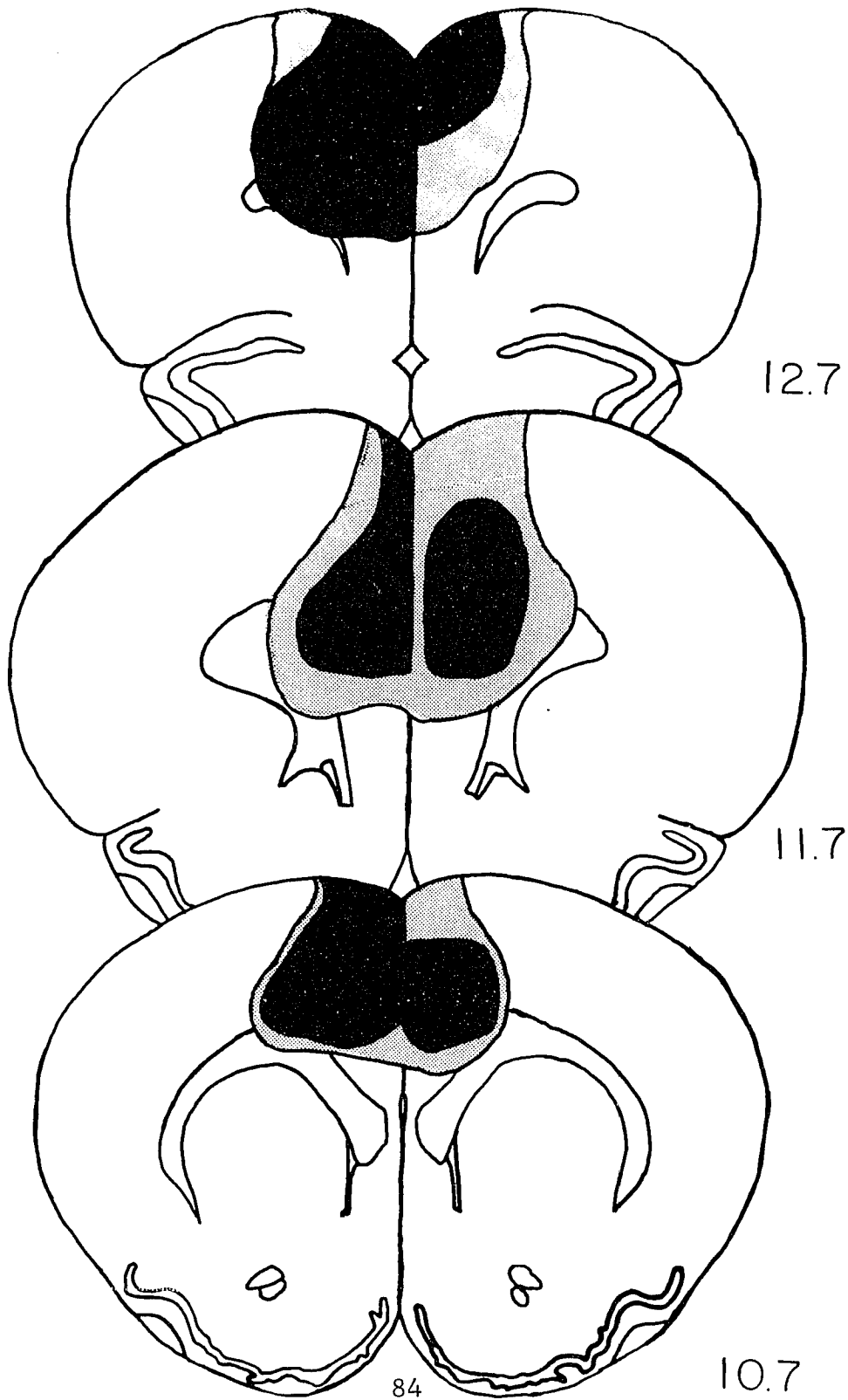Figure 8. Minimum and Maximum Drawings of the MW Lesion

12.7

11.7

84

10.7

Figure 9. Minimum and Maximum Drawings of the L-IML Lesion

7.2

6.2

5.2

85