COMPARISON OF THE AMNESIC DEFICITS ASSOCIATED WITH DAMAGE TO THE MEDIAL TEMPORAL LOBE, MEDIAL DIENCEPHALON, OR BASAL FOREBRAIN IN RATS

By
TOM JOHN KORNECOOK
B.Sc., McGill University

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY in THE FACULTY OF GRADUATE STUDIES (Neuroscience Graduate Program)

We accept this thesis as conforming to the required standards

THE UNIVERSITY OF BRITISH COLUMBIA
AUGUST, 1998

© Tom John Kornecook
In presenting this thesis in partial fulfilment of the requirements for an advanced degree at the University of British Columbia, I agree that the Library shall make it freely available for reference and study. I further agree that permission for extensive copying of this thesis for scholarly purposes may be granted by the head of my department or by his or her representatives. It is understood that copying or publication of this thesis for financial gain shall not be allowed without my written permission.

Department of Neuroscience Graduate Program

The University of British Columbia
Vancouver, Canada

Date 28/08/98
ABSTRACT

There is general agreement that human brain-damaged-produced amnesia can be caused by damage in one of three separate brain regions: (1) the medial temporal lobe, (2) the medial diencephalon, or (3) the basal forebrain. However, the issue of whether there is a unitary amnesic syndrome, or whether the amnesia produced by damage to these three different brain areas are qualitatively distinct remains a matter of debate. The major purpose of the experiments in this thesis was to compare the nature of the impairment in memory for objects associated with bilateral medial-temporal-lobe, medial-diencephalic, or basal-forebrain damage in rats.

Four experiments comprise this thesis. Experiments 1, 2, and 3 described the effects of selective damage to the medial temporal lobe, basal forebrain, or medial diencephalon on a battery of anterograde object-memory tasks. This test battery included: (i) object discrimination, (ii) discrimination reversal, (iii) eight-pair concurrent object discrimination, (iv) delayed nonmatching-to-sample (DNMS) with retention delays of 4, 15, 30, 60, and 120 s, (v) DNMS with lists of three, five, and seven sample objects, and (vi) order discrimination. In Experiment 1, rats with lesions of the hippocampus were impaired only in the acquisition of the simple and concurrent object-discrimination tasks, whereas rats with lesions of the amygdala were impaired only in the acquisition of the concurrent-object-discrimination and DNMS tasks. Both groups were able to learn all tasks to the same level as controls, and once the tasks were learned, they did not display any impairments when the mnemonic demands of the task were increased. In Experiment 2, rats with lesions of either the rhinal cortex or basal forebrain (i.e., medial septum and diagonal band) displayed DNMS deficits at all retention delays longer than 4 s and all sample list lengths, and they were impaired on the order-discrimination task. Rhinal-lesioned rats were also impaired in learning the object-discrimination, discrimination-reversal, and
concurrent-object-discrimination tasks, but not the DNMS task, whereas basal-forebrain-lesioned rats displayed the exact opposite pattern of deficits on these four tasks. In Experiment 3, lesions of the mediodorsal thalamus in rats produced a profile of anterograde object-memory deficits similar to that produced by lesions of the rhinal cortex in Experiment 2. However, thalamic-lesioned rats also displayed evidence of an abnormal perseverative tendency on the discrimination-reversal task and, unlike the delay-dependent DNMS deficit seen in the rhinal-lesioned rats, their DNMS impairment was delay-independent.

Experiment 4 was an analysis of the retrograde object-memory impairment associated with damage to the medial temporal lobe, medial diencephalon, or basal forebrain. Rats with lesions of the rhinal cortex or basal forebrain (i.e., medial septum and diagonal band) were impaired relative to controls in the retention of object-discrimination problems learned 2 or 9 days, but 16, 37, or 58 days, prior to surgery; in contrast, lesions of the mediodorsal thalamus had no significant effect.

The present experiments demonstrated that lesions of the medial temporal lobe, medial diencephalon, or basal forebrain in rats produce different profiles of anterograde and retrograde object-memory deficits, thereby establishing that different syndromes of amnesia result from damage to the various memory structures of the brain. The scope and systematic nature of the present experiments are without parallel in this field of research. Their findings confirm and extend the results of less comprehensive human clinical studies and monkey and rat experiments. In doing so, they underscore the value of the comparative approach in the study of the neuroanatomy of brain-damage-produced amnesia.
TABLE OF CONTENTS

ABSTRACT ....................................................................................................................... II

TABLE OF CONTENTS .................................................................................................... IV

LIST OF FIGURES .......................................................................................................... IX

LIST OF TABLES ........................................................................................................... XI

ACKNOWLEDGMENTS .................................................................................................. XII

GENERAL INTRODUCTION ............................................................................................ 1

I. ANTEROGRADE AMNESIA PRODUCED BY MEDIAL-TEMPORAL-LOBE DAMAGE ................................................................. 2
   Human Studies ........................................................................................................... 3
   Nonhuman Animal Studies ....................................................................................... 4
      The Monkey DNMS Model ................................................................................. 5
      The Rat DNMS Model ......................................................................................... 12

II. ANTEROGRADE AMNESIA PRODUCED BY DIENCEPHALIC DAMAGE ...................................................................................... 15
   Human Studies ........................................................................................................ 15
   Nonhuman Animal Studies ....................................................................................... 18

III. ANTEROGRADE AMNESIA PRODUCED BY BASAL FOREBRAIN DAMAGE .................................................................................. 22
   Human Studies ........................................................................................................ 22
      Alzheimer's Disease and the Cholinergic Theory of Memory ......................... 23
      Anticholinergic Drugs and Memory Impairment ............................................ 24
      Amnesia Produced by Vascular or Traumatic Injury to the Basal Forebrain .... 25
   Nonhuman Animal Studies ....................................................................................... 26

IV. BRAIN-DAMAGE-PRODUCED RETROGRADE AMNESIA ................................................................................................................. 31
   Human Studies ........................................................................................................ 31
      Methodological Difficulties .................................................................................. 31
      Retrograde Amnesia in Patients With Diencephalic Damage ....................... 34
      Retrograde Amnesia in Patients With Medial-Temporal-Lobe Damage .......... 36
      Retrograde Amnesia in Patients With Basal-Forebrain Damage .................... 38
      Temporal Gradients of Retrograde Amnesia ...................................................... 38
   Nonhuman Animal Studies ....................................................................................... 40

V. COMPARISON OF THE AMNESIA ASSOCIATED WITH BILATERAL
DAMAGE TO THE MEDIAL TEMPORAL LOBE, THE MEDIAL DIENCEPHALON, OR THE BASAL FOREBRAIN

Human Studies
Nonhuman Animal Studies

VI. RATIONALE FOR THE METHODS AND GENERAL OBJECTIVES

GENERAL METHODS
SUBJECTS
APPARATUS

BEHAVIOURAL PROCEDURES
Object Discrimination
Discrimination Reversal
Eight-Pair Concurrent Object Discrimination
Delayed Nonmatching-to-Sample (DNMS)
DNMS With Lists of 3, 5, or 7 Samples
Order Discrimination

STATISTICAL ANALYSES

SURGICAL PROCEDURES

HISTOLOGICAL PROCEDURES

EXPERIMENT 1: ANTEROGRADE OBJECT-MEMORY DEFICITS FOLLOWING BILATERAL LESIONS OF THE HIPPOCAMPUS OR AMYGDALA IN RATS

METHOD
Subjects
Apparatus
Surgical Procedure

RESULTS
Histological Results
Behavioural Results
Object Discrimination
Discrimination Reversal
Eight-Pair Concurrent Object Discrimination
Delayed Nonmatching-to-Sample (DNMS)
DNMS With Lists ................................................................. 85
Order Discrimination ......................................................... 85

DISCUSSION OF EXPERIMENT 1 ........................................... 85

EXPERIMENT 2: ANTEROGRADE OBJECT-MEMORY DEFICITS
FOLLOWING LESIONS OF THE RHINAL CORTEX OR MEDIAL
SEPTUM AND DIAGONAL BAND IN RATS .................................. 103

METHOD ........................................................................... 104
Subjects ............................................................................. 104
Apparatus .......................................................................... 105
Surgical Procedure ............................................................. 105
Behavioural Procedure ....................................................... 106

RESULTS ........................................................................... 106
Histological Results ............................................................ 107
Behavioural Results ............................................................ 110
Object Discrimination ....................................................... 110
Discrimination Reversal ...................................................... 110
Eight-Pair Concurrent Object Discrimination ...................... 115
Delayed Nonmatching-to-Sample (DNMS) ......................... 118
DNMS With Lists ............................................................... 123
Order Discrimination ........................................................ 123

DISCUSSION OF EXPERIMENT 2 ........................................... 128

EXPERIMENT 2A: IMPAIRMENTS IN DNMS FOLLOWING LESIONS
OF THE BASAL FOREBRAIN IN RATS: EFFECT OF PRESURGERY
TRAINING ........................................................................ 142

METHOD ........................................................................... 143
Subjects ............................................................................. 143
Apparatus .......................................................................... 143
Procedure .......................................................................... 143
Presurgery Training: Acquisition of Object Discrimination .. 144
Presurgery Training: Acquisition of DNMS ....................... 144
Presurgery Training: DNMS Retention Functions ............... 144
Surgery ............................................................................ 144
Post surgery Testing: Reacquisition of DNMS .................... 145
Post surgery Testing: DNMS Retention Functions ............... 145

RESULTS ........................................................................... 145
Histological Results ............................................................ 145
Behavioural Results ............................................................ 148
Presurgery Training: Acquisition of Object Discrimination .. 148
Presurgery Training: Acquisition of DNMS........................................ 148
Presurgery Training: DNMS Retention Functions.................................. 148
Posturgery Testing: Reacquisition of DNMS......................................... 148
Posturgery Testing: DNMS Retention Functions................................... 151

DISCUSSION OF EXPERIMENT 2A....................................................... 154

EXPERIMENT 3: ANTEROGRADE OBJECT-MEMORY DEFICITS
FOLLOWING LESIONS OF THE MEDIODORSAL THALAMUS IN RATS.... 160

METHOD.............................................................................................. 161
Subjects............................................................................................... 161
Apparatus............................................................................................ 161
Surgical Procedure.............................................................................. 161
Behavioural Procedure...................................................................... 162
Statistical Analyses............................................................................ 162

RESULTS.............................................................................................. 163
Histological Results............................................................................ 163
Behavioural Results.......................................................................... 166
Object Discrimination....................................................................... 166
Discrimination Reversal.................................................................... 166
Eight-Pair Concurrent Object Discrimination.................................... 171
Delayed Nonmatching-to-Sample (DNMS).......................................... 171
DNMS With Lists............................................................................... 176
Order Discrimination......................................................................... 181

DISCUSSION OF EXPERIMENT 3......................................................... 181

EXPERIMENT 4: TEMPORALLY GRADED RETROGRADE AMNESIA
FOR OBJECTS FOLLOWING LESIONS OF RHINAL CORTEX OR
MEDIODORSAL THALAMUS................................................................. 193

METHOD.............................................................................................. 195
Subjects............................................................................................... 195
Apparatus............................................................................................ 195
Procedure........................................................................................... 195
Presurgery Training: Acquisition of Object-Discrimination
Problems............................................................................................ 195
Surgery................................................................................................ 196
Posturgery Testing: Reacquisition of Object-Discrimination
Problems............................................................................................ 196
LIST OF FIGURES

Figure 1. The rat version of the delayed nonmatching-to-sample (DNMS) task .................. 13

Figure 2. Histological results from the three lesions groups in Experiment 1 .................. 71

Figure 3. The mean trials to criterion on the object-discrimination task for the rats in each group in Experiment 1 ................................................................. 74

Figure 4. The mean trials to criterion on the discrimination-reversal task for the rats in each group in Experiment 1 ................................................................. 77

Figure 5. The mean trials to criterion on the concurrent-object-discrimination task or the rats in each group in Experiment 1 ................................................................. 79

Figure 6. The mean trials to criterion on the DNMS task for the rats in each group in Experiment 1 ................................................................. 82

Figure 7. The mean percent correct on the DNMS task at different retention delays for the rats in each group in Experiment 1 ................................................................. 84

Figure 8. The mean percent correct on the DNMS task with different sample list lengths for the rats in each group in Experiment 1 ................................................................. 87

Figure 9. The mean percent correct on the order-discrimination task for the rats in each group in Experiment 1 ................................................................. 89

Figure 10. Histological results from the two lesion groups in Experiment 2 .................. 109

Figure 11. The mean trials to criterion on the object-discrimination task for the rats in each group in Experiment 2 ................................................................. 112

Figure 12. The mean trials to criterion on the discrimination-reversal task for the rats in each group in Experiment 2 ................................................................. 114

Figure 13. The mean trials to criterion on the concurrent-object-discrimination task for the rats in each group in Experiment 2 ................................................................. 117

Figure 14. The mean trials to criterion on the DNMS task for the rats in each group in Experiment 2 ................................................................. 120

Figure 15. The mean percent correct on the DNMS task at different retention delays for the rats in each group in Experiment 2 ................................................................. 122
Figure 16. The mean percent correct on the DNMS task with different sample list lengths for the rats in each group in Experiment 2 ................................. 125

Figure 17. The mean percent correct on the order-discrimination task for the rats in each group in Experiment 2 ........................................................................ 127

Figure 18. Histological results for each of the basal-forebrain-lesioned rats in Experiment 2A ...................................................................................... 147

Figure 19. The mean trials to criterion on the DNMS task, both pre- and postsurgery for the control and basal-forebrain-lesioned rats in Experiment 2A.......................................... 150

Figure 20. The mean presurgery and postsurgery DNMS retention functions for the control and basal-forebrain-lesioned rats in Experiment 2A .................................. 153

Figure 21. Histological results from the mediodorsal-thalamus lesion group in Experiment 3 ............................................................................................ 165

Figure 22. The mean trials to criterion on the object-discrimination task for the control and mediodorsal thalamic rats in Experiment 3 ............................................. 168

Figure 23. The mean trials to criterion on the discrimination-reversal task for the control and mediodorsal thalamic rats in Experiment 3 ............................................. 170

Figure 24. The mean trials to criterion on the concurrent-object-discrimination task for the control and mediodorsal thalamic rats in Experiment 3 .............................. 173

Figure 25. The mean trials to criterion on the DNMS task for the control and mediodorsal thalamic rats in Experiment 3 ............................................................... 175

Figure 26. The mean percent correct on the DNMS task at different retention delays for the control and mediodorsal thalamic rats in Experiment 3 ............................. 178

Figure 27. The mean percent correct on the DNMS task with different sample list lengths for the control and mediodorsal thalamic rats in Experiment 3 ............... 180

Figure 28. The mean percent correct on the order-discrimination task for the control and mediodorsal thalamic rats in Experiment 3 ............................................. 183

Figure 29. Histological results for the three lesion groups in Experiment 4 ......................................................................................................................... 200

Figure 30. The mean percent correct in the postoperative performance of object-discrimination problems learned at different intervals prior to surgery for each of the groups in Experiment 4 .................................................. 204
LIST OF TABLES

Table 1. Profile of anterograde and retrograde object-memory deficits in rats with lesions of the hippocampus, amygdala, rhinal cortex, basal forebrain, or mediodorsal thalamus................................................................. 212
ACKNOWLEDGMENTS

I am indebted to my supervisor, Dr. John Pinel, for his guidance, support and friendship, and for his efforts in the preparation of this thesis. I thank the other members of my supervisory committee, Dr. Don Wilkie, Dr. Ken Baimbridge, and Dr. Joanne Weinberg for their time and their helpful suggestions. I would also like to thank Dr. Liisa Galea and Dr. Rob Douglas for agreeing to serve on my thesis defense committee. Special thanks goes out to Lucille Hoover for her technical assistance and unwavering support over the years and for always finding the time to lend a hand no matter how big or small the problem. Stan Floresco also deserves thanks for his assistance in the construction of some of the figures in this thesis. I also thank Michael Liu, Alexander Anzarut, and Tod Kippin who assisted me during the conduct of some of these experiments.

I would also like to thank all of my closest friends for their support and for generally making things easier. Chris Duva, in particular, was always there to help me put things in perspective. Finally, I would like to thank my parents, Mike and Venice Kornecook, without whose encouragement and support this thesis would not have been possible.
GENERAL INTRODUCTION

Bilateral damage to the medial temporal lobe, medial diencephalon, or basal forebrain has been shown to produce syndromes of amnesia in both human patients, monkeys, and rats (see Zola-Morgan & Squire, 1993; Mishkin & Murray, 1994; Mayes, 1994). Yet despite many years of research on the amnesic syndromes produced by damage to these three areas, it is still not apparent to what degree they are qualitatively distinct.

Is brain-damage-produced amnesia most appropriately viewed as a single disorder or as a group of distinct, but related, disorders? Does selective damage to the medial temporal lobe, medial diencephalon, or basal forebrain produce similar or different patterns of mnemonic impairment? Clearly, the answers to these related questions are central to any efforts to understand the neural mechanisms of memory. Some neuropsychological theories of memory have favored the view that these three regions of the forebrain belong to a single functional system and that the same syndrome of amnesia results from damage to any portion of this system (e.g., Warrington, 1982; Weiskrantz, 1985; Zola-Morgan & Squire, 1993), whereas others have argued that there are functional differences among the amnesias associated with damage to these regions (e.g., Parkin & Leng, 1988; Hunkin, Parkin, & Longmore, 1994); however, the available evidence is insufficient to confirm or disconfirm either view. Accordingly, the objective of this thesis was to systematically characterize the nature and extent of the anterograde and retrograde amnesic syndromes produced by bilateral lesions of the medial temporal lobe, the medial diencephalon, or the basal forebrain. Laboratory rats were the subjects.

This Introduction is divided into six sections. The first three sections review research on the anterograde amnesia that is produced in human patients and laboratory animals by bilateral
damage to the medial temporal lobes, medial diencephalon, and basal forebrain, respectively; and the fourth section reviews the less extensive research literature on the retrograde amnesia that results from damage to these same three areas. The fifth section describes previous efforts to directly compare the amnesic syndromes produced by damage to these three brain areas, and it discusses why they have been unsuccessful. Finally, the sixth section states the rationale for the present experiments and introduces the recently developed object-memory tests of anterograde and retrograde amnesia that were employed.

I. ANTEROGRADE AMNESIA PRODUCED BY MEDIAL-TEMPORAL-LOBE DAMAGE

A relationship between medial-temporal-lobe pathology and anterograde memory impairment was first reported in 1890 (Behkterev, 1890). Since that time, numerous studies of neuropsychological patients, nonhuman primates, and rats have attested to the importance of the integrity of the medial-temporal-lobe region for normal memory functions. This section begins with a brief description of the anterograde memory impairment resulting from bilateral medial temporal lobectomy in human patients and follows with an overview of the findings that have emerged from the experimental study of monkeys and rats. Two related themes emerge in this section: how some of the difficulties in drawing conclusions from human neuropsychological patients about the neuroanatomical substrates of memory have been circumvented through the use of animal models of anterograde amnesia, and how the contributions of the various medial-temporal-lobe structures to memory have begun to be clarified through the interplay of research on humans, nonhuman primates, and rats.
Human Studies

Intensive investigation of the anterograde amnesic syndrome associated with medial-temporal-lobe damage began with the clinical studies of patients who had undergone bilateral excisions of medial temporal-lobe structures (uncinate-amygdalar region, hippocampus, hippocampal gyrus, and perirhinal and entorhinal cortices) for the relief of long-standing epileptic or psychotic symptoms (Scoville, 1954; Scoville & Milner, 1957). Patients with such damage were shown to display profound disturbances of memory, whereas other cognitive functions remained largely intact (Scoville & Milner, 1957). The most widely studied of these patients is H.M. At the age of 27, H.M. underwent bilateral medial-temporal lobectomy for the treatment of a severe case of epilepsy. The surgery markedly reduced the incidence of H.M.'s generalized convulsions and minor epileptic attacks; however, it left him with severe, permanent anterograde amnesia as well as some retrograde memory deficits. It was initially concluded that the memory impairments resulting from temporal lobectomy were primarily a consequence of hippocampal damage (see Milner, 1962; Penfield & Milner, 1958), and this conclusion has been widely accepted (see Iversen, 1976; Squire, Knowlton, & Musen, 1993; Zola-Morgan, Squire, & Amaral, 1986).

H.M.'s anterograde memory impairment appears to result from his inability to transfer information from short-term to long-term storage. He has a normal short-term memory as measured by digit span (Drachman & Arbit, 1966) and can hold items in short-term memory by verbal rehearsal (Milner et al., 1968), but his long-term memory is extremely poor. H.M.’s long-term memory deficit involves both verbal and nonverbal material: H.M. performs poorly on tests of verbal learning and recall (Scoville and Milner, 1957), and he is similarly impaired on
nonverbal tasks such as the delayed recall of a complex figure (i.e., the Rey-Osterich figure) and the recognition of recurrent "nonsense" shapes (Milner, Corkin, & Teuber, 1968; Scoville & Milner, 1957). H.M. suffers from global amnesia, that is, amnesia for information presented in all sensory modalities (Milner et al., 1968).

There is one exception to H.M.'s long-term anterograde memory deficits. Although H.M. displays virtually no long-term retention on tests that assess his ability to consciously recognize or recall previous events (i.e., on tests of explicit memory), his performance is normal on tests in which memory can be demonstrated by improved performance without conscious awareness (i.e., on tests of implicit memory). For example, H.M. has demonstrated retention of mirror-drawing (Milner, 1965), rotary pursuit (Corkin, 1968), classical conditioning, and incomplete-pictures (Milner et al., 1968) tasks by his improved performance on these tasks, even though he had no conscious recollection of having learned them.

**Nonhuman Animal Studies**

The study of the anterograde amnesia associated with medial-temporal-lobe damage has not focused exclusively on human clinical populations. Much has been learned through the careful assessment of memory losses experienced by laboratory animals following carefully positioned medial-temporal-lobe lesions. The monkey nonrecurring-items delayed nonmatching-to-sample (DNMS) task has proven to be particularly sensitive to medial-temporal-lobe damage, and thus it has played a major role in this research.
Monkey DNMS Model

Efforts to model medial-temporal-lobe amnesia in laboratory animals began following the first report of H.M.’s case in 1957; however, they met with little success until the development of the DNMS task by Gaffan (1974) and Mishkin and Delacour (1975) in the mid 1970s. In retrospect, it appears that the original difficulties in modelling human medial-temporal-lobe amnesia occurred because researchers were not using tests sensitive to losses of explicit memory. The monkey delayed nonmatching-to-sample (DNMS) test was the first test shown to be sensitive to the explicit memory loss characteristic of medial-temporal-lobe amnesia.

This is how the monkey nonrecurring-items DNMS test is conducted. On each trial, the monkey is first confronted with an object (the sample) that it has not seen before. The monkey pushes the sample aside to obtain food hidden beneath it. Then, the experimenter immediately removes the sample. After the prescribed delay, the sample object is again presented, along with an object that the monkey has never seen before. The monkey must remember which object was presented as the sample, and push aside the unfamiliar object to obtain the food reward hidden beneath it. Different objects are used on each trial. After a monkey has mastered this task at a brief sample-test delay, its performance is assessed at each of several longer delays, and the results are the basis of plotting its retention function.

At retention delays of less than 10 minutes, healthy human subjects perform the DNMS task almost perfectly. Intact monkeys are typically correct on over 90% of the trials at retention delays of a few seconds and on about 80% of the trials at retention delays of 10 minutes. In contrast, monkeys with large medial-temporal-lobe lesions display a time-dependent deficit: They usually perform normally at retention delays of a few seconds, but their performance
approaches chance levels at delays greater than a minute or two (Mahut, Zola-Morgan, & Squire, 1982; Squire & Zola-Morgan, 1985). Human medial-temporal-lobe amnesics display the same pattern of deficits on this task (Squire, Zola-Morgan, & Chen, 1988; Aggleton, Nicol, Huston, & Fairbairn, 1988), thus eliminating most doubts about the validity of the model.

Scoville and Milner (1957) originally attributed medial-temporal-lobe amnesia to hippocampal damage because the severity of memory loss in their few patients appeared to be correlated with the extent of hippocampal excision. However, in the 1970s, an alternative hypothesis was proposed. Mishkin (1978) hypothesized that combined hippocampal and amygdalar damage is necessary for full-blown medial-temporal-lobe amnesia. The DNMS task opened up these two hypotheses to experimental investigation. Mishkin and colleagues (Mishkin, 1978; Murray & Mishkin, 1984; Saunders, Murray, & Mishkin, 1984) observed that lesions affecting both the hippocampus and amygdala in monkeys resulted in severe anterograde memory deficits, but that lesions restricted to either structure alone produced only mild amnesic symptoms. However, in other studies, bilateral hippocampal lesions produced significant impairments in DNMS (Mahut, Moss, & Zola-Morgan, 1981; Zola-Morgan & Squire, 1986) that were not exacerbated by amygdalar damage (Mahut et al., 1981). In retrospect, one possible explanation for the observed differences in the various experiments was that the monkeys had received different degrees of preoperative training experience (Zola-Morgan & Squire, 1986). Memory impairments following hippocampal lesions are severe when monkeys have received no preoperative training (Mahut et al., 1981; Zola-Morgan & Squire, 1986), mild when they have
received preoperative training (Mishkin, 1978), and absent when they have received extensive preoperative training (Murray & Mishkin, 1984).

Evidence against the amygdala’s involvement in object-recognition memory was provided by a study by Zola-Morgan, Squire, and Amaral (1989b). They demonstrated that, unlike the original aspiration lesions of the amygdala, electrolytic amygdalar lesions that spared surrounding tissue did not exacerbate the impairment produced by hippocampal removal. It was also shown that the DNMS performance of monkeys with selective amygdalar lesions was no different than that of control monkeys (Zola-Morgan et al., 1989b). Accordingly, the early evidence from the DNMS model, therefore, seemed to favor the hypothesis first put forth by Scoville and Milner: that hippocampal damage is the critical factor underlying medial-temporal-lobe amnesia. However, recent monkey DNMS studies have challenged this hypothesis.

The challenge to the hypothesis that the hippocampus is critical to normal DNMS performance is predicated on the fact that there is considerable damage to adjacent structures during conventional hippocampectomy in monkeys. In the early monkey DNMS studies, hippocampal and amygdalar lesions were usually made by aspiration; consequently, underlying cortical tissue and white matter were removed to expose the hippocampus and amygdala to the surgeon’s pipette. Accordingly, both Squire’s and Mishkin’s initial attempts at combined lesions to both the hippocampus and amygdala have been termed “H+A+” lesions (Squire & Zola-Morgan, 1988)--the “+’s” refer to the cortical regions adjacent to the hippocampus and amygdala (i.e., to the perirhinal, entorhinal, and parahippocampal cortices) that are necessarily damaged when either of these structures is removed in monkeys by using the conventional surgical approach. The H+A+ lesion in monkeys is the closest approximation to the medial-temporal-
lobe damage sustained by patient H.M. (Corkin, Amaral, Johnson, & Hyman, 1994), and there is universal agreement that the bilateral H+A+ lesion produces severe memory impairment (Mahut et al., 1981; Mishkin, 1978; Zola-Morgan & Squire, 1985).

The first clue that the cortical damage resulting from conventional hippocampectomy may have contributed to the disruptive effects of bilateral hippocampectomy came from a study of Zola-Morgan, Squire, and Amaral (1989a). They showed that DNMS is impaired following a lesion of the posterior portion of the medial temporal lobe (i.e., the H+ lesion). The H+ lesion involves the entire hippocampus, the dentate gyrus, the subicular complex, the posterior portion of the entorhinal cortex, and the parahippocampal cortex. The DNMS impairment was not as severe as that produced by H+A+ lesions and it was not exacerbated by a circumscribed radiofrequency lesion of the amygdala (Zola-Morgan et al., 1989b). This implied that, the more severe anterograde memory impairment associated with H+A+ lesions, as compared with H+ lesions, was due to additional cortical damage, not to amygdalar damage. These findings focused attention on the cortex adjacent to the amygdala, that is, on the rhinal cortex (i.e., the entorhinal and perirhinal cortices).

The rhinal cortex has major anatomical connections with brain regions that are believed to be important for normal memory processes. The entorhinal cortex, which receives nearly two thirds of its cortical input from the perirhinal cortex, provides the major source of projections to the hippocampus and dentate gyrus (Insausti, Amaral, & Cowan, 1987). Furthermore, the perirhinal cortex receives projections from medial prefrontal, anterior cingulate, insular, parietal, subicular, and retrosplenial cortices, and from the amygdala (Deacon, Eichenbaum, Rosenberg, & Eckman, 1983)—all structures that have been shown to play a role in the performance of
memory tasks. The rhinal cortex also projects directly to the mediodorsal nucleus of the thalamus via the ventral amygdalofugal pathway (Aggleton, Desimone, & Mishkin, 1986) and to the anterior thalamic nuclei and mamillary bodies via the fornix (Murray, 1992; Rosene & Saunders, 1987)—again, all structures that have been implicated in memory.

The following four monkey studies confirmed the initial evidence that rhinal cortex damage plays the major role in the DNMS deficits that accompany large medial-temporal-lobe lesions. First, Zola-Morgan et al. (1993) found that when the H+ lesion was extended forward to include the perirhinal cortex (the H++ lesion), impairment was significantly greater than after H+ or H+A lesions. Second, Zola-Morgan and his colleagues (1989) found that ablations of the perirhinal cortex plus the cortex of the parahippocampal gyrus produced a severe deficit, even when there is no subcortical damage. Third, Murray, Bachevalier, and Mishkin (1989) found that removals of the rhinal cortical region alone resulted in dramatic DNMS deficits in monkeys. Fourth, Horel and his colleagues (1987) found a severe DNMS impairment following either ablations or reversible cooling lesions of the monkey inferior temporal gyrus, which includes a large portion of the perirhinal cortex. Together, these four findings demonstrate that damage to the rhinal cortical region is sufficient to produce a severe impairment in object-recognition memory. In contrast, hippocampal lesions or amygdalar lesions that do not damage adjacent cortex have been found to produce only mild DNMS deficits (Alvarez, Zola-Morgan, & Squire, 1995; Clower, Alvarez-Royo, Zola-Morgan, & Squire, 1991; Murray, 1992).

There is a minor controversy concerning the amnesic effects of hippocampal lesions that do not damage adjacent cortical structures. There is evidence that combined excitotoxic lesions of the monkey hippocampus and amygdala that spare adjacent cortical tissue do not produce
visual object-recognition deficits (O’Boyle, Murray, & Mishkin, 1993). However, in another study by Alvarez et al. (1995), which assessed retention at longer delays, a slight, but statistically significant, deficit was observed when the delays were 10 minutes or greater. This finding, though, has been challenged on two counts (Murray, 1996; Murray & Mishkin, 1996; Nadel, 1992). First, in the Alvarez et al. (1995) study, the monkeys were removed from the test apparatus and returned to their home cages during the two longest retention delays (i.e., delays of 10 minutes or greater), but not during the other retention delays, a procedure that could have produced the observed impairment. Second, the lesions in the Alvarez et al. (1995) study may have inadvertently damaged the fibers connecting the fornix with the rhinal cortex, and this damage may also have contributed to the observed impairment (Murray, 1996).

The finding that the removal of the hippocampus and parahippocampal gyrus are markedly exacerbated by ablation of the rhinal cortex (e.g., Meunier, Hadfield, Bachevalier, & Murray, 1993) indicates a mnemonic role for the rhinal cortex that extends beyond the fact that it is the major source of sensory input to the hippocampus. There is also neurophysiological evidence to support this conclusion. A number of recent experiments have shown that neurons that appear to encode information about stimulus repetition and familiarity are found in monkey cortex close to the rhinal sulcus (Riches, Wilson, & Brown, 1991; Fahy, Riches, & Brown, 1993).

In summary, research on the monkey DNMS model of brain-damage-produced amnesia has shifted the focus of interest in the memory functions of the medial temporal lobe away from the deep structures and to the cortex in and around the rhinal sulcus. The results of the monkey experiments strongly suggest that the rhinal cortex—not the hippocampus or amygdala—is the
major medial temporal lobe object-recognition structure, and this conclusion is supported by recent findings in rats.

**Rat DNMS Model**

The development of several new paradigms for testing nonspatial working memory in the rat (Aggleton, 1985; Rothblat & Hayes, 1987; Mumby, Pinel, & Wood, 1990) has allowed for the development of rodent models of brain-damage-produced anterograde amnesia. Mumby et al.'s DNMS paradigm has been particularly useful because it was expressly designed to mimic the standard primate DNMS object-memory task and because rats acquire the nonmatching rule at the same rate as monkeys and perform comparably to monkeys at retention delays up to about 5 min. Accordingly, this paradigm has facilitated the integration of research on object recognition in rats and monkeys.

In accordance with the latest reports from the monkey literature, the findings of Mumby and his colleagues de-emphasize the roles of both the hippocampus and amygdala in DNMS performance and emphasize the rhinal cortex. Mumby, Wood, and Pinel (1992) found that, in comparison to no-surgery control rats, rats with either separate or combined lesions of the hippocampus and amygdala were slightly, but significantly, impaired at only their longest, 10-min, retention delay. This observation of only a mild DNMS deficit following bilateral ablation of the hippocampus and amygdala is consistent with earlier reported failures to observe DNMS impairments in rats with hippocampal lesions at retention delays of 30 s (Rothblat & Kromer, 1991) and in rats with hippocampal or amygdalar lesions at delays of 60 s (Aggleton, Hunt, & Rawlins, 1986).
Figure 1. The rat version of the object delayed nonmatching-to-sample (DNMS) task.
The sample object is placed over one food cup at one end. An object identical to the sample object and a novel object are placed over the two food cups at the other end.

When the sliding door is raised, exposing the sample object, a trained food-deprived rat runs down to the sample object and pushes it aside. Then, a piece of food is deposited by a food-delivery mechanism into the exposed food cup.

The sample object is immediately removed by the experimenter, and the rat remains at the same end of the Mumby box until the prescribed delay period is over (e.g., 1 minute).

Then, the other sliding door is raised to expose the two objects at the other end. Trained rats, remembering their previous encounter with the sample object run to the novel object and push it aside; and food is delivered to the exposed food cup. The sliding door at the other end is lowered behind the rat.

The rat then runs to the center of the Mumby box, and the sliding door is closed behind it. Then, new objects are arranged for the next trial. One advantage of the Mumby box is that the rats do not have to be handled either during or between trials.
In contrast to the mild or nonexistent impairments in DNMS associated with hippocampal damage, lesions of the rhinal cortex in rats have consistently been shown to result in deficits similar to those seen following large temporal-lobe ablations in monkeys. Mumby and Pinel (1994) investigated the effects of bilateral aspiration lesions of the rhinal cortex on the ability of rats to perform the DNMS task. They found rats with rhinal cortex lesions performed normally at a 4-s delay, but were impaired at all delays ranging from 15 to 600 s. Furthermore, the addition of bilateral amygdala lesions did not increase their DNMS deficits. Recently, Wiig, Bear, and Burwell (1997) have demonstrated that rats with neurotoxic lesions of the perirhinal cortex display impairments on a DNMS task modeled after the one developed by Mumby et al., and Wiig and Bilkey (1995) have reported that electrolytic lesions of the perirhinal cortex exacerbate the memory deficit observed following damage to the fimbria-fornix.

Additional support for the suggestion that the rhinal cortex plays a preeminent role in stimulus recognition in rats comes from a study by Otto and Eichenbaum (1992) in which rats with lesions of the perirhinal and entorhinal cortex were impaired on an olfactory-guided DNMS task. There is also a recent evidence from recording studies that neurons in the rat rhinal cortex, as in the monkey rhinal cortex, signal information concerning the prior occurrence of stimuli that could be used to solve recognition tasks (Zhu, Brown, & Aggleton, 1995; Zhu, McCabe, Aggleton, & Brown, 1997).

In summary, recent studies in both monkeys and rats has required a radical reappraisal of the relative contributions of the hippocampus, amygdala, and rhinal cortex to normal DNMS performance. A substantial body of evidence has shifted the focus from the deep temporal-lobe
structures (i.e., the hippocampus and amygdala) to the surrounding cortex (i.e., the perirhinal, entorhinal, and parahippocampal cortices) as the critical substrates of object recognition.

II. ANTEROGRADE AMNESIA PRODUCED BY DIENCEPHALIC DAMAGE

It is well established that medial-diencephalic damage can produce severe and persistent memory impairments in both humans (e.g., Parkin & Leng, 1995; Victor, Adams, & Collins, 1971), monkeys (e.g., Aggleton & Mishkin, 1983a; Zola-Morgan & Squire, 1985), and rats (e.g., Delacour, 1971; Mumby, Pinel, & Dastur, 1993); however, the exact nature of this “diencephalic amnesia” and the lesion required to produce it remain a matter of much debate. This section begins with a brief survey of diencephalic amnesia in humans resulting from both Korsakoff’s syndrome and traumatic brain damage, followed by current hypotheses concerning the location of the critical lesion. Then, the various attempts to model the anterograde amnesia resulting from diencephalic damage in laboratory animals are described and their contributions discussed.

Human Studies

The first systematic studies of the relationship between diencephalic neuropathology and human memory impairment appeared in the 1950s (Malamud & Skillicorn, 1956), but subsequent progress has proceeded slowly, both because the diencephalon is an anatomically complex structure and because the majority of diencephalic amnesics have diffuse lesions.

Most studies of human diencephalic amnesia have been studies of Korsakoff patients. Korsakoff’s syndrome is a neurological disorder resulting from a nutritional (thiamine) deficiency, in which memory is profoundly impaired while other cognitive functions remain
largely intact (Victor et al., 1971). Although Korsakoff's syndrome can be produced by dietary deficiency alone, it is most often associated with chronic alcohol abuse (see Kopelman, 1995). The neuropathology associated with Korsakoff's syndrome is both extensive and diffuse, with abnormalities most prevalent in the paraventricular and periaqueductal gray matter, the walls of the third ventricle, the floor of the fourth ventricle, the cerebellum, and the frontal cortex (Cravioto, Korein, & Silberman, 1961; Victor et al., 1971).

Most frequently implicated in the development of diencephalic amnesia have been the mammillary bodies and the mediodorsal thalamic nuclei (Markowitsch, 1988; Victor, Adams, & Collins, 1989). However, the relative importance of these two pairs of structures has been the subject of much controversy. In support of a prominent role for the mammillary bodies, Mair, Warrington, and Weiskrantz (1979) reported the cases of two Korsakoff patients with severe memory problems; autopsies revealed lesions in the mammillary bodies and the anterior-medial portion of the thalamus, but not in the mediodorsal nucleus. Mair et al. suggested that these lesions might sever a critical circuit running between the temporal lobes and the frontal cortex. Mair et al.'s (1979) findings were replicated nearly a decade later in two more deceased patients (Mayes, Meudell, Mann, & Pickering, 1988). Furthermore, Von Cramon, Hebel, and Schuri (1985) reviewed findings from 11 cases of thalamic infarction, 9 of whom were amnesic and 2 who were not; they found that all 9 amnesic cases, but not the other 2, had damage to the mammillothalamic tract, which connects the mammillary bodies with the anterior thalamic nucleus. More recently, Dusoir et al. (1990) described a patient whose anterograde amnesia appears to have resulted from a traumatic selective lesion to the mammillary bodies.
Although some evidence has implicated the mammillary bodies in diencephalic amnesia, the majority of the evidence has indicated that damage to the mediodorsal nucleus, not the mammillary bodies, is crucial for the development of Korsakoff's syndrome. For example, Victor et al. (1971) found that of 24 Korsakoff's patients in whom the mediodorsal thalamic nucleus was damaged, all had persistent memory problems, whereas 5 patients in whom the mediodorsal nucleus was undamaged had other neurological symptoms but no recorded memory problems. Moreover, diencephalic amnesia in association with damage to the medial thalamus (including the mediodorsal, central, and midline thalamic nuclei), but with apparent sparing of the mammillary bodies, has been documented in several cases of tumor or infarction (Graff-Radford, Tranel, Van Hoesen, & Brandt, 1990; Speedie & Heilman, 1982; Winocur, Oxbury, Roberts, Agnetti, & Davis, 1984).

A great deal of research into the nature of diencephalic amnesia has focused on patient N.A. N.A. developed amnesia following a penetrating stab wound to the brain (Teuber, Milner, & Vaughn, 1968). The neuropsychological findings from patient N.A. were initially construed as further evidence for the critical involvement of the mediodorsal nucleus in diencephalic amnesia after CT scans indicated a small lesion seemingly restricted to the left mediodorsal thalamus (Squire & Moore, 1979). However, subsequent MRI studies have revealed damage in the left thalamic area, including the internal medullary lamina, the intralaminar nuclei, portions of the ventral lateral and ventral anterior nuclei, as well as bilateral damage to the mammillary bodies (Squire, Amaral, Zola-Morgan, Kritchevsky, & Press, 1989). Thus, although patient N.A. has proven extremely valuable to psychologists in characterizing the nature of the memory impairment associated with diencephalic damage (as opposed to the more diffuse damage typical
of Korsakoff amnesia), his case has done little to resolve the controversy surrounding the relative contributions of the mediodorsal nucleus and mammillary bodies.

The nature of N.A.'s brain injury is consistent with a recent hypothesis that diencephalic amnesia results from damage to diencephalic structures that are directly linked to hippocampal and amygdalar circuits (Graff-Radford et al., 1990; Parkin, Rees, Hunkin, & Rose, 1994). Structures directly connected to the hippocampus include the mammillothalamic tract and the mammillary bodies; structures directly connected to the amygdala include the ventroamygdalofugal pathway and the mediodorsal thalamic nucleus. On the basis of their own and other studies of amnesic patients, Graff-Radford et al. (1990) concluded that a lesion affecting both circuits could be very small provided it was properly located in the anterior extent of the thalamus. They showed, using autoradiographic examinations of two monkeys, that a component of the ventroamygdalofugal pathway runs close to the mammillothalamic tract in the ventral anterior thalamic nucleus before terminating in the mediodorsal nucleus. Similarly, Parkin et al. (1994) suggested that damage to the projection from the perirhinal cortex to the mediodorsal nucleus, which runs next to the ventroamygdalofugal pathway, may play a critical role in diencephalic amnesia. Given that rhinal cortex lesions produce severe DNMS deficits (see section I), the possible involvement of the perirhinal cortical projection in diencephalic amnesia warrants investigation.

Nonhuman Animal Studies

Animal models of human anterograde amnesia have provided another means of studying the relative effects of damage to various diencephalic structures. Aggleton and Mishkin were the
first to demonstrate that the DNMS task is sensitive to lesions of the medial diencephalon. They found that large bilateral lesions of the medial thalamus (including all of the midline nuclei and the mediodorsal nucleus) in monkeys produced marked deficits in DNMS (Aggleton & Mishkin, 1983a) comparable to the deficits observed in Korsakoff amnesics when tested on an analogous version of this task (Aggleton et al., 1988). However, interpretation of this study is complicated by the fact that many subjects sustained damage to the anterior nucleus of the thalamus and to the mammillothalamic tract, which resulted in cell loss in the mammillary bodies. Accordingly, Zola-Morgan and Squire (1985) repeated this experiment with much smaller lesions restricted largely to the posterior portion of the mediodorsal nucleus. They found that these lesions severely impaired both acquisition of the DNMS rule and DNMS performance at delays ranging from 15 s to 10 min. Together with a study showing that selective mammillary-body lesions in monkeys do not result in impaired DNMS performance (Aggleton & Mishkin, 1985), Zola-Morgan and Squire's findings reinforced the notion that mediodorsal-nucleus damage plays a critical role in diencephalic amnesia.

Indirect evidence supporting a role for the mediodorsal thalamic nucleus in object-recognition memory comes from studies of the effects of lesions to its principal projection site: the orbitofrontal cortex. Although prefrontal cortex damage in humans does not usually result in a full-blown amnesic syndrome (see Mayes, 1988), patients with prefrontal damage do sometimes display characteristic deficits on certain memory tasks (Milner, McAndrews, & Leonard, 1990; Schacter, 1987). Bachevalier and Mishkin (1986) were the first to demonstrate that lesions of the ventromedial prefrontal cortex in monkeys impair DNMS—the ventromedial lesion included both the orbitofrontal and anterior cingulate areas, which are the projection...
targets of the mediodorsal and anterior thalamic nuclei, respectively (Baleydier & Mauguiere, 1980; Barbas, Haswell, & Dermon, 1991). In a follow-up experiment, it was shown that monkeys with orbitofrontal damage (and significant neuronal degeneration in the mediodorsal thalamus) are more severely impaired on object-memory tasks than are monkeys with anterior cingulate lesions (Meunier, Bachevalier, & Mishkin, 1997). The authors concluded that object-memory processes are served by a circuit consisting mainly of the rhinal cortex, mediodorsal thalamic nucleus, and orbitofrontal cortex (Meunier et al., 1997)–see also Gaffan et al. (1993).

There have been numerous investigations of memory in rats following lesions of the medial diencephalon. However, in contrast to the study of diencephalic amnesia in monkeys, which has primarily involved tests of object recognition, experiments in rats have focused almost exclusively on spatial memory tasks. These experiments have produced inconsistent results; some studies have demonstrated deficits in spatial memory following medial-thalamic damage, whereas others have not. For example, lesions of the mediodorsal thalamus in rats have disrupted performance on the radial arm maze task (M’Harzi, Jarrard, Willig, Palacios, & Delacour, 1991; Stokes & Best, 1988; Stokes & Best, 1990), delayed alternation (Sakurai & Sugimoto, 1985; Winocur, 1985), acquisition and retention of spatial reversals (Kolb, 1977; Krazem, Beracochea, & Jaffard, 1995), and delayed nonmatching-to-position (Young, Stevens, Converse, & Mair, 1996); yet there are also many reports of preserved spatial memory abilities following similar lesions (e.g., Greene & Naranjo, 1986; Kolb, Pittman, Sutherland, & Whishaw, 1982; Neave, Sahgal, & Aggleton, 1993).

Recently, pyrithiamine-induced thiamine deficiency in rats has been used to model the etiology, diencephalic neuropathology, and memory deficits of Korsakoff’s amnesia. Using this
model, Langlais, Mair, and their colleagues have demonstrated highly reproducible lesions of the medial thalamus (including the mediodorsal nucleus and both the intralaminar and paralaminar nonspecific nuclei), the borders of the internal medullary laminae, and the medial mammillary bodies (Mair, Anderson, Langlais, & McEntee, 1988; Langlais, Mandel, & Mair, 1992). However, like lesion studies of the rat medial thalamus, behavioural studies of recovered pyrithiamine-treated rats have, for the most part, employed tasks that require rats to remember places, not objects. Because most studies of amnesia in humans and monkeys employ object-recognition tasks, comparisons with the rat studies have been difficult. Be that as it may, memory impairments have been found in pyrithiamine-treated rats on a number of spatial tasks, including the Morris water maze task, serial reversal learning, and both the delayed nonmatching- and matching-to-position tasks (e.g., Langlais et al., 1992; Langlais & Savage, 1995).

Although most studies of diencephalic amnesia in rats have focused on spatial memory tasks, recent investigations have begun to employ tests of object recognition similar to those used in studies of nonhuman primates. For example, it has been demonstrated that both rats with electrolytic lesions of the mediodorsal thalamus (Mumby, Pinel, & Dastur, 1993) and rats subjected to pyrithiamine-induced deficiency (Mumby, Mana, Pinel, David, & Banks, 1995) were impaired in the acquisition of a DNMS task and in DNMS performance over delays ranging from 15 to 300 s.

In summary, results of most human, monkey, and rat studies of the anterograde amnesia resulting from diencephalic damage, implicate damage to the mediodorsal thalamic region. However, the relative contributions to diencephalic anterograde amnesia of the mediodorsal
nucleus itself and adjacent thalamic structures (e.g., the internal medullary lamina or nonspecific thalamic nuclei) remain to be determined. One problem has been that studies of diencephalic amnesia in humans and nonhuman primates have focused on memory for objects, whereas almost all of the many studies of diencephalic amnesia in rats have focused on spatial memory.

III. ANTEROGRADE AMNESIA PRODUCED BY BASAL-FOREBRAIN DAMAGE

In addition to implicating the medial temporal lobes and medial diencephalon, case studies of human brain-damage-produced amnesia have implicated the basal forebrain in memory (see Mayes, 1988; 1995; Zola-Morgan & Squire, 1993). The major structures of the basal forebrain include the medial and lateral septal nuclei, the vertical and horizontal nuclei of the diagonal band of Broca, and the nucleus basalis of Meynert. These structures are thought to contribute to memory function by providing cholinergic innervation to the medial temporal lobes, as well as to most of the neocortex (Bartus, Dean, Beer, & Lippa, 1982). This section begins with a critical review of the different lines of evidence implicating basal-forebrain damage in anterograde amnesia in humans. Then, the various attempts to model the anterograde amnesia resulting from basal-forebrain damage in laboratory animals are described and their contributions discussed.

Human Studies

Evidence implicating the basal forebrain cholinergic system in human anterograde amnesia has come from three primary sources: (1) studies demonstrating the loss of basal forebrain neurons in neurodegenerative diseases characterized by marked memory impairment,
(2) studies demonstrating the amnesic effects in human patients of anticholinergic drugs, and (3) reports of anterograde memory impairment in individuals that have sustained basal-forebrain damage due to vascular trauma or surgical procedures. Although these three lines of evidence all suggest an important role for the basal forebrain in memory, each has particular shortcomings. Each of these three lines of evidence and its shortcomings are discussed in this subsection.

Alzheimer's Disease and the Cholinergic Theory of Memory

The study of Alzheimer's disease drew attention to the putative mnemonic functions of the basal forebrain. A loss of cholinergic neurons in the basal forebrain together with substantial reductions in the levels of cortical and limbic choline acetyltransferase is a characteristic feature of the neuropathology associated with dementia of the Alzheimer's type (Davies & Maloney, 1976; Whitehouse, Price, Struble, Clark, Coyle, & DeLong, 1982). The decrease in cholinergic markers observed in deceased Alzheimer patients has been found to be positively correlated with the degree of their cognitive impairment (Perry, Tomlinsom, Blessed, Bergmann, Gibson, & Perry, 1978). These findings precipitated the development of the "cholinergic hypothesis" of memory (Bartus et al., 1982): the hypothesis that the basal forebrain cholinergic system plays a central role in memory. Additional support for this hypothesis was provided by reports of positive correlations between basal forebrain degeneration in anterograde memory impairment in Parkinson (Perry, Curtis, Dick, Candy, Atack, Bloxham, Blessed, Fairbairn, Tomlinsom, & Perry, 1985) and Korsakoff patients (Arendt, Bigl, Arendt, & Tennstedt, 1983).

Several findings have challenged the attribution of Alzheimer's amnesia to cholinergic dysfunction (see Fibiger, 1991; Voytko, 1996). Three of the most problematic are the following: (1) levels of neurotransmitters other than acetylcholine (e.g., norepinephrine and serotonin) are
reduced in Alzheimer’s patients (see Coyle, 1987), (2) Alzheimer patients have brain damage outside the basal forebrain area to structures known to play a role in memory (e.g., the medial temporal lobes; see Hyman, Van Doesen, & Damasio, 1990), and (3) Alzheimer patients display a variety of perceptual, language, and attentional deficits, which could disrupt the performance of memory tasks (Olton & Wenk, 1987).

**Anticholinergic Drugs and Memory Impairment**

The second source of evidence implicating the basal forebrain cholinergic system in amnesia comes from psychopharmacological studies showing that human memory can be disrupted by anticholinergic drugs. For example, memory impairments have been demonstrated in normal human volunteers treated with the muscarinic-receptor antagonist scopolamine (Ghoneim & Mewaldt, 1975; Kopelman, 1986)—a finding that has been repeatedly confirmed in various animal models of memory (e.g., Aigner, Walker, & Mishkin, 1991; Eckerman, Gordon, Edwards, MacPhail, & Gage, 1980; Watts, Stevens, & Robinson, 1981). At present, however, there is considerable disagreement and debate about the psychological mechanisms underlying these deficits. On the basis that cholinergic receptors are distributed throughout the central nervous system, Fibiger (1991) has argued that the systematic application of anticholinergic drugs will almost certainly influence a broad spectrum of brain functions that could affect performance on memory tasks without affecting memory per se. The general inability of cholinergic agonists to forestall the progression of Alzheimer’s amnesia has also raised questions about theories claiming a key role for basal forebrain cholinergic neurons in memory (see Avery, Baker, & Asthana, 1997; McDonald & Overmier, 1998).
Amnesia Produced by Vascular or Traumatic Brain Injury to the Basal Forebrain

The third line of evidence in support of the involvement of the basal forebrain in normal memory function comes from reports of anterograde memory deficits in humans who have sustained basal-forebrain damage due to the rupture of anterior-cerebral or anterior-communicating-artery aneurysms (Alexander & Freedman, 1984; Damasio et al., 1985; Gade, 1982; Volpe & Hirst, 1983). In a review of these reports, Morris et al. (1992) noted that when the neuropathology included the diagonal band nuclei, the septal nuclei, and the nucleus basalis; the patients exhibited severe anterograde amnesia, with no deficits in short-term memory. Specific deficits in memory for the recency or temporal order of events have also been reported in such cases (Morris et al., 1992)—such deficits are also characteristic of patients with frontal-lobe lesions (e.g., Milner, McAndrews, & Leonard, 1990; Schacter, 1987). Indeed, a variety of cognitive deficits, other than memory deficits, have been found to be characteristic of both basal-forebrain and frontal-lobe damage: These include impaired abstract reasoning, increased distractibility, increased susceptibility to interference, and decreased cognitive flexibility (see Morris et al., 1992).

A major problem in determining the cause of memory deficits associated with the rupture of anterior communicating artery aneurysms is that structures other than the basal forebrain are often damaged: for example, orbitofrontal and cingulate cortex, the ventral striatum, and the anterior hypothalamus (Damasio et al., 1985; Gade, 1982; Parkin, Leng, Stanhope, & Smith, 1988). However, an exception to this pattern of diffuse neuropathology was recently reported; in this case, anterograde memory deficits were associated with a discrete lesion to the right diagonal band of Broca by resection of a low-grade glioma (Morris et al., 1992).
In summary, the neuropsychological investigation of the anterograde amnesia associated with damage or dysfunction of the basal forebrain cholinergic system in humans has been confounded by the possible contributions of pathology to other brain regions, by the overall decline in cognitive functioning that typically accompanies the amnesic deficit in Alzheimer patients, by the nonspecific effects of anticholinergic drugs, and by the diffuse lesions most often associated with cases of vascular trauma. Consequently, delineating the specific contributions of basal-forebrain structures to human memory impairment has proven difficult. For this reason, researchers have attempted to study anterograde amnesia in animals with selective lesions of the basal forebrain.

Nonhuman Animal Studies

Efforts to demonstrate anterograde memory deficits in monkeys following basal-forebrain damage have only recently begun. The results of these efforts have, so far, proven inconsistent. In one study, cynomolgus monkeys with combined ibotenic acid lesions of nucleus basalis, the medial septum, and the vertical nucleus of the diagonal band displayed DNMS impairments 2 weeks, but not 6 months, after surgery (Aigner, Mitchell, Aggleton, DeLong, Struble, Price, Wenk, Pettigrew, & Mishkin, 1991). In a second study, squirrel monkeys with ibotenic acid lesions of the nucleus basalis displayed deficits in DNMS, visual discrimination reversal learning, and concurrent object discrimination (Irle & Markowitsch, 1987). And in a third study, marmosets with ibotenic acid lesions of the diagonal band were impaired in learning a conditional-object discrimination task (Ridley, Aitken, & Baker, 1989). In contrast to these three studies, Aigner, Mitchell, Aggleton, DeLong, Struble, Price, Wenk, and Mishkin (1987) found
that cynomolgus monkeys with nucleus basalis damage displayed normal object-recognition memory; and Voytko, Olton, Richardson, Gorman, Tobin, and Price (1994) found that lesions of the medial septum, diagonal band, and nucleus basalis in cynomolgus monkeys disrupted attentional focusing but not DNMS, the learning of simple or concurrent visual discriminations, or the performance of a delayed-response task. Explanations of these discrepant results have focused on the possibility of functional differences between squirrel (New World) and cynomolgus (Old World) monkeys and on the differences in the topography of the lesions among the different studies (Voytko et al., 1994).

There have been numerous reports of the impaired performance of memory tasks following basal-forebrain lesions in rats. However, in contrast to the object-recognition tasks that have been used to investigate the effects of basal forebrain lesions in monkeys, the tasks that have been used to investigate the behavioral effects of basal forebrain lesions in rats have almost all been tests of memory for places. For example, rats with medial-septal damage have been found to be impaired in T-maze alternation (Rawlins & Olton, 1982), performance on the Morris water maze (Hagan, Salamone, Simpson, Inversion, & Morris, 1988), reference and working measures of performance in the eight-arm radial maze (Decker, Radek, Majchrzak, & Anderson, 1992; Hepler, Olton, Wenk, & Coyle, 1985), and performance on a delayed matching-to-position task using lever-position stimuli (Harper, McLean, & Dalrymple-Alford, 1994). Thus, the study of the amnesic effects of basal-forebrain lesions in rats has done little to resolve the inconsistencies in the primate literature.

The two studies that have examined anterograde object-recognition memory in rats following basal forebrain lesions have reported unexpected results. First, Ennaceur and Meliani
(1992) found that medial-septal-lesioned rats performed significantly better than control rats on a spontaneous object-recognition task at 15-min and 60-min retention delays. This task, however, differed substantially from the DNMS procedure used to measure object-recognition abilities in monkeys; object-recognition memory was assessed by calculating the relative amount of time rats spent exploring (i.e., directing their nose towards or touching with their nose) an unfamiliar test object in comparison to a recently presented 'sample' object. Contrary to the numerous reports of impaired spatial memory following damage to the medial septum, Ennaceur and Meliani did not find any indication of a deficit in recognition memory when their medial-septal-lesioned animals were tested on an analogous spatial version of this task.

In the second rat study of the effects of basal-forebrain damage on object-recognition memory, Kelsey and Vargas (1993) reported that rats with small lesions of the medial septum were unimpaired in the performance of a Y-maze task in which objects were the test stimuli but displayed profound deficits in the same task when arm-location was the critical discriminative stimulus. Furthermore, similar to the enhanced memory performance reported by Ennaceur and Meliani, the performance of the septal-lesioned rats was significantly better than that of controls on the object-recognition version of their task when the retention interval was 1 min (although no significant differences were reported at the two other delays of 30 s and 2 min). Again, critical task differences complicate comparisons with the monkey DNMS experiments: The same two stimulus objects were presented on each trial; the criterion for initial learning of the nonmatching rule was far less stringent; and the rats were returned to their home cages during each intertrial interval. The fact that the rats had prior experience with the spatial version of the task before the object-recognition test also raises the possibility that the poor performance of the control rats,
and hence the significantly higher scores of the septal-lesioned rats, at delays of 1 min or greater reflects a perseveration of spatial strategies.

Lesions of the basal forebrain produce behavioural deficits, in addition to memory deficits, and the nature of the observed deficits appears to be related to the particular basal-forebrain structures that are damaged. In rats, for example, deficits in attention have been reported to be the principle cognitive effect of nucleus basalis lesions (e.g., Robbins, Everitt, Ryan, Marston, Jones, & Page, 1989), whereas medial septal lesions have most often been linked to deficits in spatial memory. In a key study, Olton et al. (1988) found that rats with damage to either the medial septum or the fornix exhibited similar deficits on a memory task that required memory for the duration of a tone, but no deficits on a divided-attention task that required the timing of the duration of a tone in the presence of an interfering tone; in contrast, damage to either the nucleus basalis or frontal cortex impaired performance on the divided-attention task, but had no effect on the memory task. Olton et al. concluded that different cognitive processes in the rat might depend upon the integrity of distinct components of the basal forebrain, and this conclusion has been supported by recent findings (see Dunnett, Everitt, & Robbins, 1991; Muir, Page, Sirinathsinghji, Robbins, & Everitt, 1993). However, both Baxter et al. (1997) and Chiba et al. (1995; 1997) have recently demonstrated that lesions of the medial septum and diagonal band produce impairments on tasks that primarily assess attention.

Although the extent to which lesions of the basal forebrain in monkeys might disrupt attentional processes has not been investigated to same degree as it has in rats, there is supporting evidence for the involvement of the monkey basal forebrain in attention. Voytko et al. (1994) found that although monkeys with neurotoxic lesions of the medial septum, diagonal band, and
nucleus basalis were unimpaired on a number of different object-memory tasks, including DNMS, they had great difficulty performing a task requiring them to shift their attention from one location to another. Even though the neurotoxic injections in this experiment destroyed neurons throughout the basal forebrain, the majority of the damage was produced in the nucleus basalis. Furthermore, Voytko (1996) argued that demonstrations of a DNMS impairment in monkeys following lesions of the nucleus basalis (e.g., Irle & Markowitsch, 1987) may not represent a pure memory defect because increasing demands on memory (e.g., by increasing the retention delay) has not led to significant increases in the deficits.

In summary, the available evidence from both rat and monkey studies is confusing, and at times contradictory, but it seems to suggest that damage to the medial septum, diagonal band, or both is more likely than damage to the nucleus basalis to produce anterograde deficits on memory tasks; whereas the nucleus basalis may play a more important role in certain aspects of attentional processing. Such a dissociation might be a reflection of differences in the principal projection sites of these two distinct divisions of the basal forebrain: the medial septum and diagonal band provide the main source of cholinergic input to the hippocampal formation and adjacent rhinal cortex (Gaykema, Luiten, Nyakas, & Traber, 1990; Mesulam, Mufson, Levey, & Wainer, 1983), whereas the nucleus basalis primarily innervates the amygdala, parietal cortex, and dorsolateral frontal cortex (Kesner, 1988; Mesulam et al., 1983).
IV. BRAIN-DAMAGE-PRODUCED RETROGRADE AMNESIA

So far this introduction has focused on brain-damage-produced anterograde amnesia, amnesia for events that occurred subsequent to the damage. It now turns to a discussion of brain-damage-produced retrograde amnesia, amnesia for events that occurred before the damage.

Despite reports that retrograde amnesia is slight (e.g. Dusoir et al., 1990; Squire et al., 1989; Zola-Morgan, Squire, & Amaral, 1986) or nonexistent (e.g., Parkin et al., 1994; Winocur et al., 1984) in some amnesic patients, retrograde amnesia is often assumed to be a major component of all amnesic syndromes. Uncertainty surrounding the retrograde amnesia produced by damage to the medial temporal lobe, medial diencephalon, or basal forebrain is due in large part to the numerous methodological problems involved in assessing remote memory in human amnesics. This section begins with a consideration of these difficulties inherent to the assessment of retrograde amnesia in amnesic patients followed by a review the evidence regarding the nature and extent of the retrograde memory impairment associated with damage to the medial temporal lobe, medial diencephalon, and basal forebrain in humans. Finally, there is a review of recent studies of brain-damage-produced retrograde amnesia in monkeys and rats.

Human Studies

Methodological Difficulties

The first quantitative studies of brain-damage-produced retrograde amnesia in amnesic patients did not appear until the early 1970s (Sanders & Warrington, 1971). The relatively late inception of the study of retrograde amnesia and its relatively slow progress is largely attributable to the difficulties in objectively assessing retrograde memory deficits in these subjects.
Studies of retrograde amnesia in human patients have often used the recollection of autobiographical information as the measure of premorbid memory (see Squire, 1991). To conduct an autobiographical memory test, the researcher must first compile a list of questions concerning the patient's past history. This information is usually based on interviews with the patient's family and friends and contains questions relating to a number of different time periods prior to the patient's brain insult. This list is then used to assess the patient's recollection of past events (e.g., Borrini, Dall'ora, Della, Marinelli, & Spinnler, 1989).

In addition to the autobiographical method, researchers have tried to determine the severity of retrograde amnesia for experiences occurring at various intervals before the brain damage by assessing familiarity with historical events and individuals who were temporarily in the spotlight in different years. For example, the Boston Retrograde Amnesia Test Battery (Albert, Butters, & Levin, 1979) requires the subjects to provide the names of famous individuals presented in photographs or answer questions regarding major events over the last six decades.

Unfortunately, both the autobiographical method and the tests of retrograde memory for popular events or personalities have serious limitations. For example, during autobiographical tests of premorbid memory, many amnesic patients have a tendency to fabricate responses (Schacter, Wang, Tulving, & Freedman, 1992), which are often difficult to identify. Furthermore, each patient has a unique set of memories, thereby making quantification and generalization among the results of different studies employing the autobiographical method quite difficult. Although the development of the "popular-events tests" helped in addressing these problems, they too are faced with a major methodological shortcoming: Differences in item difficulty vary across decades. Subjects may perform better on the questions that probe
events or celebrities from the remote past than from the recent past because information from the remote past has had a longer period of exposure, allowing for easier recall (Butters, Delis, & Lucas, 1995) or because more remote personalities or historical events may simply be more famous than recent ones.

In an attempt to overcome the problem of differences in item difficulty, Squire and Slater (1975) developed a test of public events that assumed equal exposure for events taken from across the years. Their measure of retrograde amnesia, known as the “television test,” consisted of questions relating to TV programs that were broadcast for only one season. However, the rarity of programs with the necessary combination of widespread, but transient, popularity has proven to be a limiting factor of this technique. More importantly, the television test is subject to a confound: references to older programs are more likely to appear in the press or in personal discussions after they have been taken off the air.

It is clear from the methodological problems associated with the above-mentioned tests that what is ideally required of studies of retrograde amnesia is control over both the initial level of learning and the intervening exposure to the learned material. Unfortunately, the retrospective nature of these investigations in human patients precludes such controls.

Another methodological problem characteristic of many studies of human retrograde amnesia is related to the way in which putative retrograde deficits are typically quantified and reported. An important distinction should always be made between the length and the severity of a retrograde memory deficit. The length of retrograde amnesia denotes the period of time over which there is a significant loss of premorbid memories; the severity of retrograde amnesia refers to the degree to which memories have been forgotten by amnesic patients for the affected
time periods. Much of the existing research in this field, however, has avoided this distinction, and this has made comparing the retrograde amnesias reported in different studies difficult (see Parkin, 1984). To complicate matters further, both the length and severity of retrograde amnesia have been found to depend upon the manner in which retrograde memory impairment is assessed (autobiographical recall vs. recall of public events or famous faces; see Squire, 1992).

Aside from the methodological issues associated with the testing of remote memory in humans, measures of retrograde amnesia in brain-damaged patients are subject to the confounding problem of drugs and illness before either surgery or clinical diagnosis. For example, determining the true extent of H.M.'s retrograde memory loss is an impossible task considering both his frequent epileptic seizures and heavy doses of anticonvulsant medication in that he received in the months prior to surgery. Similarly, the study of retrograde amnesia is complicated in Korsakoff's amnesics, by premorbid alcohol consumption and the insidious onset of the disease.

**Retrograde Amnesia in Patients With Diencephalic Damage**

Most studies of human retrograde amnesia are studies of Korsakoff patients suffering diencephalic damage. There are several reports that Korsakoff amnesics can remember events from their childhood and early adulthood, but have great difficulty in recollecting events that occurred in the years immediately prior to their disorder (e.g., Albert et al., 1979; Butters & Stuss, 1989; Seltzer & Benson, 1974; Squire, Haist, & Shimamura, 1989).

Despite the widespread belief that the diencephalic pathology associated with Korsakoff's syndrome produces severe retrograde amnesia (Parkin, 1984; Squire, 1991), there is good reason for cautious skepticism because the ostensible retrograde memory impairment
observed in Korsakoff amnesics at diagnosis may actually be an anterograde deficit produced by heavy alcohol consumption and premorbid phases of the disorder. This view, termed the "continuity hypothesis" (Ryback, 1971), can account for the fact that recent memories are more affected than remote memories in Korsakoff patients (Parkin, 1991).

The notable single-case study of patient P.Z. (Butters & Cermak, 1986) challenges the continuity hypothesis; it provides evidence that the retrograde amnesia seen in Korsakoff amnesics can, at least in one case, be distinct from the anterograde deficit. P.Z. was a scientist with a history of heavy drinking that culminated in full-blown Korsakoff's syndrome. At diagnosis, he had a temporally-graded retrograde memory deficit extending back almost 20 years, yet only 2 years before diagnosis he had written a detailed autobiography attesting to the fact that his general cognitive status and remote memory prior to the disorder was reasonably good.

Additional support for the view that the retrograde memory impairment in Korsakoff patients is distinct from the anterograde memory impairment comes from the failure to find significant positive correlations between the severity of anterograde and retrograde deficits in groups of Korsakoff patients (Kopelman, 1989, 1991; Parkin, 1991; Shimamura & Squire, 1986). This finding has led to the hypothesis that anterograde and retrograde amnesia involve damage to different structures in Korsakoff patients (Parkin, 1991). In one test of this hypothesis, Kopelman (1991) found only 21% shared variance between measures of anterograde and retrograde memory impairment in Korsakoff patients but 68% shared variance between measures of frontal lobe function and retrograde amnesia. On the basis of these results, Kopelman (1995) speculated that frontal-lobe damage might underlie the retrograde amnesia associated with
Korsakoff's syndrome, whereas medial-diencephalic damage might underlie the anterograde amnesia.

Support for a functional distinction between the anterograde and retrograde components of Korsakoff's syndrome also comes from case studies of patients with medial diencephalic tumours, infarctions, or lesions. In one such case, patient M.G., resection of a hypothalamic glioma produced an anterograde impairment as severe as that of most Korsakoff amnesics but no retrograde memory impairment (referenced in Parkin, 1991). Other cases of severe diencephalic anterograde amnesia without substantial retrograde amnesia have been documented following discrete thalamic infarctions (Parkin & Leng, 1995; Parkin et al., 1994; Winocur et al., 1984) or penetrating paranasal brain injuries (Dusoir et al., 1990; Squire et al., 1989).

Retrograde Amnesia in Patients With Medial-Temporal-Lobe Damage

In contrast to Korsakoff patients, patients who have undergone bilateral temporal lobectomy seem to be better suited to the study of retrograde amnesia because the amnesia-inducing event (i.e., the surgery) is punctate. However, there are still major difficulties in assessing the retrograde amnesia of most temporal lobe amnesics. For example, in the period before his surgery, H.M. was experiencing grand mal seizures at the rate of more than once per week, despite heavy and varied anticonvulsant medications (Milner, 1966; Scoville, 1968). Clearly, H.M.'s epileptic condition and medication may have interfered with the processes of memory formation in the period preceding his lobectomy and confounded attempts to assess his retrograde amnesia. Not surprisingly, there has been debate over the length of the period over which H.M.'s retrograde memory deficits extend. Initially, H.M. was reported to have a relatively mild memory deficit for events occurring in the 2 to 3 years prior to his surgery (Milner
et al., 1968), but more recent neuropsychological assessments have suggested that his retrograde amnesia may extend as far back as 11 years before his surgery (Corkin, 1984; Sagar, Cohen, Sullivan, Corkin, & Growdon, 1985). However, whether his poor memory for experiences before his surgery reflects a bona fide retrograde deficit will always remain in doubt.

In general, studies of retrograde amnesia in medial-temporal-lobe amnesics have provided inconsistent results. Reports range from relatively severe impairments extending back as far as 20 years (Dimsdale, Logue, & Piercy, 1964; Squire et al., 1989), to moderate deficits encompassing only a year or two prior to injury (Milner, 1959; Victor, Angevine, Mancall, & Fisher, 1961), to no retrograde amnesia whatsoever (Muramoto, Kuru, Sugishita, & Toyokura, 1979). However, like H.M., many of these patients underwent temporal lobe resections for the treatment of severe cases of epilepsy, and reports of their retrograde amnesia must be viewed with reservation.

The variability in retrograde memory impairment observed in medial-temporal lobectomy patients extends to those with medial-temporal-lobe damage caused by herpes simplex encephalitis. Parkin (1984) concluded that postencephalitic amnesics are likely to experience a lengthier period of retrograde amnesia than that experienced by temporal lobectomy patients; however, the extent of the retrograde deficit reported in postencephalitic patients has varied from 2 years to over 30 years. Moreover, many cases of herpes simplex encephalitis involve damage outside the medial temporal lobes (e.g., diencephalic structures), and the neuropathology associated with this disease also has an insidious onset, both of which could contribute to the relatively long period of retrograde amnesia that is sometimes observed in these patients (Parkin, 1984).
Retrograde Amnesia in Patients with Basal-Forebrain Damage

Varying degrees of retrograde memory impairment are typically observed in cases of basal-forebrain damage (e.g., Damasio, Tranel, & Damasio, 1989; Damasio et al., 1985; Gade, 1982; Volpe & Hirst, 1983). However, these reports are difficult to interpret because the rupture of anterior cerebral or anterior communicating artery aneurysms, the most common cause of basal-forebrain damage, often produces damage that extends far beyond the boundaries of the basal forebrain. Commonly damaged additional structures include the orbitofrontal cortex, the cingulate cortex, the nucleus accumbens, and the anterior hypothalamus.

Evidence that discrete damage to the basal forebrain alone can cause severe retrograde amnesia, comes from the study of patient S.J. He developed both anterograde and retrograde memory loss following surgical removal of a glioma that resulted in a small lesion centered in the right diagonal band (Morris et al., 1992). His retrograde amnesia reportedly spans the 4 to 5 years prior to his surgery; however, these memory deficits could be premorbid anterograde effects of the tumor.

Temporal Gradients in Retrograde Amnesia

One of the most widely accepted conclusions to emerge from the study of amnesic patients is the notion that retrograde amnesia is most often temporally graded, that is, that amnesic patients are likely to experience a greater loss of recent memories than of more remote memories. This view can be traced back to 1881, when Theodule Ribot concluded on the basis of a large sample of case reports of human amnesia, that “the new perishes before the old” (ref. Squire, 1991). The temporally-graded nature of retrograde amnesia is the basis for the concept of memory consolidation: the idea that memories are actively transferred from a temporary, limited
memory store in the brain (short-term memory) to a more permanent store capable of holding an infinite amount of information (long-term memory). The preferential sparing of memories for remote events following brain damage also suggests that the damaged brain systems play only temporary roles in memory storage, that memories are temporally dependent on these structures before gradually becoming independently established in other areas of the brain.

In contrast to the typical pattern of loss of recently acquired memories and sparing of more remote memories, some amnesic patients have retrograde amnesia with no evidence of a temporal gradient (see Squire, 1992). This pattern of impairment, in which retrograde memories are similarly affected across all time periods has been observed following unilateral temporal lobectomy and in cases of diencephalic amnesia, encephalitis, and Alzheimer's disease (Barr, Goldberg, Wasserstein, & Novelty, 1990; Beatty, Salmon, Butters, Heindel, & Granholm, 1988; Cermak & O'Connor, 1983; Graff-Radford et al., 1990). One possibility is that ungraded retrograde amnesia may simply represent the extreme on a continuum of severity; the retrograde deficit may extend so far back in some cases that it makes it extremely difficult to detect a temporal gradient.

Squire (1992) has suggested an alternative hypothesis to the hypothesis that ungraded retrograde amnesia reflects an extreme amnesic condition characterized by correspondingly severe anterograde amnesia. He proposed that severe, ungraded retrograde amnesia requires damage in addition to (or different from) the medial-temporal-lobe, diencephalon, or basal-forebrain structures. This additional damage might impair performance on remote-memory tests without contributing proportionally to anterograde amnesia. Some support for this view comes from the study of patient D.R.B. (Damasio, Eslinger, Damasio, Van Hoesen, & Cornell, 1985),
who developed amnesia following extensive medial-temporal-lobe and basal-forebrain damage caused by herpes simplex encephalitis. Although the extent of D.R.B. ’s anterograde memory loss is typical of that seen following cases of similar etiology, he suffers from a flat retrograde deficit extending back over the entire 5 decades of his life. What separates D.R.B. ’s neuropathology from other postencephalitic amnesics is the involvement of the lateral temporal lobes, and the authors suggest that it is this additional damage that contributes to his severe retrograde amnesia (Damasio et al., 1985). Lesions in lateral or anterior temporal cortex have also been noted in several other reports of ungraded retrograde amnesia (Squire, 1991), and cases of retrograde amnesia in the absence of any anterograde memory impairment may be associated with relatively selective damage to this brain region (see Kapur, 1993).

In summary, although damage to the medial temporal lobes, medial diencephalon, or basal forebrain does seem to produce retrograde memory deficits, these deficits have been difficult to characterize in human patients. To clearly define the structures responsible for retrograde amnesia, experimenters need groups of subjects with precisely positioned lesions and they need to control the information that subjects are exposed to prior to brain surgery.

Animal Studies

The difficulties involved in studying retrograde amnesia in human patients have encouraged the study of retrograde amnesia in animal models. Still, retrograde amnesia is difficult to study in laboratory animals, and studies of retrograde amnesia in animal models have been relatively rare in comparison to the many studies that have assessed anterograde memory deficits in laboratory animals following brain damage. Most studies of brain-damage-produced
retrograde amnesia in animals have focused on the effects of damage to the hippocampus and adjacent cortical areas.

The results of experiments in monkeys support the notion that bilateral medial-temporal-lobe damage produces retrograde memory impairments. For example, Zola-Morgan and Squire (1990) had monkeys learn sets of different object-discrimination pairs at varying intervals before surgery, and then they retested the animals on the same discrimination problems following surgery. Monkeys with large medial-temporal-lobe lesions, including the hippocampus as well as the surrounding entorhinal and parahippocampal cortices, displayed temporally graded retrograde amnesia: They remembered object-discrimination pairs learned 8, 12, or 16 weeks before surgery as well as controls, but their retention of object pairs learned 2 or 4 weeks before surgery was impaired.

Retrograde amnesia was also demonstrated in an earlier study by Salmon, Zola-Morgan, and Squire (1987), however, in this case an ungraded retrograde deficit was observed in monkeys for object discriminations learned up to 8 months prior to surgery. The lack of a temporally graded impairment in Salmon et al.’s study has been attributed to the extensive medial-temporal-lobe lesions (which included the amygdala, the hippocampus, as well as entorhinal, perirhinal, and parahippocampal cortices) and to preoperative overtraining of object-discrimination pairs (Zola-Morgan & Squire, 1990). Although the results of these studies confirm that medial-temporal-lobe damage in monkeys can produce impairments in retrograde memory, the size of the lesions precludes any conclusions concerning the role of specific structures such as the hippocampus or rhinal cortex.
In contrast to the study of retrograde amnesia in monkeys, which has focused primarily on object memory, experiments designed to assess retrograde amnesia in rats have mostly employed tests of either implicit memory or spatial memory. For example, hippocampectomy in rats has been reported to produce temporally graded retrograde amnesia for both conditioned fear (Kim & Fanselow, 1992) and trace-eyeblink conditioned responses (Kim, Clark, & Thompson, 1995). Also, there have been several reports of temporally graded retrograde memory deficits for spatial discriminations following lesions of either the rhinal cortex or hippocampus (e.g., Cho, Beracochea, & Jaffard, 1993; Cho & Kesner, 1996; Cho, Kesner, & Brodale, 1995). Despite the fact that these findings suggest a role for various medial-temporal-lobe structures in the consolidation process in the rat, important task differences make it difficult to directly compare these results to those of either the monkey or human studies.

In order to facilitate direct comparison of retrograde amnesia in monkeys and rats, Mumby, Sutherland, Astur, and Weisand (1994) developed a paradigm for assessing retrograde amnesia in rats based on Zola-Morgan and Squire’s (1990) procedure for testing retrograde amnesia in monkeys. Mumby et al. trained rats on five different object-discrimination problems at different times prior to either hippocampectomy or a sham surgical procedure, and then they tested them for their retention of each problem following surgery. Mumby et al. found that the hippocampectomized rats displayed normal retention of all preoperatively-learned object-discrimination problems; however, the same rats, who were also trained on two separate water-maze place-memory problems at different times prior to surgery, displayed postsurgical deficits in retention of only the more recently acquired water-maze problem. These results support consolidation theories of hippocampal function; however, they indicate that in rats, at least, this
role applies to information about places, but not about objects. Also, Mumby et al.'s findings suggest that the lesion responsible for the retrograde amnesia for objects seen in monkeys with diffuse medial-temporal-lobe damage may lie outside the hippocampus.

Despite the numerous accounts of retrograde memory impairment in human patients following damage to the medial diencephalon and basal forebrain, studies of retrograde amnesia in laboratory animals with lesions of these brain areas are notably lacking. In one of the few studies to investigate the effect of diencephalic damage on retrograde memory in nonhumans, Winocur (1990) found that rats with lesions of either the mediodorsal thalamus or dorsal hippocampus displayed absolutely no retention of a preoperatively learned socially transmitted food preference if the food preference was acquired immediately prior to surgery. However, thalamic-lesioned rats displayed normal retention if the food preference was acquired 2, 5, or 10 days prior to surgery, whereas hippocampal-lesioned rats reached normal performance levels only when the learning-surgery interval was 5 days or more. Winocur (1990) proposed that the absence of any retention for the food preference when it is acquired immediately prior to either lesion may be a result of nonspecific trauma associated with brain surgery itself. If this interpretation is correct, the loss of retrograde memories in the hippocampal-lesioned rats up until 5 days before surgery still suggests a time-limited role for this brain structure in memory consolidation, but the lack of a retrograde deficit in the thalamic-lesioned rats for all learning intervals aside from the immediate condition questions whether the mediodorsal thalamus is involved in a similar process.

Another experiment in which both retrograde and anterograde memory were tested in rats was published by Langlais et al. (1992). They assessed the effects of pyrithiamine-induced
medial thalamic and mammillary body lesions. In this experiment, acute thiamine deficiency was found to cause an anterograde learning impairment, but not a retrograde impairment for the position of a hidden platform in the Morris water maze.

In summary, the results of the available nonhuman animal studies suggest that the medial diencephalon and medial temporal lobes may make unequal contributions to the retention of retrograde memories: Medial-thalamic damage has generally failed to produce retrograde memory deficits in rats, whereas medial-temporal-lobe damage has been shown to produce temporally graded retrograde amnesia in both monkeys and rats with relative consistency. However, comparisons between studies examining the effects of damage to different brain structures in the same species, or to similar structures in different species, have often been confounded by the fact that these studies have assessed retrograde memory for very different types of information.

V. COMPARISON OF THE AMNESIAS ASSOCIATED WITH DAMAGE TO THE MEDIAL TEMPORAL LOBE, MEDIAL DIENCEPHALON, OR BASAL FOREBRAIN

Damage to the medial temporal lobe, the medial diencephalon, or the basal forebrain causes severe memory impairment in humans and nonhuman animals. Although the amnesias produced by damage to these three brain areas share many general features, some differences have been reported (see Cohen & Squire, 1981; Gainotti & Marra, 1992; Parkin, 1984; Parkin & Leng, 1993). Are these differences simply a matter of degree, or do these three areas of the brain play different roles in memory? This question is the major focus of this thesis.
Although ostensibly simple, the question of whether amnesia caused by damage to different brain areas reflects a unitary disorder or a group of distinct disorders has been a difficult one to answer. The major reason for this lack of progress is that the controlled parametric experiments needed to answer the question are not possible in amnesic patients, on whom efforts to answer this question have focused. Accordingly, efforts to compare the amnesias associated with damage to the medial temporal lobe, medial diencephalon, or basal forebrain have shifted to the study of monkeys and rats. This section begins with a brief review of previous efforts to distinguish among the amnesias produced by damage to these three brain areas in human patients, and it is followed by a discussion of recent experiments in laboratory animals that have attempted to address this issue.

**Human Studies**

Although basal-forebrain damage has been shown to result in a syndrome characterized by disproportionate memory impairment relative to other cognitive functions (Damasio et al., 1985; Mayes, 1995), systematic investigations of the amnesia produced by damage to the basal forebrain have been infrequent. Therefore, the debate over whether damage to different brain areas produces similar or different kinds of memory impairment has focused on the differences between the amnesia produced by lesions of the medial temporal lobe and the medial diencephalon. In particular, much attention has been paid to comparing the forgetting rates associated with these two amnesias.

In a series of experiments in the late 1970s, Huppert and Piercy were the first to systematically compare the rate of forgetting in medial-temporal-lobe and diencephalic amnesia.
In their initial study, Huppert and Piercy began by equating the memory performance of Korsakoff amnesics and control subjects on a visual recognition test at the shortest test delay by allowing amnesics longer to study the test items during the learning presentation. Forgetting rates in these patients were then assessed by measuring retention of the test material one day and one week following learning. The amnesic subjects were found to forget at the same rate as their normal controls (Huppert & Piercy, 1978). However, Huppert & Piercy (1979) subsequently found using the same procedure that H.M. forgot at a pathologically fast rate. These patterns of normal and increased rates of forgetting in patients with presumed medial-diencephalic and medial-temporal-lobe damage, respectively, were replicated in an experiment by Squire (1981).

Although the aforementioned studies initially suggested that medial-temporal-lobe amnesics forget at an abnormally fast rate, whereas medial-diencephalic amnesics forget at a normal rate, subsequent research has failed to confirm this hypothesis. For example, Freed, Corkin, and Cohen (1987) reported a normal rate of forgetting in H.M. over a one week period; and McKee and Squire (1992) and Mayes, Downes, Symons, and Shoqirat (1994), found that forgetting rates were exactly the same in patients with medial-diencephalic amnesia as they were in patients with medial-temporal-lobe amnesia. In yet another experiment, Leng and Parkin (1989) found that postencephalitic patients who likely had medial-temporal-lobe damage forgot significantly faster than Korsakoff patients over the first 5 minutes, but not thereafter. Clearly, the results of studies of forgetting rates in human amnesics have proven inconsistent.

A number of other qualitative differences, other than differences in forgetting rates, have been hypothesized to exist between the amnesias associated with temporal-lobe and medial-diencephalic pathology. These include differences in the sensitivity to interference during short-
term memory tasks, in perseverative errors, in the ability to release from proactive interference, in the memory for the temporal order of events, and in the length of retrograde amnesia (see Parkin, 1984; Winocur et al., 1985). Of these hypothetical differences, memory for temporal order, and length of retrograde amnesia have been the focus of some research in human amnesics.

In one clinical study of memory for temporal order, Parkin, Leng, and Hunkin (1990) found poorer recency judgments in diencephalic (i.e., Korsakoff's) amnesics than in temporal-lobe (i.e., postencephalitic) amnesics. The superior performance of the postencephalitic amnesics was subsequently shown to be the result of neither a faster rate of forgetting in these amnesics nor increased proactive interference in the Korsakoff patients (Hunkin & Parkin, 1993). In another study of memory for temporal order in human patients, diencephalic and medial-temporal-lobe amnesics performed similarly on a measure of verbal word recognition, but the diencephalic amnesics performed more poorly than the medial-temporal-lobe amnesics on a test of temporal discrimination for similar information (Hunkin, Parkin, & Longmore, 1994).

The length of retrograde amnesia, another putative difference between medial-temporal-lobe and medial-diencephalic amnesia that has been the focus of some research in human patients, is thought to be greater in diencephalic amnesics than in temporal-lobe amnesics. This conclusion is based on the observation that the retrograde amnesia associated with Korsakoff's disease is often longer than that associated with medial-temporal-lobe amnesia (e.g., Butters & Albert, 1982; Parkin, 1984). However, Kopelman (1995) has argued that it is Korsakoff-related damage to structures outside the diencephalon, for example, to the frontal lobe, that underlies the extensive retrograde memory loss often observed in Korsakoff patients—retrograde memory
deficits following selective damage to the diencephalon (due to vascular or traumatic brain injury) are often either very short in duration or nonexistent (e.g., Dusoir et al., 1990; Parkin et al., 1994; Squire et al., 1989; Winocur et al., 1985).

In conclusion, although several differences between human medial-temporal-lobe and diencephalic amnesia have been hypothesized, studies of human amnesics have yet to provide strong support for any one of them. Indeed, it is often argued that the medial temporal lobes and medial diencephalon belong to a single, larger functional “memory system,” and that damage to either of these brain areas produces a comparable amnesic syndrome (see Victor et al., 1989; Zola-Morgan & Squire, 1993).

As previously mentioned, one of the difficulties in comparing the amnesias associated with damage to different brain areas in human patients stems from the difficulty in specifying the exact location and extent of the brain lesion responsible for the behavioural changes in question. Another reason is that until recently there have been few ways, other than etiology, by which to differentiate amnesic groups, and many theorists have emphasized that if etiology does not respect functional “information processing boundaries” in the brain, then members of an etiological group may represent different amnesic states (e.g., Downes & Mayes, 1997; Pickering, 1997). This in turn could lead to an increase in within-group variance and a reduction in the power of between-group comparisons (DeLuca & Diamond, 1995; Pickering, 1997). Both of these reasons may help explain why the results from one lab or neuropsychological study often fail to replicate those of other labs or studies.

The diffuse neuropathology that often accompanies human amnesia has frequently led to the suggestion that the effects associated with some amnesic cases are incidental to the syndrome
because they are the result of adventitious brain damage to structures that have nothing to do with
the syndrome (e.g., Squire, 1982). This point is especially critical because the majority of the
data characterizing “diencephalic” amnesia come from studies of patients suffering from
Korsakoff’s syndrome. Although pathological investigations of Korsakoff amnesics have
generally indicated brain damage centered around the medial diencephalon (see Section II), the
underlying neuropathology is far more extensive. In particular, post mortem examination of the
brains of Korsakoff patients quite often reveal extensive cortical atrophy in the frontal regions
(Harper, Kril, & Daly, 1987; Wilkinson & Carlen, 1980). This raises the possibility then, that
certain features thought to be characteristic of diencephalic amnesia, such as perseveration and
temporal-order memory deficits, might actually be products of frontal-lobe damage.

Evidence to support the hypothesis that frontal-lobe pathology may be responsible for
certain aspects of the amnesic syndrome associated with Korsakoff’s disease comes from recent
functional neuroimaging studies. In one study (Paller, Acharya, Richardson, Plaisant,
Shimamura, Reed, & Jagust, 1997), high-resolution positron emission tomography was used to
measure regional cerebral metabolic rates for glucose utilization in five alcoholic Korsakoff
patients and nine alcoholic control subjects. Results indicated that, compared to controls,
Korsakoff patients demonstrated both a marked memory impairment in delayed recognition and a
widespread decline in glucose metabolism in frontal and cingulate regions.

Frontal lobe dysfunction has also been implicated in reports of diencephalic amnesia
arising from unilateral thalamic infarcts. Pepin and Auray-Pepin (1993) tested three such
patients and found that they displayed decreased cerebral blood flow in ipsilateral occipital and
dorsolateral prefrontal areas, in addition to within the diencephalon itself.
Nonhuman Animal Studies

The study of laboratory animals provides a means of circumventing several of the methodological problems inherent in comparing the amnesias produced by damage to different brain areas in humans. However, despite the methodological advantages and despite the existence of well established methods of studying brain-damage-produced amnesia in monkeys and rats, there have been only a few attempts to systematically compare in nonhumans, the amnesic deficits arising from damage to the medial temporal lobes, the medial diencephalon, or the basal forebrain. Efforts to understand the relation between basal-forebrain, medial-diencephalic and medial-temporal-lobe amnesia have had to largely rely on comparisons between different lines of experiments.

A few recent attempts have been made to directly compare the amnesic effects of medial-diencephalic damage and medial-temporal-lobe damage in monkeys. For example, Parker, Eacott, and Gaffan (1997) tested monkeys with bilateral ablation of the medial portion of the mediodorsal thalamic nucleus on a series of recognition memory and associative memory tasks that had been previously been used to assess mnemonic dysfunction in monkeys with rhinal cortex ablation (Eacott, Gaffan, & Murray, 1994). They reported that both mediodorsal thalamic lesions and rhinal cortex lesions impaired delayed matching-to-sample (DMS) performance with a large stimulus set; however, the thalamic lesions were significantly less disruptive than the rhinal lesions. The fact that the thalamic lesions in this study spared significant portions of the mediodorsal nucleus might account for the difference in impairment between the groups. Nonetheless, this experiments provides one of the first attempts to directly compare the
mnemonic effects of damage to the medial temporal lobe and medial diencephalon in monkeys on tasks sensitive to human amnesia.

There have also been some studies comparing the memory impairment produced by lesions of the medial temporal lobe, medial diencephalon, or basal forebrain in rats (e.g., Gray & McNaughton, 1983; Gross, Chorover, & Cohen, 1965; Winocur, 1985); however, the majority of these have focused on tests of spatial memory. This has made it difficult to integrate the findings with the findings of comparable studies of human amnesics and nonhuman primates, which have focused on tests of object recognition. Furthermore, the rat studies have typically compared the effects of hippocampal lesions with the effects of lesions to other brain structures such as the medial thalamus (Gross et al., 1965; Winocur, 1985) or medial septum (Gray & McNaughton, 1983), although it is now widely acknowledged that hippocampal damage has little or no effect on object recognition.

Recent demonstrations of object-recognition impairments in rats with medial-temporal-lobe and medial-diencephalic damage have begun to facilitate comparisons with the monkey literature. For example, Mumby, Pinel, and colleagues have shown that lesions of either the rhinal cortex (Mumby & Pinel, 1994) or mediodorsal thalamus (Mumby et al., 1993) produce deficits in DNMS performance in rats that have undergone extensive presurgical training. However, despite virtually identical training and testing procedures in these two experiments, there were three key differences in the DNMS impairment displayed by rhinal-lesioned and thalamic-lesioned rats: (1) thalamic-lesioned, but not rhinal-lesioned, rats were impaired in the rate at which they reacquired the DNMS rule following surgery, (2) after relearning the DNMS task to criterion, thalamic-lesioned, but not rhinal-lesioned, rats were impaired at the shortest
(i.e., 4-s) delay during mixed-delay testing, and (3) thalamic lesions produced a delay-independent DNMS deficit across all delays tested, whereas rhinal lesions produced deficits only at the longer delays. These differences are suggestive of the fact that the rhinal cortex and the mediodorsal thalamus, although both crucial to normal DNMS performance, may make different contributions to mnemonic functioning.

In summary, there has been little progress in determining whether or not the amnesias produced by damage to different brain areas are qualitatively distinct. The comparison of human patients has been complicated by methodological difficulties, including the inherent difficulty in specifying the location and extent of brain damage, whereas necessary large-scale systematic comparisons, which are possible in laboratory animals, are notably absent.

VI. RATIONALE FOR METHODS AND GENERAL OBJECTIVES

Does bilateral damage to the medial temporal lobe, medial diencephalon, or basal forebrain produce qualitatively similar amnesic syndromes, or does selective damage to these three brain areas produce different patterns of mnemonic impairment? I have argued that this question is one of the fundamental questions faced by those who study brain-damage-produced amnesia. I have also explained why studies of human patients have been unable to answer this question and why the potential answer lies in the conduct of large-scale systematic experiments comparing the deficits produced in laboratory animals by lesions of these three areas. The research reported here constitutes such a series of experiments.

In the present experiments, rats with lesions to structures within the medial temporal lobe, medial diencephalon, and basal forebrain were tested on a battery of object-memory tasks.
Because human brain-damage-produced amnesia is typically characterized by an inability to form new long-term memories as well as a difficulty in recalling long-term memories laid down prior to the amnesia-inducing brain trauma, this battery included tests of both anterograde and retrograde memory. The anterograde memory tasks included: (1) object discrimination, (2) object discrimination reversal, (3) concurrent object discrimination, (4) nonrecurring-items delayed nonmatching-to-sample (DNMS) with retention delays of 4, 15, 30, 60, and 120 s, (5) DNMS with lists of three, five, and seven sample objects, and (6) order discrimination. Retrograde memory was assessed by measuring the retention for different object-discrimination problems learned at varying time intervals prior to surgery.

These object-memory tasks were expressly designed to mimic in key respects object-memory tasks are routinely employed in studies of brain-damage-produced amnesia in monkeys (see Squire, 1992). This was the major determining factor in their selection because differences between the tasks that have been used to assess memory in rodents (i.e., spatial tasks) and primates (i.e., object tasks) have reduced the possibilities for converging operations and comparative analysis. The fact that task variables affect normal rats’ and monkeys’ performance on these tasks in qualitatively similar ways (see Mumby, Pinel, & Anzarut, 1991) provides strong support for the view that these tasks assess similar mnemonic processes in the two species. Moreover, the fact that some of these tasks had already proven helpful in dissociating the effects of damage to different medial-temporal-lobe structures in monkeys suggested that they might also be useful in dissociating the effects of other areas of damage.

In evaluating the effects of any instance of brain damage, it is essential to consider the profile of performance on a number of tests: Any individual test can be failed for a variety of
reasons. This principle has important implications for the study of brain-damage-produced amnesia and was a key factor in the design of the present experiments. For example because rats, monkeys, and humans with damage to the medial temporal lobe all display DNMS deficits it is often assumed that they have the same cognitive impairment; however, it is only when the same profile of deficits is observed across several tasks that it is reasonable to assume that memory is affected in the same way in different species (see Ridley and Baker, 1991). Similarly, although damage to different brain areas within a particular species may produce the same impairment on any given task, it is only by considering performance on a number of different tasks that a reasonable assessment of the contributions of those brain areas to memory function can be made. By testing rats with selective lesions to a number of different brain structures on a battery of object-memory tasks similar to those that have been used in many monkey studies, the present series of experiments made it possible to compare not only the memory profiles associated with these different lesions but also the nature of the performance deficits produced by damage to similar brain areas in these two species.

It should be emphasized that the object-memory tasks employed in this series of experiments were not chosen on the basis of their ability to characterize the various mnemonic functions of the brain structures in question. Medial-temporal-lobe, medial diencephalic, and the basal forebrain structures have all been implicated in a wide range of mnemonic processes, and it would be far beyond the scope of this thesis to attempt to ascribe precise functional roles to each of these brain areas. Rather, the current tasks were selected because of the similarities they bear to many of the object-memory tests that have been employed in studies of amnesia in monkeys and humans, thereby facilitating cross-species comparisons.
The use of rats as subjects in these experiments avoided the most serious drawback of the monkey model of brain-damage-produced amnesia—namely, its expense. Few researchers have been able to make extensive use of the monkey model, and those that have, have had difficulty in conducting the large-scale parametric experiments that are needed to precisely compare the effects of damage to various medial-temporal-lobe structures. When one considers the notorious variability of lesion studies and the fact that it is not uncommon for experiments involving the monkey model to focus on groups of only three or four monkeys (with data from control animals often being used from one experiment to the next), it is not surprising that progress in understanding the neural basis of brain-damage-produced amnesia has come about rather slowly. However, recent rat models of brain-damage-produced amnesia (e.g. Mumby et al., 1990) have facilitated the conduct of large-scale parametric studies and have allowed for comparisons of the performance of three species—humans, monkeys, and rats—on the similar memory tasks.

In addition to the fact that the current battery of object-memory tasks was expressly designed to mimic some of the object-memory tasks employed in monkey studies (Mumby et al., 1991), their strongest features are their simplicity and the fact that the rats do not have to be handled during testing. The importance of this latter point becomes evident when one considers that distraction disrupts DNMS performance (Zola-Morgan & Squire, 1985; Zola-Morgan, Squire, & Amaral, 1989a) and that different results have been obtained in monkey DNMS studies depending on whether or not subjects have, or have not, been handled during the retention intervals (Alvarez et al., 1995; Murray & Mishkin, 1996). Although placing different demands on object memory, the tasks used in these experiments involve the same apparatus (i.e., the
Mumby box), the same stimuli (i.e., objects), the same reinforcement (i.e., food), and the same operant response (i.e., displacement of an object). These similarities make it unlikely that dissociations on these tasks between rats with damage to different brain structures could arise from differences in motivational, perceptual, or motor effects.

In summary, the general objective of the following experiments was to systematically compare the nature of the object-memory impairment associated with medial-temporal-lobe, medial-diencephalic, or basal-forebrain damage in rats. Experiments 1, 2, and 3 were analyses of the anterograde object-memory profiles for rats following lesions to structures of the medial temporal lobe, medial diencephalon, or basal forebrain. Experiment 4 was an analysis of the retrograde object-memory impairment associated with damage to each of these brain areas.
GENERAL METHODS

This section describes methods common to the present experiments. Methods particular to individual experiments are described later.

SUBJECTS

The subjects were experimentally naive male Long-Evans rats (Charles River Laboratories, Quebec) that weighed between 275-350 g at the beginning of each experiment. The rats were housed individually and maintained on a 12/12 hr dark-light cycle. Prior to behavioral testing, their body weights were reduced to approximately 85% of ad libitum levels. This weight was maintained throughout the experiment by limiting the food intake of each rat to 20-25 g of rat chow per day. Behavioral testing began after the rats were on the restricted feeding regimen for 14 days. Rats were allowed free access to water when in their home cages.

APPARATUS

The DNMS testing apparatus was described in detail by Mumby et al. (1990). Briefly, it consists of an elevated runway separated from identical goal areas at each end by opaque guillotine doors. Each goal area contains two food wells in which food pellets (45 mg, Bio-Serv Inc., Frenchtown, N.J.) can be delivered by hand through plastic tubes. Test stimuli consisted of over 500 “junk” objects of various sizes, shapes, colors, and textures. Each object was large enough to cover the food well, but small enough to be displaced easily by the rats. No objects with obvious odors were used, and all of the objects were washed approximately once every week in a solution of water and chlorine bleach.
BEHAVIOURAL PROCEDURES

All training took place during the light phase of the dark-light cycle between 14 and 21 hr after the rats' last meal. The rats were tested no more than once per day and no fewer than 4 times per week, and they were not handled during a testing session once they were placed in the apparatus. All experimenters were blind to the surgical condition of each rat. The duration of the entire behavioural testing period, including the habituation procedure, for Experiments 1 - 3 was approximately 8 months.

Prior to the actual collection of behavioral data, the rats first underwent a habituation phase in order to familiarize them with the operation of the apparatus. During habituation training, which lasted of six or seven sessions, the rats were initially allowed to explore the apparatus and eat from any of the four continuously baited food wells. As the rats became accustomed to finding food in the wells, they were shaped to alternate between opposite ends of the box. Once they were alternating consistently, the operation of the guillotine doors was introduced. The rats were shaped to approach the doors by baiting a food well on the far side of a closed door. When the rat approached the door, the door was raised, allowing access to the food well. If the rat did not approach the well after a few seconds, the door was lowered and the procedure was repeated. The rat was trained to approach each door alternatively until the rat was alternating between the ends without hesitation.

In Experiments 1, 2, and 3, the subjects, once habituated, were tested on a battery of six object-memory tasks in the following order: 1) simple two-choice object discrimination, 2) discrimination reversal, 3) eight-pair concurrent object discrimination, 4) DNMS with retention
delays of 4, 15, 30, 60, and 120 s, 5) DNMS with lists of 3, 5, and 7 samples, and 6) temporal-order discrimination.

**Task 1: Object Discrimination.** This task assessed each rat’s ability to learn which of two objects is associated with food. The same two objects served as stimuli for all rats on all trials. One of the objects was designated S+ (rewarded); the other object was designated S- (not rewarded). To begin each session, the rat was placed in the center compartment of the apparatus; one door was raised and the other was closed. The S+ and S- were placed over the food wells behind the closed door. The position of S+ (left or right) varied from trial to trial according to a pseudorandom pattern. After the experimenter opened the closed door, the rat then approached and displaced one of the two objects. If the rat displaced S+, a food pellet was delivered to that food well; if the rat displaced S-, no food pellet was delivered. The experimenter then closed the door at the other end of the apparatus and positioned S+ and S- behind it to begin the next trial. There were 25 trials per session, with an intertrial interval of approximately 20 s between the time a rat displaced either object to the time when the experimenter raised the far door to begin a new trial. Training for each rat continued until it chose S+ on at least 22 of the 25 trials on two consecutive sessions.

**Task 2: Discrimination Reversal.** This task assessed the each rat’s ability to respond appropriately to a change in reinforcement contingency: each rat’s ability to form a new object-reward association that is incompatible with a previous one and to use the new association to guide its behaviour. The same two objects were presented to the rats that were used for the object discrimination task, but the object that had previously been S- became S+, and vice versa.
Training for each rat continued until it chose the new S+ on at least 22 of the 25 trials on two consecutive sessions.

**Task 3: Eight-Pair Concurrent Object Discrimination.** This task assessed each rat's ability to simultaneously learn several different object-reward associations. Sixteen objects were divided into eight pairs; one object in each pair was designated S+, and the other S-. Each of the eight pairs was presented five times each session, thus there were 40 trials per session. The eight pairs were always presented in the following order: pair 1, pair 2, ... pair 8, pair 1, pair 2, and so on. All other procedures were the same as for the object discrimination task. The intertrial interval was approximately 20 s; thus, the interval between each presentation of a particular pair was approximately 160 s. Training continued with all eight pairs until the rat chose S+ on at least 36 trials out of 40 on two consecutive sessions.

**Task 4: Delayed Nonmatching-to-Sample (DNMS).** There were two phases of DNMS training and testing: (1) Acquisition of the DNMS task with a brief (i.e., 4-s) retention delay, and (2) DNMS testing at delays of 15, 30, 60, and 120 s. DNMS training begins with the use of a 4-s delay between the sample and test phase of a trial to ensure that only a small demand is placed on each rat's ability to remember each sample object; therefore, the rate at which a rat masters the DNMS task at this brief delay is often used as an index of its ability to learn and apply the nonmatching principle. Training at the 4-s delay continued for each rat until it chose the novel object on at least 17 trials out of 20 on two consecutive sessions.

Once each rat mastered the DNMS task at the 4-s delay, the interval between the sample and choice phases of a trial was lengthened; first to 15 s, then to 30, 60, and, finally, to 120 s. Each rat received six sessions (20 trials per session) at each delay before moving onto the next
longest delay. This phase of DNMS testing assessed the rats’ ability to retain information about the identity of an object over various delay intervals.

**Task 5: DNMS With Lists of 3, 5, and 7 Samples.** DNMS with lists assessed each rat’s ability to retain information for numerous sample objects over a delay interval. On each trial, the rat was first be presented with a sequence of sample objects, one every 20 s, over a baited food well. Approximately 20 s after the presentation of the last sample in the list, the first sample object was presented again, along with a novel object, and then the remaining samples from the list were presented at 20 s intervals, each with a different novel object. The rat was rewarded with a food pellet each time it displaced the novel object from a novel-sample pairing. Each rat received seven sessions with each list length before moving onto the next longest list length. On sessions with lists of three sample objects, eight lists were presented; on sessions with lists of five sample objects, five lists were presented; on sessions with lists of seven sample objects, three lists were presented.

**Task 6: Order Discrimination.** This task assessed the rats’ ability to remember the order in which a sequence of objects has been presented to them. This task is similar to one developed for monkeys by Gower (1992), which in turn was modeled after a protocol used to study serial-order memory in humans (Hacker, 1980). The procedure was similar to that of DNMS with lists of five sample objects, except that 20 s after the presentation of the last object in the list, two of the objects from the list were presented together. The rat was rewarded if it displaced the object that had been presented earlier in the sample list. The difference in the two objects’ positions in the list (referred to as the “lag”) can be either two (e.g., sample 1 vs. sample 4), one (e.g., sample 3 vs. sample 5), or zero (e.g., sample 2 vs. sample 3); the smaller the lag, the
more difficult it should be to remember which of the two objects came earlier in the list. Each of
the rats received seven sessions with a lag of three, then seven sessions with a lag of two, then
seven sessions with a lag of one. There were 10 trials per session; that is, 10 lists of five
samples, with a test following the presentation of each list.

STATISTICAL ANALYSES

The main performance measure for the object discrimination, discrimination reversal,
concurrent object discrimination, and the acquisition stage of DNMS testing was the number of
trials that each rat required to reach the respective performance criteria. The trials of the two
sessions on which the respective criteria were met were not included in the calculation of this
measure. Following conventional analysis of variance (ANOVA), pairwise comparisons were
performed with all possible group pairings, using variance estimates based only on the two
groups involved in each comparison instead of a pooled variance estimate. The number of
errors-to-criterion was subjected to the same analyses.

The primary performance measure on DNMS at the various retention delays, on DNMS
at various list lengths, and on the order-discrimination task was percent correct. These data were
analyzed with repeated measures ANOVA's using group (lesion type) as a between-subjects
factor and session (sessions within each condition) and condition (i.e., retention delay, list length,
or lag) as within-subjects factors. Pairwise comparisons were then conducted among the groups
in each condition of each task.
SURGICAL PROCEDURE

All surgery was performed under pentobarbital anesthesia (60 mg/kg, i.p.). Atropine sulphate (0.2 ml, 0.4 mg/ml, i.p.) was administered approximately 20 min prior to anesthetization to reduce mucous secretion. Immediately following surgery, rats were placed under a heat lamp until they regained consciousness. Once rats regained consciousness, they were returned to their home cages where they were allowed continuous access to food and water for a period of at least one week before being put back on a restricted feeding schedule. In the first 14 days following surgery, all rats were handled by the experimenters twice a day for a minimum of 15 min each time. Behavioural testing did not begin until 3 weeks after surgery.

HISTOLOGICAL PROCEDURE

Following the completion of behavioral testing, the subjects were anesthesized with sodium pentobarbital (100 mg/kg, i.p.) and transcardially perfused with 10% formalin in 0.05% phosphate buffer (pH 7.4). Their brains were immediately removed and stored in phosphate buffered formalin for at least 24 hr. The brains were then frozen, mounted on a cryostat, and cut into coronal sections, 30 um thick. Every tenth section was mounted on a gelatin coated slide and stained with 0.1% cresyl violet.
EXPERIMENT 1: ANTEROGRADE MEMORY DEFICITS FOLLOWING LESIONS OF THE HIPPOCAMPUS OR AMYGDALA IN RATS

The study of brain-damage-produced amnesia in laboratory animals has traditionally focused on the effects of lesions to structures within the medial temporal lobe, and in particular, on the effects of hippocampal and amygdalar damage. Through the use of different memory tasks, researchers have begun to differentiate between the effects of lesions to the hippocampus or amygdala on memory for objects in monkeys (see Squire, 1992). For example, monkeys with damage to the hippocampus and surrounding structures perform poorly on tasks of object discrimination (Zola-Morgan, Squire, & Amaral, 1989b), concurrent object discrimination (Mahut et al., 1982; Zola-Morgan et al., 1989a) and DNMS (Zola-Morgan & Squire, 1985; Zola-Morgan et al., 1989a), whereas monkeys with damage to the amygdala and surrounding structures do not (Horel, Keating, & Misantone, 1975; Zola-Morgan et al., 1989a).

Unfortunately, in most of the experiments that have compared the mnemonic consequences of hippocampal and amygdalar lesions in monkeys, the nature of the surgical procedure has resulted in damage to adjacent cortical tissue (Mahut et al., 1982; Zola-Morgan & Squire, 1985; Zola-Morgan et al., 1989a; Zola-Morgan et al., 1989b). This incidental damage to rhinal and parahippocampal cortices has confounded the interpretation of the differences between so-called hippocampal and amygdalar lesions. This is cause for serious concern given the recent evidence suggesting that damage to the rhinal cortex, not the hippocampus or amygdala, is primarily responsible for the impairment in DNMS seen following large medial-temporal-lobe lesions. Only recently have stereotaxic surgical procedures, in combination with neuroimaging
techniques, allowed for lesions limited to the hippocampal region itself to be produced in monkeys, and have the effects of these lesions on object recognition been examined (Alvarez et al., 1995; O’Boyle et al., 1993; Murray & Mishkin, 1996).

The incidental damage characteristic of conventional hippocampal and amygdalar ablation studies can be circumvented in rats because of the size and location of the rat hippocampus and amygdala. The dorsal position of the hippocampus in rats means that it can be removed by aspiration from the superior surface of the brain, thus sparing the rhinal cortex and limiting extraneous damage to a small amount of parietal neocortex. Furthermore, the rat hippocampus and amygdala can be readily lesioned electrolytically or with intracerebral neurotoxin injections; in either case, there is little extraneous damage. Thus, many experiments have assessed the effects of selective hippocampal or amygdalar damage on memory in rats (see Eichenbaum, Otto, & Cohen, 1994; Kesner, 1992). Unfortunately, almost all of these rat experiments have focused on memory for places, whereas almost all of the comparable monkey experiments have focused on memory for objects. Because different neural systems appear to underlie memory for places and memory for objects (Goldman-Rakic, 1988; O’Keefe & Nadel, 1978; Ungerleider & Mishkin, 1972), it has been difficult to compare the effects of various temporal-lobe lesions on memory in monkeys and rats.

Accordingly, the main purpose of Experiment 1 was to compare the mnemonic effects of selective lesions of the hippocampal formation and the amygdala in the rat on the performance of a battery of object-memory tasks, expressly designed to mimic those object-memory tasks routinely employed in monkey experiments. By testing rats on object-memory tasks analogous to
those used in many studies of amnesia in humans and monkeys, Experiment 1 was intended to increase the possibilities for comparative analysis.

A secondary purpose of Experiment 1 was to assess the effects of pretraining on the object-recognition abilities of rats with lesions to the hippocampus or amygdala. Mumby et al. (1992) had assessed the effects of hippocampal and amygdalar lesions on DNMS in rats that had received extensive presurgery DNMS training. Because the rats in Experiment 1 received no presurgery training, it was possible to assess the degree to which extensive pretraining was responsible for the mild DNMS deficits observed by Mumby et al. Deficits produced by hippocampal lesions are less in monkeys exposed to presurgery DNMS training (Murray, 1990).

METHOD

Subjects

The 20 subjects were divided into four groups of 5 rats each: (1) the rats in the hippocampus-lesion group received bilateral aspiration lesions of the dorsal hippocampus and the overlying parietal cortex, and electrolytic lesions of the ventral portions of the hippocampal formation; (2) the rats in the amygdala-lesion group received bilateral electrolytic lesions of the amygdala; (3) the rats in the sham-lesion control group received sham surgery and sustained no brain damage; and (4) the rats in the parietal-lesion control group received bilateral aspiration lesions of the parietal cortex, thus serving as controls for the cortical damage sustained by the rats in the hippocampus-lesion group.
Apparatus

The apparatus is described in the General Methods section.

Surgical Procedure

Hippocampal lesions were made using a combination of aspiration to remove the dorsal hippocampus and electrolysis to destroy the ventral portion of the hippocampus, dentate gyrus, and subiculum. In preparation for hippocampal surgery, the scalp was incised, and holes were cut in the skull over each hemisphere with a dental drill; the holes extended over approximately 2 mm posterior to the coronal suture to 2 mm anterior to the lamboid suture and from 1.5 mm lateral to the sagittal suture to within 1 mm of the temporal ridge.

The electrolytic lesions of the ventral hippocampal formation were made first, followed immediately by the aspiration lesions of the dorsal hippocampus. The electrolytic lesions were made bilaterally at two sites (2 mA for 20 sec) with a bipolar stainless steel electrode that was insulated with Teflon except for approximately 1 mm at its tip. The following were the electrode coordinates, in millimeters relative to bregma: AP -4.8, ML 4.6, DV -8.0; AP -5.8, ML 4.6, DV -7.7. For the aspiration lesions, the dura mater was cut and a portion of the underlying parietal cortex and white matter was aspirated with a glass Pasteur pipette, exposing the dorsal hippocampus. The dorsal hippocampus was aspirated, the cavity was filled with Gelfoam (Upjohn Co., Don Mills, Ontario), and the skin was sutured. Diazepam was administered as soon as the rat began to regain consciousness; for the next 24 hr, smaller doses were periodically administered to control convulsions that have sometimes been reported in rats following hippocampal lesions. No convulsions were observed in the present subjects.
The amygdala lesions were made bilaterally at four sites with an electrode similar to the one used to make the electrolytic component of the hippocampal lesions. The following were the electrode coordinates for the amygdala lesions, in millimeters relative to bregma: AP -1.5, ML 4.4, DV -9.6 (2 mA for 20 sec); AP -3.3, ML 4.5, DV -10.0 (2 mA for 20 sec); AP -4.3, ML 4.5, DV -10.2 (2 mA for 20 sec).

The procedures for making the parietal cortex lesions in the control rats were identical to the procedures for removing this overlying cortex prior to the hippocampal aspirations. The sham-lesion controls received a scalp incision, but no damage was done to either the skull or the brain.

**Behavioural Procedure**

Following recovery from surgery, each rat was habituated to the apparatus. Then, it was trained on each of the six object-memory tasks described in the General Methods section.

**RESULTS**

Rats in both the hippocampus-lesion and amygdala-lesion groups were able to reach the same performance levels as their respective control groups on every task. There were, however, some minor differences in the rate of acquisition: Hippocampal lesions, but not amygdalar lesions, impaired the rate at which rats were able to learn the object-discrimination task, whereas lesions of the amygdala, but not the hippocampus, resulted in a deficit in DNMS acquisition; and both lesion groups were significantly slower than controls in learning the concurrent-object-
discrimination task, the rats with hippocampal damage being significantly slower than the rats with amygdalar damage.

**Histological Results**

Figure 2 illustrates the location and extent of the lesions. The hippocampal lesions included the entire dorsal hippocampus, most of the lateral and ventral hippocampus, and a portion of the parietal cortex and corpus callosum overlying the dorsal hippocampus. Each lesion extended rostrally to include some of the fimbria fornix. Small infarcts were also present in the dorsal thalamus of each of the brains with hippocampal lesions. Most of these were unilateral and involved the habenular nuclei, lateral dorsal nucleus, lateral posterior nucleus, lateral geniculate, and medial geniculate nucleus (see largest lesion in Figure 2). Two of the brains with hippocampal lesions also sustained partial unilateral damage to the colliculi.

As intended, the area of posterior parietal cortex that was removed in the rats of the parietal-lesion group tended to be slightly larger than that in the rats of the hippocampal-lesion group. The same area of cortex that was removed in the hippocampal-lesion rats was also removed in each of the parietal cortex lesions. The area of cortex that was removed in both groups included posterior portions of areas FL and Fr1, virtually all of areas HL, superior portions of Par1, and anterior portions of Oc2MM, Oc2ML, and Oc2L (Zilles, 1985). There tended to be slightly more damage to white matter in the rats with hippocampal lesions than in the rats with parietal cortex lesions. Two of the rats with parietal cortex lesions sustained bilateral damage to the alveus, and in both of these rats a small portion of the dorsal CA1 region was damaged unilaterally (see the largest parietal-lesion in Figure 2); one rat in the parietal-lesion group sustained unilateral damage to the alveus.
Figure 2. Reconstructions of the largest (gray) and smallest (black) hippocampal (HPC), amygdalar (AM), and parietal cortex (PC) lesions. Planes of section are shown in millimeters, relative to bregma. The drawings are adapted from the atlas of Paxinos and Watson (1986).
The amygdalar lesions varied in the extent of damage to specific nuclei, but there was consistent damage to the medial two-thirds of the amygdaloid complex. No specific amygdaloid nuclei were consistently spared. The caudal extent of the amygdalar lesions in 2 rats included small portions of medial entorhinal cortex in both hemispheres (see the largest amygdala lesion in Figure 2), and another included slight unilateral damage to the medial entorhinal cortex. The amygdala lesions of one of the rats extended much more posterior than any of the others; it included portions of the ventral subiculum and dentate gyrus bilaterally. This rat was consequently excluded from the analysis, leaving 4 rats in the amygdala-lesion group.

**Behavioural Results**

Statistical analyses revealed that errors-to-criterion and trials-to-criterion were equally sensitive measures of acquisition, thus, only one of them is described here. Because trials-to-criterion had been the measure of acquisition in most relevant monkey and rat studies, it is the one selected for presentation here.

**Object Discrimination**

Figure 3 illustrates the mean number of trials that the rats in each group required to reach the criterion of at least 22 out of 25 correct trials on two consecutive object-discrimination sessions. The rats in the hippocampus-lesion group required more trials to reach criterion than did the rats in the three other groups. This difference was statistically significant—a one-way ANOVA revealed a significant group effect \([F(3,15) = 3.26, p = 0.05]\), and Tukey’s pairwise comparisons revealed significant differences between the hippocampus-lesion and the parietal-lesion groups \((p = 0.016)\) and between the hippocampus-lesion and sham-lesion groups \((p = \)
Figure 3. Mean number of trials that the rats in each group required to reach criterion on the object-discrimination task. Groups were SHAM (sham-surgery controls), PC (parietal cortex lesions), HPC (hippocampus lesions), and AM (amygdala lesions). Errors bars represent SEMs.
Object Discrimination

Trials to Criterion

SHAM  PC  HPC  AM
0.026). None of the other differences among the groups was statistically significant (all $p$'s > 0.20).

**Discrimination Reversal**

Figure 4 illustrates the mean number of trials that the rats in each group required to reach the criterion of at least 22 out of 25 trials correct on two consecutive discrimination-reversal sessions. Although both hippocampus-lesion and amygdala-lesion rats required more trials to reach criterion than did the rats in either of the control groups, these differences were not statistically significant—-a one-way ANOVA revealed a nonsignificant group effect [$F(3,15) = 3.05, p = 0.061$], and none of the pairwise differences among the groups was statistically significant (all $p$'s > 0.05).

**Eight-Pair Concurrent Object Discrimination**

Figure 5 illustrates the mean number of trials that the rats in each group required to reach the criterion of at least 36 out of 40 trials correct on two consecutive concurrent-object-discrimination sessions. It is readily apparent from Figure 5 that there were large group differences on this task, and the significance of these differences was confirmed by statistical analysis [$F(3,15) = 19.25, p < 0.001$]. The rats in both the hippocampus-lesion and amygdala-lesion groups required significantly more trials to reach the criterion than did the rats in the sham-lesion group (both $p$'s < 0.005); in addition, the rats in the hippocampus-lesion group required significantly more trials to each criterion than did the rats in the parietal-lesion group ($p < 0.005$) or amygdala-lesion group ($p = 0.014$). In sum, hippocampal and amygdalar lesions both produced deficits in concurrent object discrimination, but the deficit was significantly greater following hippocampal lesions.
Figure 4. Mean number of trials that the rats in each group required to reach criterion on the discrimination-reversal task. Groups were SHAM (sham-surgery controls), PC (parietal cortex lesions), HPC (hippocampal lesions), and AM (amygdala lesions). Error bars represent SEMs.
Discrimination Reversal

Trials to Criterion

SHAM  PC  HPC  AM
Figure 5. Mean number of trials that the rats in each group required to reach the criterion on the eight-pair concurrent-object-discrimination task. Groups were SHAM (sham-surgery controls), PC (parietal cortex lesions), HPC (hippocampal lesions), and AM (amygdala lesions). Error bars represent SEMs.
Concurrent Object Discrimination

Trials to Criterion

CON  PC  HPC  AM
Delayed Nonmatching-to-Sample (DNMS)

Figure 6 illustrates the mean number of trials that rats in each group required to reach the criterion of at least 17 out of 20 correct trials on two consecutive DNMS sessions at a 4-s delay. It is apparent from the figure that the rats in the amygdala-lesion group required substantially more trials to learn the nonmatching rule than did rats in each of the three other groups. There was a significant group effect \([F(3,15) = 3.79, p = 0.032]\), and pairwise comparisons revealed a significant difference between the amygdala-lesion and hippocampus-lesion rats \((p = 0.016)\), whereas the differences between the amygdala-lesion and parietal- or sham-lesion rats approached, but did not reach, statistical significance \((p = 0.079 \text{ and } 0.060, \text{ respectively})\). None of the other differences among the groups was statistically significant (all \(p\)'s > 0.10).

Figure 7 illustrates the mean DNMS performance for each group across the different delay conditions. It is apparent from the figure that the percentage of correct responses made by each group on the DNMS task declined as the retention-delay was increased \([F(3,30) = 23.2, p < 0.001]\). Both the hippocampus-lesion and parietal-lesion groups made fewer correct choices compared to the sham-lesion group at all delays tested; however, the hippocampus-lesion rats and the parietal-lesion rats were significantly impaired relative to the rats in the sham-lesion rats only at the 120-s delay (hippocampus vs. sham, \(p = 0.002\); parietal vs. sham, \(p = 0.045\)). The performance of the hippocampus-lesion and parietal-lesions groups was not significantly different at any of the delays (all \(p\)'s > 0.1).
Figure 6. Mean number of trials that the rats in each group required to reach the criterion on the DNMS task at a 4-s delay. Groups were SHAM (sham-surgery controls), PC (parietal cortex lesions), HPC (hippocampal lesions), and AM (amygdala lesions). Error bars represent SEMs.
Figure 7. Mean percent correct in each group on DNMS at different retention delays. Groups were SHAM (sham-surgery controls), PC (parietal cortex lesions), HPC (hippocampal lesions), and AM (amygdala lesions). Error bars represent SEMs.
DNMS Delays

Percent Correct

Delay (sec)

- SHAM
- PC
- HPC
- AM
DNMS With Lists of 3, 5, or 7 Sample Objects

Figure 8 illustrates DNMS performance across the different list-length conditions. Scores decreased as the sample list length increased \( [F(2,30) = 18.37, p < 0.001] \); however, there were no statistically significant differences among the groups in the performance of this task.

Order Discrimination

Figure 9 shows that scores on the temporal order discrimination task decreased as the lag decreased \( [F(2,30) = 24.47, p < 0.001] \). However, there were no statistically significant differences among the groups on this task. Furthermore, none of the groups displayed serial-position effects within any of the lag conditions. For example, within-group performance on the lag-of-two trials on which Samples 1 and 4 were paired was not significantly different from those trials on which Samples 2 and 5 were paired (all \( p \)'s > 0.10); within-group performance was also similar on all lag-of-one trial types (all \( p \)'s > 0.08) and on all lag-of-zero trial types (all \( p \)'s > 0.15).

DISCUSSION OF EXPERIMENT 1

The object-memory tasks that were used in Experiment 1 resemble in key respects object-memory tasks that have commonly been employed in studies of brain-damage-produced amnesia in monkeys. Although rats with bilateral lesions of the hippocampus or amygdala displayed different patterns of deficits across these tasks, it should be emphasized that their ability to perform the tasks once acquired was little affected by the lesions.
Figure 8. Mean percent correct in each group on DNMS with different sample list lengths. Groups were SHAM (sham-surgery controls), PC (parietal cortex lesions), HPC (hippocampal lesions), and AM (amygdala lesions). Error bars represent SEMs.
DNMS with Lists

Percent Correct

List Length

SHAM
PC
HPC
AM
Figure 9. Mean percent correct in each group on the order-discrimination task.

Groups were SHAM (sham-surgery controls), PC (parietal cortex lesions), HPC (hippocampal lesions), and AM (amygdala lesions). Error bars represent SEMs.
Order Discrimination

Percent Correct

Lag

SHAM
PC
HPC
AM
One interpretation of acquisition deficits such as those observed in this experiment is that they reflect the loss of some function that is not essential for normal task performance but that normally plays a role in the establishment of effective behavioural or cognitive strategies for solving the task—that is, it takes longer for the lesioned rats to establish either the strategies that normal rats use to solve the task or equally effective alternative strategies for solving it. Put another way, some of the processes that mediate performance while a task is being learned are different from those that maintain performance after a task is solved. The point is that the functions of the hippocampus, the amygdala, and the parietal cortex are not necessary for normal performance of any of the object-memory tasks in this experiment, and that the deficits observed in acquiring some of these tasks need not be purely mnemonic in nature.

The fact that certain task variables in the present experiment affect normal rats’ performance in a manner similar to that in which normal monkeys’ performance has been shown to be affected (Gower, 1992; Squire, 1992) provides support for the view that these tasks assess similar mnemonic processes in the two species. For example, increasing either the retention delay or the number of objects in a sample list in the DNMS task, or decreasing the lag condition in the order discrimination task, decreases the performance accuracy in both rats and monkeys. Accordingly, comparisons of object-memory performance of rats and monkeys with similar lesions should provide insights into the neural circuitry underlying mnemonic processing in both species.
Object Discrimination

Rats with hippocampal lesions needed significantly more trials to master this task than did rats with amygdalar, parietal, or sham lesions. This finding is consistent with reports of deficits in the rate at which monkeys with hippocampal lesions acquire an object discrimination (Zola-Morgan et al., 1989b); however, in a previous study of object-discrimination learning in rats, Wible et al. (1992) found only a small and insignificant acquisition deficit following lesions of the hippocampus. One potentially important difference between the present experiment and that of Wible et al. was that their rats received presurgery object-discrimination training, whereas the present rats did not—it has recently been found that pretrained rats with ischemia-induced hippocampal damage relearned an object discrimination postoperatively at a normal rate (Wood, Mumby, Pinel, & Phillips, 1993). It should also be noted, that nonpretrained monkeys with hippocampal lesions have been shown to learn some visual discriminations (e.g., pattern discriminations) at a normal rate (e.g. Zola-Morgan et al., 1989b), and nonpretrained rats with hippocampal lesions have been shown to learn some visual discriminations (e.g. brightness discriminations) at a normal rate (Kimble, 1963).

The object-discrimination task requires rats to learn which of two objects is associated with food reward. The present findings demonstrate that hippocampal lesion effects can be obtained on the acquisition of a task that requires neither working (Honig, 1978) nor spatial (O'Keefe & Nadel, 1978) memory and that neither hippocampal nor amygdalar damage precludes normal object-discrimination performance in rats.
Discrimination Reversal

None of the lesions produced statistically significant deficits on the discrimination-reversal task. The finding that rats with amygdalar lesions learned the discrimination-reversal task at a comparable rate to control rats is consistent with reports that monkeys with amygdalar damage learn a single reversal of an object discrimination at a normal rate (Jones & Mishkin, 1972).

The failure of hippocampal damage to produce a statistically significant impairment in the rate at which the rats acquired an object discrimination reversal is consistent with Mahut's (1971) report of unimpaired object-reversal learning in monkeys with hippocampal lesions. However, the fact that the hippocampal-lesioned rats required considerably more trials to reach criterion on this task than did the rats in any of the three other groups should not be ignored. There have been numerous reports of impaired discrimination-reversal learning in rats following hippocampal damage (e.g., Kimble, 1968; Silveira & Kimble, 1968; Thompson, 1982; Whishaw & Tomie, 1997), and it is possible that the present deficit would have reached significance if more subjects had been tested. The relative insensitivity of the present discrimination-reversal task may have been, in part, due to its unique features--features such as the use of objects as stimuli or the required operant response of object displacement, as opposed to the more common operant requirement of navigation to a goal location.

The discrimination-reversal task requires rats to respond appropriately to a change in the reinforcement contingency; the rats must form a new object-reward association that is incompatible with an existing one and use it to guide their behavior. Thus, the large, but insignificant deficit in the rate at which hippocampal-lesioned rats were able to learn the reversal
of the discrimination problem acquired in the previous task is not incompatible with notions that the hippocampus mediates the "flexible" use of memory representations stored in neocortical brain areas (e.g., Eichenbaum, Otto & Cohen, 1992; 1994) or that hippocampal damage results in a failure to suppress interfering response tendencies (e.g., Douglas, 1967; Winocur & Olds, 1978).

**Eight-Pair Concurrent Object Discrimination**

The rats with lesions of either the hippocampus or amygdala displayed deficits in the acquisition of the concurrent-object-discrimination task, but the deficits were significantly more severe in the rats with hippocampal lesions. Despite these deficits, all the rats were eventually able to reach criterion on this task. These findings are consistent with reports of deficits in concurrent-object-discrimination learning in monkeys with hippocampal lesions (Mahut et al., 1982; Zola-Morgan et al., 1989a), but inconsistent with reports of normal acquisition of this task in monkeys with amygdalar lesions (e.g. Zola-Morgan et al., 1989a). One possible explanation for this discrepancy is that damage to medial entorhinal cortex, which some of the rats with amygdalar lesions sustained, may have contributed to their deficits; the amygdalar lesions in the Zola-Morgan et al. study did not include the entorhinal cortex. Wible et al. (1992) concluded that the amygdala is unimportant for the acquisition of an eight-pair concurrent object discrimination because rats with lesions of both the hippocampus and amygdala were not significantly impaired on this task relative to rats with lesions of only the hippocampus. However, in Wible et al.'s study, 6 of the 7 rats with selective hippocampal lesions never reached criterion on the concurrent object discrimination and averaged only 66% correct during the last 3
days of testing; the fact that hippocampal lesions alone can produce such a severe impairment on this task may have obscured any effect of additional amygdalar damage. The acquisition deficits displayed by the present rats with lesions to the amygdala suggest that Wible et al.'s conclusions may have been premature.

The concurrent object-discrimination task requires rats to concurrently form several object-reward associations. It differs from the two-choice discrimination task by introducing interference among the many associations that must be concurrently formed. Olton and Shapiro (1993) suggested that hippocampal lesions produce deficits in concurrent object discrimination because hippocampal function is especially critical when stimuli are presented in a way that maximizes interference. However, their hypothesis also predicts that hippocampal lesions should have little effect on a two-pair object discrimination and a substantial effect on discrimination reversals; in fact, the present experiment revealed the opposite pattern of results on those two tasks. Still, lesions of the hippocampus have been shown to increase susceptibility to interference in past studies of spatial memory (Jarrard, 1965; Winocur, 1982; 1985), and a high degree of interference on the concurrent-object-discrimination task might account in part for the deficits of the hippocampal rats.

Although inadvertent damage to medial entorhinal cortex may have contributed to impaired acquisition of the concurrent-object-discrimination task by rats in the amygdala-lesion group, this deficit might alternatively reflect the amygdala's involvement in stimulus-reward associative learning. This hypothesis is consistent with the demonstration that monkeys with bilateral amygdalar ablations were impaired in the acquisition of a series of two-choice visual discriminations when the discriminative stimuli are associated directly with the incentive value
of the food (Gaffan & Murray, 1990) and in the performance of a one trial win-stay lose-shift task (Spiegler & Mishkin, 1981)—a task that has been commonly used to assess the formation of stimulus-reward associations. However, the fact that the amygdala-lesioned rats in the present experiment were impaired in the acquisition of eight-pair concurrent object discriminations, but not a two-choice object-discrimination, suggests that the demand placed on stimulus-reward association(s) by a particular task must be sufficiently high before amygdalar damage produces a disruptive effect; Kentridge et al. (1991) have proposed a similar explanation to account for the pattern of deficits in amygdala-lesioned rats on two versions of a spatial win-stay lose-shift task.

Delayed Nonmatching-to-Sample (DNMS)

Acquisition

The rats with amygdalar lesions required significantly more trials to master the DNMS task at a 4-s delay than did control rats or rats with hippocampal lesions. The fact that rats with hippocampal lesions were unimpaired in the learning of this task is consistent with the most recent reports of normal rates of DNMS acquisition in monkeys with damage limited to the hippocampal formation (Murray & Mishkin, 1996; O'Boyle et al., 1993). However, this finding is inconsistent with reports of normal DNMS acquisition in monkeys with amygdalar lesions (Zola-Morgan et al., 1989a). The following are four possible explanations for this discrepancy: One possibility is that rats and monkeys solve their respective DNMS tasks differently, despite a number of key conceptual and methodological similarities between the rat and monkey DNMS tasks. A second possibility is that the mnemonic functions of the amygdala are different in rats and monkeys; however, there is no compelling evidence for this view (Squire, 1992). A third
possibility relates to differences in training histories prior to DNMS training. The present rats were trained on object discrimination, discrimination reversal, and eight-pair concurrent object discrimination, prior to training on the DNMS task. In most experiments with monkeys, DNMS training has preceded training on other tasks. Ideally, the order in which subjects are trained on the various tasks in a battery should be counterbalanced, but this could require a prohibitively large number of subjects in an experiment that also included different lesion groups. A fourth possibility is that there are important differences in the brain damage sustained by monkeys and rats with amygdalar lesions—for example, the presence of a small amount of medial-entorhinal-cortex damage in the present amygdalar-lesioned rats but not in monkeys (Zola-Morgan et al., 1989a).

To master the DNMS task at the 4-s delay, rats must learn the nonmatching rule and consistently apply it. Whereas in the past, a lack of presurgery training has been found to be associated with the likelihood of postsurgery DNMS deficits (Murray, 1990), the present findings from naive hippocampal-lesioned rats together with the results of recent monkey studies (Alvarez et al., 1995; O’Boyle et al., 1993), serve to reinforce the notion that the hippocampus is not critical to normal learning of the nonmatching rule. On the other hand, the deficit displayed by the rats in the amygdala-lesion group suggests that damage to this brain structure interfered with the rats’ ability to establish a successful cognitive strategy with which to solve this task. However, the fact that amygdala damage did not prevent rats from eventually reaching the same high level of performance on the DNMS task at a 4-s delay as controls, together with Mumby et al.’s (1992) previous report of normal DNMS reacquisition in amygdala-lesioned rats given
extensive presurgery training, indicates that the amygdala is not crucial to successful performance of this task at a short delay.

**Delay Performance**

Neither hippocampal nor amygdalar damage produced significant impairments in DNMS performance upon the introduction of progressively longer retention delays: Although rats in the hippocampus-lesions group performed significantly worse than sham-lesion controls at the 120-s delay, rats in the parietal-lesion control group also displayed a DNMS deficit at the 120-s delay, and this deficit was not significantly different from that of the rats with hippocampal lesions. The observation of normal DNMS performance over a wide range of retention delays in rats with amygdalar lesions is consistent with similar reports in monkeys (e.g., Zola-Morgan et al., 1989a) and rats (Mumby et al., 1992). In previous studies, rats with hippocampal lesions also performed normally on slightly different versions of object DNMS (Kesner, Bolland & Dakis, 1993; Rothblat & Kromer, 1991) and on a continuous object-recognition task (Jackson-Smith, Kesner & Chiba, 1993), and monkeys with selective damage to the hippocampus have been shown to be unimpaired on DNMS at retention delays of up to 40-min (Murray & Mishkin, 1996). Nevertheless, Alvarez et al. (1995) and Mumby et al. (1992) have reported a mild DNMS deficit at very long delays following hippocampal lesions in monkeys and rats, respectively. However, the Alvarez et al. study is confounded by both the fact that monkeys were returned to their home cages during long, but not the short, retention delays and the possibility that the lesions in this study may have disrupted projection fibers from the rhinal cortex (see Murray, 1996); and in the Mumby et al. study, the performance of rats with aspiration lesions of the hippocampus (and
overlying parietal cortex) was compared to that of a no-surgery control group but not to that of a proper parietal-lesion control group.

The finding that the control rats with damage to the parietal cortex displayed a DNMS impairment at the 120-s delay is an interesting one. Lesions of the parietal cortex have been shown to consistently produce impairments on a variety of spatial memory tasks in both rats and monkeys (e.g., Cho & Kesner, 1996; Poucet & Benhamou, 1997; Soper, 1979); whether similar cortical damage might have a reliable effect on object recognition requires further testing.

The introduction of progressively longer retention delays to the DNMS task requires rats to retain information about the identity of an object for longer periods of time. Successful performance over these longer delays implies that the initial exposure to each sample object has resulted in a relatively stable stimulus trace (engram) against which the choice objects have been accurately compared (Mishkin & Murray, 1994). The fact that hippocampal or amygdalar damage failed to produce a significant impairment at any of the longer delays suggests that both the hippocampus and amygdala are not critical for the formation or retention of new object memories needed to guide correct DNMS performance.

DNMS With Lists

There were no significant differences among the groups on this task, which suggests that this ability does not depend upon the functions of the hippocampal formation or the amygdala (or the parietal cortex). The normal performance of the hippocampus-lesion and parietal-lesion groups on DNMS with lists as long as seven sample objects makes one wonder whether the mild deficit that was observed in both groups with a single sample object over a 120-s delay is a
reliable effect. When the list length is seven objects, the delay interval between the sample presentation of any object in the list and the later presentation of the same object in the test phase is about 105 s. Although this delay is slightly shorter than 120 s, the mnemonic demands of the DNMS task are great because the rat must retain information about several different sample objects concurrently. That rats in the hippocampus-lesion and parietal-lesion groups are not impaired under these task conditions suggests that their mild DNMS deficit with a single sample object might have disappeared with extended practice at the 120-s delay.

The introduction of progressively longer lists of sample objects to the DNMS task requires rats to retain information about the identity of progressively more objects. This requirement, together with the fact that the delay interval during list-length testing ranges from approximately 45 to 105 s, makes the DNMS-with-lists task a particularly difficult test of object-recognition memory. When the present DNMS findings are considered together with previous findings in rats with extensive presurgery DNMS training (Mumby et al., 1992), with the findings of other studies of object DNMS in rats (e.g., Rothblat & Kromer, 1991), and with the preponderance of recent findings in monkeys (Alvarez et al., 1995; Murray & Mishkin, 1996; O’Boyle et al., 1993), it does not appear that the hippocampus or the amygdala are critical components of the circuitry that underlies normal object-recognition abilities.

Order Discrimination

There were no significant differences among the groups on the order-discrimination task. Unlike the other tasks in this battery, the order-recognition task has not been used in monkey experiments involving lesions of the hippocampus or amygdala, and thus comparisons with the
primate literature cannot yet be made. Still, the inclusion of this task in the present experiment makes several important contributions. First, the object-based order discrimination task is similar to a task in which rats are required to remember the order in which a sequence of familiar spatial locations in a radial-arm maze was visited (Kesner & Holbrook, 1987). The fact that the present rats were able to perform the order-discrimination task at above-chance levels with object stimuli that varied across trials indicates that rats encode and store information about the order of objects, as well as the identity of objects. Second, this experiment is the first to assess this ability in rats and, thus, serves to introduce a novel test protocol. Third, the finding of a severely deleterious effect on performance of decreasing the lag between the two objects involved in the order discrimination (see Figure 9) demonstrates the sensitivity of rats' order-discrimination abilities to this parameter. This sensitivity should make the task particularly useful in future experiments on order memory in rats. For example, rats' order memory for spatial locations is impaired by lesions of medial prefrontal cortex (Kesner & Holbrook, 1987) but not parietal cortex (Kesner & Gray, 1989), and it would be interesting to know whether a similar dissociation exists for rats' order memory for objects.

The order-discrimination task requires rats to remember information about the order in which a sequence of objects was presented. The fact that none of the lesioned groups in Experiment 1 were impaired on this task suggests that this ability does not depend upon the functions of the hippocampal formation, the amygdala, or the parietal cortex. However, it is possible that the poor performance by sham-lesion control rats on this task, relative to the other tasks in the battery, might have obscured subtle effects of the lesions. Gower (1992) recently demonstrated that monkeys are capable of good performance on an object-based order-
discrimination task that similar to the present one, and it is likely that the present rats’ performance would have improved with additional training. In retrospect, performance on this task might have been more sensitive to lesion effects if the rats had first been trained to a very high level of competence in the easiest condition (i.e., lag of three) and then given mixed-lag sessions during which the various lags were presented randomly across trials.

General Conclusions: Experiment 1

Regardless of the interpretation of any of the individual results of Experiment 1, the following general points can be taken from it: (1) memory for objects can be tested in the same way in rats as it is in human and nonhuman primates; (2) the mnemonic effects of damage to the hippocampus and amygdala in rats can be dissociated with a battery of object-memory tasks; (3) the profiles of object-memory deficits in rats with hippocampal and amygdalar lesions are similar in major respects to those of monkeys with lesions that involve these structures; and (4) the functions of the hippocampus, the amygdala, and the parietal cortex are not essential for normal performance of object-memory tasks.

Although rats with hippocampal, amygdalar, or parietal cortex lesions were impaired in acquiring some of the present object-memory tasks, the results showed that all rats could: (1) learn which of two objects is associated with food reward, (2) form an incompatible object-reward association and respond on the basis of it, (3) form several object-reward associations concurrently, (4) acquire, retain, and consistently apply the nonmatching principle, (5) retain information about the identity of an object over retention delays of up to 120 s, (6) retain information concurrently about the identity of up to seven objects, and (7) encode and retain
information about the order in which a sequence of objects was presented. Whereas hippocampal lesions produce permanent impairments of place learning in rats (Barnes, 1988) and amygdalar lesions appear to produce permanent deficits on tasks requiring the association of stimuli with strong affective consequences (e.g., Kesner, 1992), the present findings indicate, at most, a transient and minor role for these two structures in encoding, retaining, and expressing information about the identity and temporal order of objects and their associations with food reward.
EXPERIMENT 2: ANTEROGRADE MEMORY DEFICITS FOLLOWING LESIONS OF THE RHINAL CORTEX OR BASAL FOREBRAIN IN RATS

There is strong evidence that the rhinal cortex plays a critical role in object-recognition memory: In both rats and monkeys, selective lesions of the rhinal cortex, parahippocampal cortex, or both produces severe deficits in DNMS performance at all but the shortest of delays (e.g., Meunier et al., 1993; Mumby & Pinel, 1994; Zola-Morgan et al., 1989). In monkeys, there have also been numerous demonstrations that damage to the rhinal cortex impairs performance on other object-memory tasks, such as delayed retention of object discriminations and concurrent object-discrimination learning (Moss et al., 1981; Zola-Morgan & Squire, 1985; Zola-Morgan et al., 1993). However, in many of these studies, the rhinal cortex lesion has included the hippocampus, the amygdala, or both. It has therefore proven difficult to determine the relative contribution of the rhinal cortex to these different tasks.

Be that as it may, evidence from two separate monkey studies of selective temporal lobe lesions does suggest that the rhinal cortex itself is involved not only in object recognition, but also in object-discrimination learning. First, Zola-Morgan et al. (1989) demonstrated that lesions of the perirhinal and parahippocampal cortex that spare the amygdala and hippocampus produce severe impairments on simple and concurrent-object-discrimination tasks. Second, Buckley and Gaffan (1997) have recently found that preoperatively-trained monkeys are significantly impaired in the postoperative learning of large sets of new object-discrimination problems following perirhinal cortex ablation.
The amnesia associated with basal forebrain damage has often been assumed to result from disruption of information processing within the medial-temporal-lobe due to the strong anatomical (cholinergic) connections between these two brain regions (Damasio, Graff-Radford, Eslinger, Damasio, & Kassell, 1985; Squire, 1987). This assumption suggests that the destruction of the cholinergic projections from the basal forebrain (in particular, the medial septum and diagonal band nuclei) should produce a pattern of memory impairments similar to those produced by medial temporal lobe lesions (Ridley & Baker, 1991).

In Experiment 2, rats with selective lesions of the rhinal cortex or the medial septum and diagonal band were tested on a battery of tasks designed to assess different object-memory abilities. These tasks were identical to those used in Experiment 1 to investigate the effects of hippocampal and amygdalar lesions on object memory. There were three purposes: to provide valuable information that will help characterize the nature and extent of the mnemonic impairment produced by damage to the rhinal cortex or basal forebrain, to directly compare the performance of rats with lesions to these two brain areas across a number of different memory tasks, and to contrast the pattern of mnemonic deficits associated with damage to the rhinal cortex or basal forebrain in rats with the amnesia profile produced for rats with hippocampal damage in Experiment 1.

METHOD

Subjects

The subjects were 21 experimentally naive, male Long-Evans rats (Charles River, St-Constant, Quebec, Canada) that were between 10 and 12 weeks old at the beginning of the
experiment. They were housed individually under a 12:12-hr light-dark cycle with light onset at 8:00 a.m. Their body weights were maintained throughout the experiment at approximately 85% of ad libitum levels by limiting their daily rations of rat chow. Training began after the rats had been on the restricted feeding regimen for 10 days.

Apparatus

The apparatus and test objects were the same as those described in the General Methods section.

Surgical Procedure

To make the rhinal cortex lesions, a sagittal scalp incision was made and the skull overlying the perirhinal cortex was exposed. A hole was cut in the skull with a small dental drill, the dura overlying the rhinal cortex was incised, and portions of the entorhinal cortex and perirhinal cortex were aspirated with a vacuum pump and a glass Pasteur pipette. The cavity was then filled with Gelfoam (Upjohn Company, Don Mills, Ontario, Canada), the skin was sutured, and the rat was placed under a heat lamp until it regained consciousness. Of the 8 rats undergoing this ablation procedure, 1 died during surgery from complications associated with the anesthesia, and another developed a serious eye infection following completion of habituation to the apparatus, thus leaving a total of 6 rats in the rhinal-lesion group.

In preparation for the basal forebrain lesion (n = 8), each rat was positioned in a stereotaxic instrument with its head held horizontally, and its scalp was incised to expose the skull. The medial septum and diagonal band were lesioned electrolytically at three sites (2 mA
for 15 s at each site) with a bipolar stainless steel wire electrode, which was insulated with Teflon except for approximately 1 mm at its tip. The following were the electrode coordinates of the three sites, relative to bregma: AP 0.7, ML 0.0, DV -7.2; AP 0.3, ML 0.6, DV -8.2; AP 0.3, ML -0.6, DV -8.2. After the electrode was retracted, the skin was sutured, and the rat was placed under a heat lamp until it regained consciousness.

The sham-surgery controls (n = 7) were anesthetized and positioned in the stereotaxic instrument. Their scalps were then incised, but neither their skulls nor their brains were damaged.

**Behavioural Procedure**

Following recovery from surgery, each rat was habituated to the apparatus and then was trained on each of the same six object-memory tasks used in Experiment 1 and described in the General Methods section.

**RESULTS**

Selective lesions of the rhinal cortex or basal forebrain produced different profiles of object-memory impairment: Rhinal cortex lesions, but not basal forebrain lesions, retarded the acquisition of the object-discrimination, discrimination-reversal, and concurrent-object-discrimination tasks. In contrast, basal forebrain lesions, but not rhinal cortex lesions, retarded the acquisition of DNMS at the 4-s retention delay. However, both lesion groups were impaired in DNMS performance at retention delays of 15 s or longer or with lists of three or more sample objects, and both displayed deficits on the order-discrimination task.
Histological Results

Figure 10 illustrates the location and extent of the lesions. The 6 rats with lesions of the rhinal cortex had rhinal damage that was bilaterally symmetrical, although damage to areas other than the rhinal cortex was more variable between hemispheres. In all 6 of the rhinal rats, there was bilateral damage to the perirhinal cortex, both ventral and dorsal to the rhinal fissure, and to the lateral entorhinal cortex. In addition, there was bilateral damage to the medial entorhinal cortex in 2 rats and unilateral damage in another. Each of the rhinal rats also sustained slight-to-moderate damage to ventro-posterior portions of the temporal association cortex (area Te2); in 2 of them, it was damaged only unilaterally. Area Te3 was also damaged in 2 of the rhinal rats; this damage was bilateral in one case (see the largest lesion in Figure 10A) and unilateral in the other. The amount of temporal association cortex that was involved in the lesions appeared to be unrelated to the severity of any of the behavioural deficits.

The basal forebrain lesions were similar in all 8 rats. All 8 rats had bilateral damage to the medial septum as well as to the vertical and horizontal limbs of the diagonal band. The lesion consistently affected both the rostral and caudal divisions of the medial septum, and within the damaged area there was little evidence of neuronal sparing. Each of the basal forebrain rats also sustained slight damage to the lateral septal nuclei; in 5 rats this damage was unilateral, and in 3 rats it was bilateral. In addition, there was also some bilateral damage to the medial preoptic area and the median preoptic and septohypothalamic nuclei in 6 of the rats; and in 4 of these, there was slight unilateral damage to the ventral pallidum and lateral preoptic area, and in 2, the lesion extended slightly in one hemisphere into the shell of the nucleus accumbens (see the
Figure 10. Reconstructions of the largest (striped) and smallest (black) rhinal cortex (A) and basal forebrain (B) lesions. Planes of section are shown in millimeters, relative to bregma. The drawings are adapted from the atlas of Paxinos and Watson (1986).
largest lesion in Figure 10B). None of the extraneous damage was predictive of greater deficits on any of the behavioural tasks.

**Behavioural Results**

**Object Discrimination**

Figure 11 illustrates the mean number of trials that the rats in each group took to reach the criterion of at least 22 out of 25 correct trials on two consecutive object-discrimination sessions. The rats in the rhinal-lesion group required more trials to reach criterion than did the rats in the other two groups. This difference was statistically significant—a one-way ANOVA revealed a significant group effect \( F(2,18) = 11.64, p = 0.001 \), and Tukey’s pairwise comparisons revealed significant differences between the rhinal-lesioned rats and both the basal-forebrain-lesioned \((p < 0.001)\) and sham-lesioned \((p < 0.01)\) rats.

**Discrimination Reversal**

Figure 12 illustrates the mean number of trials that the rats in each group required to reach the criterion of at 22 out of 25 correct trials on two consecutive discrimination-reversal sessions. Rats with rhinal-cortex damage took longer than both control rats and rats with damage to the basal forebrain to learn the discrimination reversal \( F(2,18) = 9.45, p = 0.002 \). Post-hoc pairwise comparisons revealed that rhinal-lesion group was significantly impaired with respect to each of the two other groups (both \( p \)'s < 0.05).

In order to more closely analyze the rhinal-lesion group’s impairment on the discrimination-reversal task, the number of errors made by control rats and lesion rats during each reversal session was divided into two types, Stage I and Stage II. Stage I errors were
Figure 11. Mean number of trials that the control rats (SHAM), rhinal-cortex-lesioned rats (RH), and basal-forebrain-lesioned rats (BF) required to reach the criterion on the object-discrimination task. Error bars represent *SEMs*. 
Object Discrimination

Trials to Criterion

SHAM | RH | BF
Figure 12. Mean number of trials that the control rats (SHAM), rhinal-cortex-lesioned rats (RH), and basal-forebrain-lesioned rats (BF) required to reach the criterion on the discrimination-reversal task. Error bars represent SEMs.
Discrimination Reversal

Trials to Criterion

SHAM  RH  BF
defined as all errors made by a rat while performing significantly below chance (i.e., when 8 or fewer correct responses were made during a 25 trial session). Stage I errors were assumed to indicate a rat’s ability to learn to inhibit responding to a previously correct stimulus. Stage II errors included all remaining errors and were assumed to indicate a rat’s ability to learn to respond to the correct stimulus (see Jones & Mishkin, 1972; Meunier, Bachevalier, & Mishkin, 1997). Although rats in the rhinal-lesion group did commit slightly more Stage I errors (mean = 91.7) than did the rats in either the basal-forebrain-lesion (mean = 90.6) or sham-lesion (mean = 78.6) groups, this difference was not statistically significant \( F(2,18) = 0.24, p > 0.1 \). However, there was a significant difference among the three groups in the number of Stage II errors committed \( F(2,18) = 7.9, p < 0.005 \). Tukey’s post-hoc comparisons revealed that the rats in the rhinal-lesion group made significantly more Stage II errors (mean = 250.0) than did rats in the basal-forebrain-lesion group (mean = 69.4) or rats in the sham-lesion group (mean = 121.4) (both \( p’s < 0.05 \)), whereas the difference between the sham-lesion and basal forebrain-lesion groups was not statistically significant (\( p > 0.1 \)).

**Eight-Pair Concurrent Object Discrimination**

Figure 13 illustrates the mean number of trials that the rats in each group required to reach the criterion of at least 36 out of 40 correct trials on two consecutive concurrent-object-discrimination sessions. It can be seen from Figure 13 that rats in the basal-forebrain-lesion and sham-lesion groups acquired the concurrent-discrimination task at approximately the same rate, whereas rats in the rhinal-lesion group took considerably longer. An ANOVA revealed a significant main effect of group \( F(2,18) = 10.28, p = 0.001 \). Pairwise comparisons revealed that the rats in the rhinal-lesion group required significantly more trials to reach the learning
Figure 13. Mean number of trials that the control rats (SHAM), rhinal-cortex-lesioned rats (RH), and basal-forebrain-lesioned rats (BF) required to reach the criterion on the eight-pair concurrent-object-discrimination task. Error bars represent SEMs.
Concurrent Object Discrimination

Trials to Criterion

SHAM  RH  BF
criterion than did the rats in the other two groups (rhinal vs. basal forebrain, \( p = 0.006 \); rhinal vs. sham, \( p = 0.003 \)).

**Delayed Nonmatching-to-Sample (DNMS)**

Figure 14 illustrates the mean number of trials required by the rats in each group to reach the criterion of at least 17 out of 20 correct trials on two consecutive DNMS sessions at a 4-s delay. It is evident from the figure that the rats in the basal-forebrain-lesion group were severely impaired on this task. An ANOVA revealed a significant group effect \( [F(2,18) = 201.7, p < 0.001] \), which reflected the fact that 7 of the 8 rats with basal-forebrain damage failed to learn the DNMS task to criterion after the maximum of 1500 trials. Despite failing to reach the learning criterion, all 7 of these basal-forebrain-lesioned rats were nonetheless performing well above chance after the 1500 trial limit (averaging 70.1% correct), and testing was continued at the longer delays. The difference in the rates at which rats in the rhinal-lesion and sham-lesion groups acquired the DNMS task was not significant \( (p > 0.1) \).

Figure 15 illustrates mean DNMS performance across the different delays. It is apparent from this figure that rats in the rhinal-lesion group made fewer correct choices than rats in the sham-lesion group at all retention delays and that the rats in both of these groups performed considerably better than rats with damage to the basal forebrain. An ANOVA revealed a significant main effect of both group \( [F(2,18) = 122.3, p < 0.001] \) and delay \( [F(3,54) = 22.6, p < 0.001] \) as well as a significant interaction effect \( [F(6,54) = 2.57, p < 0.05] \). Pairwise comparisons revealed that rhinal-lesioned rats performed significantly worse than sham-lesioned rats, and significantly better than basal-forebrain-lesioned rats at all delays (all \( p \)'s < 0.05).
Figure 14. Mean number of trials that the control rats (SHAM), rhinal-cortex-lesioned rats (RH), and basal-forebrain-lesioned rats (BF) required to reach the criterion on the DNMS task at the 4-s delay. Error bars represent SEMs. (Note—Seven of the eight rats in the BF group were unable to reach the criterion within the maximum of 1500 trials).
DNMS Acquisition

Trials to Criterion

CON  RH  BF
Figure 15. Mean percent correct in the control rats (RH), rhinal-cortex-lesioned rats (RH), and basal-forebrain-lesioned (BF) on the DNMS task across different retention delays. Error bars represent SEMs.
DNMS with Delays

Percent Correct

Delay (sec)
**DNMS With Lists**

Figure 16 illustrates mean DNMS performance in each group across the different list-length conditions. Rats in both the basal-forebrain-lesion and rhinal-lesion groups made fewer correct choices than rats in the sham-lesion group on this task at all list length conditions, and the scores of all three groups decreased as the sample list length increased. A repeated measures ANOVA confirmed the statistical significance of these group \([F(2,18) = 53.1, p < 0.001]\) and list-length \([F(2,36) = 53.9, p < 0.001]\) effects. Pairwise comparisons revealed that basal-forebrain-lesioned rats and rhinal-lesioned rats were significantly impaired with respect to sham-lesion controls at all three list-lengths (all \(p\)'s < 0.01). Rats with basal-forebrain damage were significantly more impaired relative than the rats with rhinal-cortex damage with lists of three and five, but not seven, sample objects (both \(p\)'s < 0.01).

**Order Discrimination**

Figure 17 illustrates mean percent correct in each group on the order-discrimination task across the different lag conditions. It can be seen from this figure that scores decreased as the lag decreased \([F(2,36) = 11.5, p < 0.001]\) and that performance of rats in both the rhinal-lesion and basal-forebrain-lesion groups was poorer than that of rats in the sham-lesion group. Analysis of variance confirmed the statistical significance of these group differences \([F(2,18) = 37.4, p < 0.001]\), and pairwise comparisons revealed that the basal-forebrain-lesion and rhinal-lesion groups were not significantly different from each other at any of the lag conditions, whereas the basal-forebrain-lesion group was significantly impaired relative to the sham-lesion group at all
Figure 16. Mean percent correct in the control rats (RH), rhinal-cortex-lesioned rats (RH), and basal-forebrain-lesioned (BF) on the DNMS task across different sample list lengths. Error bars represent SEMs.
DNMS with Lists

Percent Correct

List Length

- SHAM
- RH
- BF
Figure 17. Mean percent correct in the control rats (RH), rhinal-cortex-lesioned rats (RH), and basal-forebrain-lesioned (BF) on the order-discrimination task. Error bars represent SEMs.
Order Discrimination

Percent Correct

Lag

SHAM
RH
BF
lags (all $p$'s < 0.001), and the rhinal-lesion group was significantly impaired relative to the sham-lesion group at lags of two and one (both $p$'s < 0.001) but not zero ($p = 0.12$).

DISCUSSION OF EXPERIMENT 2

Rats with bilateral lesions of the rhinal cortex or of the medial septal and diagonal band regions of the basal forebrain displayed different profiles of object-memory deficits. On three separate measures of object-reward associative learning (i.e., two-choice object discrimination, discrimination reversal, and concurrent object discrimination), rhinal cortex lesions produced a moderate to severe impairment, whereas basal forebrain lesions had no effect. In contrast, rhinal-cortex lesions produced no deficit in DNMS acquisition, whereas basal-forebrain lesions did--all but one of the basal-forebrain-lesioned rats failed to reach criterion on this task. Despite the normal rate of DNMS acquisition by rats with rhinal cortex damage, they displayed significant deficits in DNMS performance at the longer retention intervals and with lists of multiple sample objects. Nevertheless, the rats with rhinal cortex lesions performed significantly better that did the rats with basal forebrain lesions on the DNMS task at all conditions, with the one exception of the list length of seven. Finally, lesions of either the rhinal cortex or basal forebrain produced deficits on the order-discrimination task.

Object Discrimination

Rats with lesions to the rhinal cortex, but not the medial septum and diagonal band, took longer to reach criterion on the object-discrimination task. These results suggest that in rats at least, the rhinal cortex, but not the medial septum or diagonal band, is involved in the normal
acquisition of single object-reward associations. The finding that despite their acquisition deficit, rats with lesions of the rhinal cortex eventually acquired the object discrimination indicates that they retain the ability to form, store, and retrieve associative memories.

The impairment in the rhinal-lesioned rats is consistent with the results of some previous monkey studies (e.g., Zola-Morgan et al., 1989); however, there are also reports of preserved object-discrimination learning in monkeys with damage to both the rhinal and parahippocampal cortices (e.g., Suzuki, Zola-Morgan, Squire, & Amaral, 1993). The lack of impairment in rats with basal forebrain lesions is consistent with Voytko et al.’s (1994) finding of normal rates of object-discrimination learning in monkeys with combined damage to the medial septum, diagonal band, and nucleus basalis. It is also consistent with Ridley, Samson, Baker, and Johnson’s (1988) finding of normal object-discrimination learning in marmosets with neurotoxic lesions of the diagonal band.

Results of monkey studies that have examined the effect of rhinal cortex ablation on simple object-discrimination have been inconsistent (Suzuki et al., 1993; Zola-Morgan et al., 1989). One explanation that has been offered to account for these inconsistencies focuses on the potential involvement of small amounts of hippocampal damage—the suggestion being that deficits in object discrimination following lesions of the rhinal cortex occur only if there is additional damage to the hippocampal formation (Suzuki et al., 1993). However, because the lesions in the present experiment did not involve any hippocampal tissue, it would seem that, in rats at least, damage to the rhinal cortex alone is sufficient to disrupt normal object-discrimination learning.
The lack of impairment in the rats with lesions of the medial septum and diagonal band, together with the similar results of previous studies in monkeys (Ridley et al., 1988; Voytko et al., 1994) suggests that the basal forebrain is not involved in object discrimination. However, there is some evidence that the basal forebrain plays an important role in the learning of discrimination tasks in which spatial information is crucial to the correct solution (Ridley et al., 1988).

**Discrimination Reversal**

Rats with lesions of the rhinal cortex were significantly impaired in the rate at which they were able to acquire the reversal of a previously learned object discrimination, whereas rats with lesions of the medial septum and diagonal band were not. The reversal task requires rats to extinguish a previously correct object-reward association and to form a new one appropriate to the change in reinforcement contingency. The fact that rhinal-lesioned rats did not require a significantly greater number of trials than controls to eliminate their existing response bias (as assessed by Stage I of the reversal-learning process) suggests that their deficit on this task does not result from an abnormal perseverative tendency. Instead, the reversal-learning impairment displayed by rhinal-lesioned rats appears to result from a difficulty in the formation of a new object-reward association to guide their behavior. It appears, therefore, that performance on the discrimination-reversal task was disrupted for the same reason that learning of the initial object-discrimination task was disrupted, namely, an impairment in the ability to recognize an object and form a reward association with it.
Object-discrimination-reversal learning has yet to be tested in monkeys with selective lesions of the rhinal cortex, but Eacott et al. (1994) have shown that monkeys with rhinal cortex lesions are impaired in reversing from a matching-to-sample to a nonmatching-to-sample rule. Although this result might reflect a specific impairment in reversal learning, Eacott et al. (1994) argued that a more parsimonious explanation is that an impairment in object-identity judgment (as evidenced by their slower rate of delayed matching-to-sample reacquisition following surgery) was itself responsible for their inability to switch from the matching to nonmatching rule as quickly as controls. This kind of interpretation is consistent with both the fact that normal animals learn visual-discrimination-reversals more slowly if the stimuli are difficult to discriminate from each other than if the stimuli are clearly discriminable (Mackintosh, 1969) and with the present finding that the deficit displayed by rhinal-lesioned rats on the discrimination-reversal task was not attributable to an effect of abnormal perseveration.

The normal performance of rats with basal-forebrain damage on the discrimination-reversal task is further testimony to their lack of impairment in the formation of single object-reward associations. However, an interesting comparison can be drawn between the rats in the present experiment, in which the lesions encompassed mainly the medial septal and diagonal band areas of the basal forebrain, and animals in which the nucleus basalis was the primary site of basal-forebrain damage: In both monkeys (Irle & Markowitsch, 1987) and marmosets (Roberts, Robbins, Everitt, Jones, Sirkia, Wilkinson, & Page, 1990), it has been shown that visual-discrimination-reversal learning is impaired following neurotoxic lesions of the nucleus basalis, and, in the one case in which it was examined, this impairment reflected a tendency to perseverate on the previously correct stimulus as opposed to an inability to learn a new stimulus-
reward association (Roberts et al., 1990). This suggests that the nucleus basalis, but not the
medial septum or diagonal band, plays an important role in response inhibition, perhaps by virtue
of its major projection to the orbitofrontal cortex, damage to which produces perseverative
tendencies in humans, monkeys, and rats (e.g., Butter, 1969; Hannon & Bader, 1974; Iverson &
Mishkin, 1970; Milner, 1982).

Eight-Pair Concurrent Object Discrimination

Rats with lesions of the rhinal cortex were impaired in the rate at which they
concurrently acquired eight different object discriminations. These findings are consistent with
reports of impaired concurrent-discrimination learning in monkeys following rhinal cortex
ablation (Buckley & Gaffan, 1998; Zola-Morgan et al., 1989). However, it has been
demonstrated that monkeys with lesions of the rhinal cortex can learn concurrent-object-
discriminations at a normal rate under certain task conditions (Buckley & Gaffan, 1997; Gaffan
& Murray, 1992). Buckley and Gaffan (1998) have suggested that postoperative discrimination-
learning deficits in monkeys following rhinal cortex lesions depends upon the difficulty of the
discrimination. In Buckley and Gaffan's experiments, monkeys with rhinal cortex lesions were
not impaired in the acquisition of a set of either 10 or 20 concurrent-visual-discrimination
problems with one distractor item per problem, but impairments were observed when the set size
was increased to 40 or more problems, when the number of distractors was increased to 2 or
more, or when the objects were presented in different views on each trial.

Buckley and Gaffan's suggestion that the rhinal cortex is important only in more
difficult discrimination-learning tasks seems inconsistent with the present findings. In the
present experiment, concurrent-object discrimination was disrupted in rhinal-lesioned rats even though the stimulus set size was relatively small (i.e., eight problems), only one distractor item was used for each problem, and the objects were presented in the same orientation on every trial. Moreover, the results from the simple object-discrimination task in the present experiment indicate that the rhinal cortex is involved in object identification even when only a single pair of objects must be discriminated. It would, therefore, seem that there is a greater likelihood of finding an impairment in object-discrimination learning following rhinal-cortex damage in rats than following similar damage in monkeys. Whether this might reflect a difference in the inherent ease of object identification in rats and monkeys remains to be determined.

In contrast to the impairment displayed by rats with rhinal cortex damage, rats with lesions of the medial septum and diagonal band were able to master the concurrent-object-discrimination task at a rate comparable to that of controls. This finding is consistent with a previous report of normal acquisition of a similar task in monkeys following combined lesions of the medial septum, diagonal band, and nucleus basalis (Voytko et al., 1994). However, their failure to observe a deficit in concurrent-discrimination learning may have been due, in part, to the extensive preoperative experience that the monkeys received with this task. Nevertheless, the present results suggest that the medial septum and diagonal band are not required for the normal learning of concurrent object-reward associations even in animals with no preoperative training.
Delayed Nonmatching-to-Sample (DNMS)

Acquisition

Rats with lesions to the rhinal cortex mastered the DNMS task at a rate comparable to that of controls, whereas all but one of the rats with lesions to the medial septum and diagonal band were unable to learn the nonmatching rule within the maximum number of trials. The impairment in the basal-forebrain-lesioned rats is consistent with Aigner et al.’s (1991) finding that monkeys with combined damage to the medial septum, diagonal band, and nucleus basalis required significantly more trials to reacquire the DNMS task to criterion following surgery than they did to initially learn the task prior to surgery and significantly more trials than unoperated control monkeys required to reacquire the nonmatching rule after an equivalent rest period. In contrast, the finding of normal DNMS acquisition in rats with lesions of the rhinal cortex, although consistent with the results of previous studies in rats (Mumby & Pinel, 1994), is inconsistent with many reports of impaired DNMS acquisition in monkeys with similar medial-temporal-lobe damage (e.g., Meunier et al., 1993; Suzuki et al., 1993; Zola-Morgan et al., 1989).

One explanation that might account for this discrepancy between the effects of rhinal cortex lesions on DNMS acquisition in monkey and rats studies is the fact that rats in both the present experiment and Mumby and Pinel’s study were trained to acquire the DNMS rule with a 4-s delay between the sample presentation and the choice phase, whereas in monkey studies this delay is typically between 8 and 10 s. Because both rats and monkeys with rhinal cortex lesions show deficits in DNMS performance at delays as brief as 15 s, it is possible that an impairment in DNMS acquisition might have been observed in the present experiment if the delay used during the acquisition procedure had been slightly longer. This explanation, though, cannot
account for Eacott et al.'s (1994) demonstration that monkeys with rhinal cortex ablations are impaired in acquiring the DNMS rule when computer graphic stimuli are presented on a touchscreen with no delay between the sample and choice phases. With the recent advent of an automated touchscreen procedure for testing visual recognition in rats (Bussey, Muir, & Robbins, 1994), future studies should be able to determine whether rhinal cortex damage in rats produces an acquisition impairment when DNMS is tested under conditions similar to those reported by Eacott et al. (1994).

The present finding that rats with damage to the basal forebrain, but not to the rhinal cortex, were impaired in the acquisition of the DNMS task at a 4-s delay is an interesting one in view of the fact that rhinal-lesioned rats displayed deficits on the three previously discussed object-memory tasks (i.e., object discrimination, discrimination reversal, and concurrent object discrimination), whereas the basal-forebrain-lesioned rats did not. A key difference between the three previously discussed object-discrimination tasks and the DNMS task is that the former are all trial-independent tasks, tasks in which the relationship between stimulus and reward is constant across trials, whereas the latter is a trial-dependent task in which the relationship between stimulus and reward is different on each trial. The normal performance of rats with lesions of the medial septum and diagonal band on tasks requiring trial-independent memory and impairment on trial-dependent tasks mirrors the pattern observed in experiments assessing spatial memory abilities following basal-forebrain damage in rats (Knowlton, Wenk, Olton, & Coyle, 1985). Although it is possible that the impairment of the basal-forebrain-lesioned rats in acquiring the DNMS rule reflects a severe impairment in short-term memory (because DNMS acquisition does involve a brief delay), another possibility is that the trial-dependent nature of the
DNMS task places higher demands on other nonmnemonic processes, such as attention or the ability to avoid distraction, that might influence normal task performance; and these might be more susceptible to disruption by basal forebrain lesions than by rhinal cortex lesions.

**Delay Performance**

Although rhinal-cortex damage did not disrupt DNMS acquisition at a 4-s retention delay, it did disrupt DNMS performance at longer delays. Mumby and Pinel (1994) reported a similar finding following rhinal cortex ablation in rats that had undergone extensive preoperative DNMS training: They found that rhinal-lesioned rats were unimpaired in both the postsurgical reacquisition of the DNMS rule and in subsequent DNMS performance at a 4-s delay during mixed-delay testing but displayed significant deficits during mixed-delay testing at delays ranging from 15 to 120 s. Consistent with these findings are reports of DNMS performance deficits in monkeys with lesions of the rhinal cortex at all but the shortest delays (Meunier et al., 1993; Murray et al., 1989; Zola-Morgan et al., 1989).

The introduction of progressively longer retention delays to the DNMS task requires rats to retain information about the identity of an object for longer periods of time. The observation that rats with rhinal cortex lesions were impaired in DNMS performance at delays of 15 s or longer, but not in DNMS acquisition at a 4-s delay, suggests that they had a memory impairment. Because they learned to apply the nonmatching rule as quickly and as well as controls at the 4-s delay, their deficits are unlikely a consequence of an inability to discriminate between the test objects or to motivational or motor difficulties. Moreover, the finding that DNMS performance in the rhinal-lesioned rats was disrupted in a proportionately greater manner as the retention delay lengthened.
delay was increased between 15 and 120 s is further evidence that their deficit was likely mnemonic.

Basal-forebrain damage produced severe impairments in DNMS performance at all retention intervals; however, the interpretation of these deficits is difficult because all but one of the rats with lesions to this brain area failed to reach the same stable, high level of performance that control animals did during DNMS acquisition. In order to accurately compare working memory performance between two groups across a range of delays (or lists) on the DNMS task, it must first be established that the reference memory component of this task has been equally well learned by both groups. For this reason, the DNMS deficits displayed by rats with lesions of the basal forebrain, rather than reflecting an impairment in working memory per se, might simply reflect the fact that these rats were unable to learn to consistently apply the nonmatching-rule required to guide correct performance on this task. Perhaps this problem could have been by testing basal-forebrain-lesioned rats that had received extensive presurgical DNMS training: Presurgical training makes reacquisition of the DNMS rule following surgery proceed much more quickly; thus, if performance deficits were subsequently observed they would be less amenable to nonmnemonic interpretations (see Mumby et al., 1993; Murray et al., 1990).

**DNMS With Lists**

In addition to displaying a DNMS impairment when the retention delay was greater than 4 s, rats with lesions of the rhinal cortex or basal forebrain also performed poorly on DNMS when lists of three or more sample objects were presented. However, because the basal-forebrain-lesioned rats were unable to reach the same high level of performance attained by
control rats during DNMS testing with a 4-s delay, their impairment across the different sample list-lengths is difficult to interpret. In contrast, the normal performance displayed by rhinal-lesioned rats during testing with a 4-s delay suggests that their deficit on the list version of the DNMS task is likely to have arisen either from the fact that the task required the rats to retain information about multiple objects on each trial, from the fact that a considerable delay (approximately 45 s for a list length of 3) was interposed between the sample and choice phases of each trial, or from some combination of these two factors. In any case, these results, together with similar results from monkey studies (e.g., Eacott et al., 1994), support the notion that rhinal-cortex damage disrupts object recognition when the demands placed on recognition are sufficiently high.

**Order Discrimination**

Lesions of either the rhinal cortex or medial septum and diagonal band produced significant impairments on the order-discrimination task: Both groups of animals performed at near chance levels under each of the three different conditions of this task. Successful performance on this task requires that rats recognize and retain the order in which two different objects were presented within a larger sequence of objects. A similar deficit in order-memory has been observed in rats with medial-septal damage when they were required to remember the sequence of arm-visits in a radial maze (Kesner, 1988). The current finding, therefore, seems to support Kesner's (1988) hypothesis that the basal forebrain plays an important role in the coding of temporal information. However, there is an alternative interpretation of the present findings. Because the order-discrimination task followed extensive DNMS training, it is possible that rats
might have attempted to solve the order-discrimination task by following a “nonmatching-like” rule (i.e., by choosing the least familiar of the two objects presented on the choice part of each trial), and because the basal-forebrain-lesioned rats never learned DNMS as well as the control rats, they may have been less able to make use of this type of strategy. The possibility also remains that the deficits displayed by the rhinal-lesioned rats on the order-discrimination task were a result of their impairment in object recognition, because if a rat has difficulty in recognizing recently presented objects then it will almost certainly have difficulty in discriminating the temporal order in which those objects were encountered.

General Conclusions: Experiment 2

At the same time as confirming previous reports of DNMS deficits in rats following ablation of the rhinal cortex (e.g., Mumby & Pinel, 1994; Mumby, Wood, & Pinel, 1992; Wiig & Bilkie, 1995), the present findings indicate a mnemonic role for the rhinal cortex that extends well beyond object-recognition abilities involved in DNMS. It appears as if rhinal-cortex damage in rats affects a variety of object-memory abilities in addition to recognition, including the formation of object-reward associations and memory for the temporal order in which objects are presented. Lesions of the rhinal cortex impaired performance on both the DNMS and order-discrimination tasks and retarded the acquisition of object discrimination, concurrent object discriminations, and discrimination reversal. A number of similar deficits have also been reported in monkeys following damage to the perirhinal cortex, entorhinal cortex, or both: deficits in DNMS (Meunier et al., 1993), delayed matching-to-sample (Eacott et al., 1994),
reversal learning (Eacott et al., 1997), and concurrent object discrimination (Buckley & Gaffan, 1997; 1998).

The present results suggest that the rhinal cortex in rats plays an important role in memory for objects in general, and similar suggestions have been put forth regarding its role in monkeys. For example, Meunier et al. (1997) have proposed that the rhinal cortex, together with the orbitofrontal cortex and mediodorsal thalamic nucleus, forms part of a neural circuit that participates in various object-memory processes, ranging from object recognition to object-reward association. In a somewhat similar vein, Eacott et al. (1994) have suggested that rhinal cortex ablation in monkeys produces a general impairment in the capacity for knowledge about visual stimuli. These authors argue that this type of memory impairment is analogous to some of the cognitive deficits seen in the clinical syndrome known as "semantic dementia," in which rhinal-cortex damage in human patients is associated with a loss of knowledge about objects while leaving episodic memory relatively intact—a condition different from the global loss of episodic memory seen in amnesia resulting from radical medial temporal lobectomy (see Eacott et al., 1994; Hodges, Patterson, Oxbury, & Funnell, 1992; Warrington, 1975). There is, however, evidence to suggest that, in rats at least, the mnemonic deficits produced by rhinal-cortex damage are not limited uniquely to information about objects. For example, lesions of the rhinal cortex in rats have also been shown to impair spatial working memory (Johnson & Kesner, 1994; Wiig & Bilkey, 1994) as well as odour recognition (Otto & Eichenbaum, 1992).

The profile of anterograde object-memory impairments produced by lesions of the basal forebrain was clearly different from that produced by lesions to its major target areas. Although the medial septum and diagonal band provide strong cholinergic projections to the medial temporal lobe (Gaykema et al., 1990), the pattern of deficits displayed by the basal-forebrain-
lesioned rats was different from that of rhinal-cortex-lesioned rats and from the hippocampal-
lesioned rats of Experiment 1. These results suggest that the basal forebrain may make a unique
contribution to object-memory processes, independent of the contributions made by medial-
temporal-lobe structures. The discovery of neurons within the basal forebrain that fire
differentially in response to familiar and unfamiliar visual stimuli (Wilson & Rolls, 1990) would
seem to support a direct involvement of the basal forebrain in object recognition. However, an
alternative possibility is that cholinergic input from the basal forebrain to its temporal-lobe
projection sites may serve as an attention modulator that “primes” these areas when important
information is presented to them, and thus basal forebrain lesions may disrupt the ability to
distinguish important from trivial (see Johnson & Kesner, 1994). Basal forebrain involvement in
attention has recently been demonstrated in both monkeys (Voytko et al., 1994) and rats (Baxter
et al., 1997; Robbins et al., 1989).
EXPERIMENT 2A: IMPAIRMENTS IN DNMS FOLLOWING LESIONS OF THE BASAL FOREBRAIN IN RATS: EFFECT OF PRESURGERY TRAINING

In Experiment 2, all but one of the basal-forebrain-lesioned rats were unable to achieve criterion on the DNMS task at a 4-s delay. Consequently, DNMS deficits at longer delays were difficult to interpret. Did the deficits reflect a bona fide object-recognition deficit, or did they reflect deficits in nonmnemonic abilities required to perform the task? Evidence from two sources indicate that deficits in DNMS can result from difficulties in acquiring specific nonmnemonic skills that are necessary to reliably perform the task at longer delays: (1) the observation that DNMS deficits following medial-temporal-lobe lesions tend to be greater in animals that have not received training prior to surgery (see Murray, 1990), and (2) the observation that DNMS performance at long delays improves with practice even when stringent criteria have been achieved at short delays (Mumby et al., 1990).

The purpose of Experiment 2A was to verify if damage to the basal forebrain produces an anterograde object-recognition impairment in rats by ruling out the possible contributions of procedural-learning deficits. To do this, rats were given extensive presurgery DNMS training. In addition, DNMS performance was reexamined 3 months after completion of the initial postsurgery testing period because there have been reports that DNMS impairments in monkeys following lesions of the basal forebrain disappear with extended recovery time (e.g., Aigner et al., 1991).
METHOD

Subjects

The subjects were 8 experimentally naive, male Long-Evans rats (Charles River, St. Constant, Quebec, Canada) that were between 10 and 12 weeks old at the beginning of the experiment. They were housed individually with continuous access to water under a 12:12-hr light-dark cycle with lights on at 8:00 a.m. Their body weights were maintained throughout the experiment at approximately 85% of ad libitum levels by limiting their daily rations of rat chow. Training began after the rats had been on the restricted feeding regimen for 10 days.

Apparatus

The testing apparatus and objects were those described in the General Methods section.

Procedure

Each rat was habituated to the apparatus, and then it progressed through three phases of training and testing: (a) acquisition of a simple object discrimination task; (b) acquisition of the DNMS task at a 4-s retention delay and training at 15-, 30-, 60-, and 120-s delays; and (c) determination of the presurgery DNMS retention function. Following recovery from surgery, each rat received two phases of testing: (a) reacquisition of DNMS at a 4-s delay, and (b) determination of its postsurgery DNMS retention function. Three months following completion of the last portion of this postsurgery testing phase, all rats were once again trained to criterion at a 4-s delay and then tested on mixed-delay DNMS sessions.
**Presurgery Training: Acquisition of Object Discrimination**

Following habituation to the apparatus, each rat received five 25-trial object-discrimination sessions, as described in the General Methods section.

**Presurgery Training: Acquisition of DNMS**

The DNMS training procedure was identical to that of Experiment 1. For each rat, training continued at the 4-s delay until a criterion of at least 17 correct trials out of 20 on two consecutive sessions was achieved, whereupon the delay was increased to 15 s. The delay was subsequently increased to 30, 60, and then finally to 120 s, whenever a rat either reattained this same criterion or had six sessions at a particular delay without reattaining the criterion.

**Presurgery Training: DNMS Retention functions**

Each rat's retention function was assessed during the final phase of presurgery testing. Rat's received eight mixed-delay sessions, each consisting of 25 trials. On mixed-delay sessions, 5 trials were conducted at each of the following delays: 4, 15, 30, 60, and 120 s. These delays appeared in an ascending then descending order (i.e., 4, 15, 30, 60, 120, 120, 60, 30, 15, 4, 4, 15s, and so on).

**Surgery**

Following presurgery testing, rats received bilateral electrolytic lesions of the medial septum and diagonal band nuclei (basal-forebrain-lesion group, n=4), or they were exposed to a sham surgical procedure (sham-lesion group, n=4). All surgical procedures were identical to those of Experiment 2. All rats were allowed between 21 and 24 days to recover from surgery before testing resumed. During the second and third week following surgery, both the lesioned and sham animals were handled for approximately 15 min twice each day. All rats were allowed
continuous access to food for the first 14 days following surgery, after which they were returned to the restricted feeding regimen.

*Postsurgery Testing: Reacquisition of DNMS*

Following recovery from surgery, the rats were tested on the DNMS task at 4-s delays until they reattained the criterion of at least 17 correct trials out of 20 on two consecutive sessions.

* Postsurgery Testing: DNMS Retention Functions*

Next, the rats were given eight mixed-delay sessions identical to those that had been used to determine their retention functions prior to surgery. To determine whether or not any observed deficits in DNMS performance would recover, retention functions were also reassessed in a similar fashion 3 months after the completion of the initial postsurgical DNMS testing.

**RESULTS**

**Histological results**

Figure 18 illustrates the location and extent of each basal forebrain lesion. In all the rats, there was extensive damage to the rostral and caudal divisions of the medial septum, as well as bilateral damage to both the horizontal and vertical limbs of the diagonal band. Within the region of the lesion there was little or no evidence of neuronal sparing. Three of the four lesions extended slightly into the surrounding lateral septal nuclei. All rats also sustained a moderate amount of damage to both the strial and medial preoptic areas as well as to the septohypothalamic nuclei. In the case of the largest lesion (rat BF 2), slight unilateral damage was observed in both shell of the nucleus accumbens and the medial division of the ventral
Figure 18. Coronal sections illustrating the extent of each basal forebrain lesion. Sections are redrawn from the stereotaxic atlas of Paxinos and Watson (1986). The numbers on the left of the sections indicate the distance from bregma in mm.
pallidum, and the lesion extended caudally to include a portion of the anterior commissure. The basal forebrain lesions in the present experiment were comparable to those in Experiment 2 (see Figure 10).

**Behavioural Results**

*Presurgery Training: Acquisition of Object Discrimination*

All the rats initially learned the object discrimination. On Session 2, the first session on which they were not allowed to correct their errors, they averaged 67.5% correct (range = 48% to 88%); on the fifth and final session, they averaged 96% correct (range = 88% to 100%).

*Presurgery Training: Acquisition of DNMS*

The rats required a mean of 415 trials (SE = 39.2) to reach the DNMS performance criterion of 17 of 20 correct trials on 2 consecutive days at the 4-s delay. This mean does not include the trials of the two criterion sessions. Prior to surgery, the sham-lesion and basal-forebrain-lesion groups were matched in terms of their initial rates of DNMS acquisition.

*Presurgery Training: DNMS Retention Functions*

As shown in Figure 20, scores on the presurgery mixed-delay sessions declined significantly as the delay was lengthened \([F(4, 28) = 32.77, p < 0.001]\). There were no significant presurgery differences between the scores of the lesion and control rats at any of the delays (all \(p\)'s > 0.05).

*Postsurgery Testing: Reacquisition of DNMS*

The basal-forebrain-lesioned rats were significantly impaired on reacquisition of the DNMS task after surgery, but all subjects eventually reattained the criterion (see Figure 19). A
Figure 19. The mean number of trials that were required to attain the performance criterion on the DNMS task at the 4-s delay both before (black) and after (striped) surgery by the control rats and the rats with basal forebrain (BF) lesions. Error bars represent SEMs.
repeated measures ANOVA on the number of trials to criterion with group as the between-subjects factor and time-of-testing (preoperative vs. postoperative) as the repeated measure revealed a significant main effect of group \[F(1, 6) = 23.87, p < 0.01\] and a significant group x time-of-testing interaction \[F(1, 6) = 12.53, p < 0.05\]. The main effect of time-of-testing was not significant. Post hoc analyses (Tukey) revealed that there were no significant differences between the two groups before surgery, but that after surgery, the lesioned rats took significantly more trials to achieve criterion than did the sham-lesion controls \(p < 0.01\). The sham-lesion rats required significantly fewer trials to achieve criterion after surgery \(M = 75\) trials than they did before surgery \(M = 395\) trials \[t(3) = 6.23, p < 0.01\], whereas the basal-forebrain-lesioned rats did not \[t(3) = 0.76, p > 0.05\].

**Postsurgery testing: DNMS Retention Functions**

It is apparent in Figure 20 that the rats in the basal-forebrain-lesion group were severely impaired on the DNMS task following surgery. A repeated measures ANOVA with one between-subjects factor (group) and two repeated measures (time-of-testing and delay) revealed a significant difference between the two groups \[F(1, 6) = 41.78, p < 0.001\], a significant main effect of time-of-testing \[F(1, 6) = 44.79, p < 0.001\], and a significant main effect of delay \[F(4, 24) = 18.42, p < 0.001\]. The group x time-of-testing interaction was the only significant interaction \[F(1, 6) = 87.78, p < 0.001\]. Post hoc analyses showed that there were no significant differences between the two groups before surgery \[F(1, 6) = 0.30, p > 0.05\], but that the lesioned rats performed significantly worse overall than the controls after surgery \[F(1, 6) = 91.89, p < 0.001\]. This effect of group was statistically significant at all delays (all \(p\)'s < 0.05).
Figure 20. The mean presurgery and postsurgery retention functions that were determined on mixed-delay DNMS testing sessions for the controls (top) and the rats with basal forebrain lesions (bottom). Error bars represent $SEMs$. 
The graph shows the percent correct data for controls and BF lesions over different time periods:

- **Controls**
  - Presurgery
  - 3 weeks postsurgery
  - 20 weeks postsurgery

- **BF Lesions**

The x-axis represents delay (seconds), and the y-axis represents percent correct. The data points indicate a decrease in percent correct with increasing delay for both groups.
The basal-forebrain-lesioned rats displayed a similar pattern of DNMS deficits when they were retested 3 months after the completion of the original postsurgical testing: They required significantly more trials (mean = 60.0) than sham-lesion rats (mean = 265.0) to once again reacquire the DNMS task \( t(3) = 2.61, p < 0.05 \), and after having relearned the task, they made significantly fewer correct choices than the sham-lesion rats at all the retention delays \( F(1, 6) = 38.80, p < 0.001 \).

**DISCUSSION OF EXPERIMENT 2A**

In Experiment 2A, electrolytic lesions to the medial septum and diagonal band disrupted DNMS performance in rats despite the fact that they had all achieved the postsurgery performance criterion at the 4-s retention delay. The deficit was delay independent, that is, their postsurgical DNMS performance was significantly impaired relative to that of control rats, at all of the delays, ranging from 4 to 120 s. In addition, the lesioned rats required significantly more trials to relearn the nonmatching rule in comparison to sham-operated controls, and they were also impaired relative to their own DNMS performance prior to surgery. This impairment did not diminish over the 3 months between the first and second postsurgery test.

The present finding of impaired DNMS performance following a bilateral lesion of the medial septum and diagonal band is ostensibly inconsistent with the results of the only previous study to examine the effects of basal forebrain lesions on DNMS in rats, the study of Kelsey and Vargas (1993). Kelsey and Vargas found that rats with small lesions of the medial septum had difficulty performing a spatial DNMS task that required them to remember the location of the arm of a Y-maze that they had been forced to enter on the preceding sample run, but they displayed no difficulty performing a similar nonspatial DNMS task that required them to
remember the object they had encountered in a straight alley on the sample run. There are, however, three important differences between the present study and that of Kelsey and Vargas that may account for the seeming inconsistency. First, the differences in the rats’ experiences prior to training on the respective nonspatial DNMS tasks might account for the discrepant results. In the present study, all rats were experimentally naive prior to training and testing on the nonrecurring-items DNMS task, whereas the rats in the Kelsey and Vargas study had all received extensive training on a spatial DNMS task. As Kelsey and Vargas themselves pointed out, this raises the possibility that the failure to find a lesion-induced deficit in nonspatial memory in their study might reflect some kind of carryover effect of prior training on the spatial DNMS task, such as perseveration of spatial strategies by the controls. Second, differences in the extent of basal-forebrain damage might account for the discrepant results. The lesions in Kelsey and Vargas’ study were small and confined mainly to the medial septum, whereas the present lesions were considerably larger and consistently included the medial septum, and most of the vertical and horizontal limbs of the diagonal band. Third, the fact that Kelsey and Vargas used the same two stimulus objects on every trial, whereas different objects were used on each trial of the present experiment might account for the discrepant results. Using the same two stimulus objects on each trial of DNMS is a test of recency memory rather than recognition memory.

The DNMS impairment of the basal-forebrain-lesioned rats in the present experiment cannot easily be attributed to a simple perceptual, motivational, or motor deficit because rats with identical lesions were unimpaired on comparable two-choice discrimination, discrimination reversal, and eight-pair concurrent object-discrimination tasks in Experiment 2. This conclusion is supported by the observation that the lesioned rats were able to relearn the DNMS task, albeit
at a significantly slower rate than controls. However, the observation that rats with basal-
forebrain damage were equally impaired at all retention delays, including the shortest 4-s delay,
indicates that their rate of forgetting is no different than that of controls. Although it has been
argued that this type of delay-independent deficit reflects encoding or retrieval deficits, rather
than retention per se (see Ringo, 1991), it is possible that the DNMS deficit displayed by the rats
with basal-forebrain damage reflects a severe disruption of short-term memory consolidation
resulting in impaired performance at delays as brief as 4 s, but not at shorter delays.
Alternatively, the observed pattern of impairment may be attributable to a disruption of some
nonmnemonic process such as attention.

The fact that rats with basal forebrain lesions were significantly impaired relative to control
rats in reacquiring the nonmatching rule is an interesting finding. Indeed, they displayed no
preserved memory for the reference component of the task. Although it remains possible that
basal-forebrain damage produced a retrograde amnesia for the reference memory component of
the DNMS task, the lesioned rats were clearly able to make use of some of the information they
acquired before surgery. For example, they displaced objects and searched for food in the food
wells efficiently on the first trial following surgery, which suggests that they were able to
remember some procedural aspects of the task. However, it is not clear whether their lack of
savings reflected retrograde effects, anterograde effects, or both.

The finding that the rats with basal forebrain lesions, but not the control rats, performed
substantially worse at the 4-s retention delay during postsurgery mixed-delay testing (M =
73.1%) compared to the 17 or more out of 20 (i.e., 85% or greater) criterion they achieved upon
relearning the DNMS rule is an interesting one. The change in procedures, from sessions where
the delay was the same on all trials (i.e., during reacquisition) to sessions where the delay changed from trial to trial (i.e., mixed-delay testing), appeared to disrupt the ability of the basal-forebrain-lesioned rats to perform the DNMS task at the 4-s delay. A similar reduction in scores has been reported in amnesic patients (Squire et al., 1988) and in rats following either lesions of the mediodorsal thalamus (Mumby et al., 1993) or ischemia-induced damage to the CA1 cell layer of the hippocampus (Wood, Mumby, Pinel, & Phillips, 1993) when subjects were switched from sessions in which all trials were conducted at a 4-s delay to sessions in which some of the trials were conducted at a 4-s delay and the other trials were conducted at longer delays. The inevitable errors made at longer delays may disrupt DNMS performance at brief delays during the same session.

The delay-independent DNMS deficit of the lesioned rats is similar to that seen in monkeys with combined damage to the medial septum, diagonal band, and nucleus basalis (Aigner et al., 1991) or to the nucleus basalis alone (Irle & Markowitsch, 1987). In both of these studies, it was found that lesioned monkeys scored significantly worse than controls on a DNMS task, however, as the memory demands of the task were increased, the lesioned monkeys' performance was not disrupted to a proportionately greater extent. Moreover, a number of recent studies in rats have shown that spatial-recognition memory is also disrupted in a delay-independent manner by lesions of the basal forebrain (e.g., Baxter, Bucci, Gorman, Wiley, & Gallagher, 1995; McAlonan et al., 1995; Numan, 1991; Steckler, Keith, Wiley, & Saghal, 1995; Walsh et al., 1996).

Experiment 2 revealed that the DNMS deficits produced in rats and monkeys by lesions of the basal forebrain differ from those produced by medial temporal lobe lesions in two major
respects. First, in contrast to the delay-independent deficit observed in basal-forebrain-lesioned rats in the present experiment, both rats and monkeys with rhinal lesions display delay-dependent DNMS deficits: At the shortest DNMS delays they display no impairment, but as the delay increases, the impairment becomes progressively greater (Meunier et al., 1993; Mumby & Pinel, 1994; Zola-Morgan et al., 1989) (see also Experiment 2). Second, in contrast to the basal-forebrain-lesioned rats in the present study, pretrained rats with rhinal lesions reacquire the DNMS rule as readily as controls (Mumby & Pinel, 1994).

Experiment 2 also revealed differences in the effects of rhinal-cortex and basal-forebrain damage on tests of two-choice object discrimination and concurrent object discrimination. Lesions of the rhinal cortex produced severe learning deficits on these tests, whereas lesions of the medial septum and diagonal band did not. Therefore, despite the fact that damage to the medial temporal lobes and the basal forebrain have both been implicated in cases of human amnesia, the present research suggests that the effects of medial-temporal-lobe and basal-forebrain damage are fundamentally different.

The severe impairment displayed by the basal-forebrain-lesioned rats in reacquiring the DNMS task, together with the delay-independent nature of their impairment in DNMS performance (including an impairment at the 4-s delay following reacquisition), suggest that their problem may not be one in memory per se. If the DNMS deficit is not primarily the result of a mnemonic deficit or of a simple sensory, motor, or motivational deficit; what is the nature of the deficit? Recent research suggests that the deficit may be related to attentional processing. Evidence in primates has shown that combined neurotoxic lesioning of the medial septum, diagonal band, and nucleus basalis can result in a disruption of attentional focusing without
affecting several different measures of nonspatial memory (Voytko, et al., 1994). In rats, one study (Dunnett, Everitt, & Robbins, 1991) suggested a dissociation of cognitive processes within the rat basal forebrain, with visual attention being dependent upon the nucleus basalis and learning and memory being dependent upon the medial septum and diagonal band. However, the present findings, along with several other recent reports of delay-independent impairments on spatial memory tasks following selective lesions of the medial septum and diagonal band (Baxter, et al., 1995; Numan, 1991; Robinson, Wiley, Wenk, Lappi, & Crawley, 1996; Steckler et al., 1995) argue against a clear-cut dissociation. Further studies of rats with lesions to the medial septum and diagonal band on tasks specifically designed to assess attention are needed to help determine what role, if any, the various structures of this brain region play in attentional processing of information and if attentional deficits are entirely responsible for the delay-independent performance deficits that are often observed following basal-forebrain damage.
EXPERIMENT 3: ANTEROGRADE MEMORY DEFICITS FOLLOWING LESIONS OF THE MEDIODORSAL THALAMUS IN RATS

Data from human clinical studies suggest that diencephalic structures contribute significantly to various cognitive and memory processes (Aggleton & Mishkin, 1983; Mumby et al., 1993; Squire & Zola-Morgan, 1988; Winocur et al., 1984). Neuropathological studies in humans have linked damage to both the anterior (Barbizet, Degos, Louarn, Nguyen, & Mas, 1981) and midline thalamic nuclei (Mair, Warrington, & Weiskrantz, 1979) to severe memory loss, but the most commonly affected structure in cases of diencephalic amnesia appears to be the mediodorsal thalamic nucleus (Markowitsch, 1982; Speedie & Heilman, 1982; Victor et al., 1971).

Experiments on nonhuman animals have confirmed the role of the mediodorsal thalamus in memory. Monkeys with lesions of the mediodorsal thalamus display deficits on both DNMS (Aggleton & Mishkin, 1983a; Aggleton & Mishkin, 1983b; Zola-Morgan & Squire, 1985) and spatial delayed-alternation (Isseroff, Rosvold, Galkin & Goldman-Rakic, 1982) tasks. Similarly, in the case of rats, mediodorsal-thalamic lesions have been found to disrupt the performance of both spatial (e.g., Delacour, 1971; Krazem et al., 1995; Winocur, 1985) and object-recognition (Mumby et al., 1993) tasks.

An issue of great interest remains whether the contributions of the medial thalamus to mnemonic functioning can be dissociated from those of the medial temporal lobe. In a recent review, Eichenbaum, Otto, and Cohen (1994) suggested that although medial-thalamic lesions produce some deficits in memory similar to those produced by medial-temporal-lobe lesions,
they also seem to produce a number of unique deficits. However, Eichenbaum et al. qualified their suggestion by emphasizing the paucity of studies that have directly compared the effects of damage to the two areas. Accordingly, in Experiment 3, the effects of lesions of the mediodorsal thalamus in rats were assessed using the same battery of anterograde object-memory tasks that were used to characterize the mnemonic effects of lesions to the hippocampus, amygdala, or rhinal cortex in Experiments 1 and 2.

The primary purpose was to provide an empirical basis for comparing the roles of the mediodorsal thalamus and the medial-temporal-lobe structures in the memory for objects. A secondary purpose as to provide an empirical basis for comparing the profile of mnemonic deficits in rats with lesions of the mediodorsal thalamus with the previously characterized profile of deficits in monkey studies with mediodorsal nucleus lesions.

METHOD

Subjects

The 12 rats that served as subjects were divided into two groups of 6 rats each. Rats in the thalamus-lesion group received bilateral electrolytic lesions of the mediodorsal thalamus; and rats in the sham-lesion group received sham surgery.

Surgical Procedure

Surgery, as in previous experiments, was performed under pentobarbitol anesthesia (60 mg/kg). The lesions were made with a stainless steel bipolar electrode, which was insulated with Teflon except for approximately 1 mm at its tip. With the incisor bar positioned at 3.3 mm
below the interaural line, the electrode was lowered into the mediodorsal thalamic nucleus of each hemisphere, at the following coordinates, relative to bregma in mm: AP -2.8, ML +0.6, DV -6.5. To produce the thalamic-lesions, 2 mA of current was passed through the electrode for 20 s; to produce the sham lesions, the electrode was left in position for approximately 30 s, but no current was passed through it.

Apparatus

The apparatus and test objects were those used in Experiments 1 and 2. They are described in the General Methods section.

Behavioural Procedure

Following recovery from surgery, each rat was habituated to the apparatus and then trained on each of the six object-memory tasks described in the General Methods section.

Statistical Analyses

Because Experiment 3 involved only two separate groups, statistical analyses on the trials-to-criterion or errors-to-criterion measures for the object discrimination, discrimination reversal, concurrent discriminations, and the acquisition stage of DNMS testing were carried out using two-sample t-tests rather than ANOVAs.
RESULTS

Selective lesions of the mediodorsal thalamus in rats produced a significant impairment on a variety of different object-memory tasks. Thalamic lesioned rats were retarded in the rate at which they learned an object discrimination, the reversal of that discrimination, and an eight-pair concurrent object discrimination. Despite acquiring the DNMS task at a rate comparable to that of controls, rats with mediodorsal thalamic lesions displayed significant deficits on this task at longer retention delays and with lists of sample objects, but these deficits were not delay-dependent. Thalamic damage also disrupted performance on the order-discrimination task.

Histological Results

Figure 21 illustrates the location and extent of the largest and smallest mediodorsal thalamic lesions. In the 6 rats composing the thalamus-lesion group there was extensive bilateral damage to the mediodorsal and intermediodorsal nuclei. In addition, there was usually bilateral damage to several nuclei adjacent to the mediodorsal nuclei: the paraventricular, paracentral, paratenial, central medial, and habenular nuclei. One of the rats also sustained moderate amounts of unilateral damage to both the anteroverentral and anterodorsal thalamic nuclei, as well as slight unilateral damage to the dentate gyrus (see the largest lesion in Figure 21); however, this additional unilateral damage did not appear to be related to the severity of any of the object-memory deficits.
Figure 21. Reconstructions of the largest (striped) and smallest (black) mediodorsal thalamic lesions. Planes of section are shown in millimeters, relative to bregma. The drawings are adapted from the atlas of Paxinos and Watson (1986).
Behavioural Results

Object Discrimination

All of the rats were able to solve the object-discrimination task. Figure 22 illustrates the mean number of trials that rats in the thalamus-lesion and sham-lesion groups required to reach the learning criterion of at least 22 out of 25 correct trials on two consecutive object-discrimination sessions. Compared to the sham rats, rats in the thalamus-lesion group required more trials to reach criterion, and this difference was statistically significant \( t(10) = 1.82, p = 0.05 \).

Discrimination Reversal

After solving the initial object discrimination, all rats were able to learn the reversal. Figure 23 illustrates the mean number of trials that the rats in both groups required to reach the criterion of at least 22 out of 25 trials correct on two consecutive discrimination-reversal sessions. The rats in the thalamus-lesion group took significantly longer to learn this task than the rats in the sham-lesion group \( t(10) = 3.11, p = 0.004 \).

In order to clarify the nature of the performance deficit of the thalamic-lesioned rats on the discrimination-reversal task, the number of errors made by each rat during each reversal session was divided into two types. As in Experiment 2, Stage I errors were defined as all errors made by an animal while performing significantly below chance (i.e., when 8 or fewer correct responses were made during a 25 trial session); Stage II errors included all remaining errors. Significantly more Stage I errors were made by rats in the thalamus-lesion group (M = 103.3) than by rats in the sham-lesion group (M = 66.2) \( t(10) = 2.67, p = 0.02 \). Although thalamic-
Figure 22. Mean number of trials that the control rats (SHAM) and the rats with lesions of the mediodorsal thalamus (MD) required to reach the criterion on the object-discrimination task. Error bars represent SEMs.
Object Discrimination

Trials to Criterion

SHAM  MD
Figure 23. Mean number of trials that the control rats (SHAM) and the rats with lesions of the mediodorsal thalamus (MD) required to reach the criterion on the discrimination-reversal task. Error bars represent SEMs.
lesioned rats also made more Stage II errors (M = 36.0) than did sham-lesion rats (M = 20.2), this difference was not statistically significant (p > 0.1).

**Eight-Pair Concurrent Object Discrimination**

Figure 24 illustrates the mean number of trials required by both groups of rats to reach the criterion of at least 36 out of 40 correct trials on two consecutive concurrent-object-discrimination sessions, as well as the mean number of errors that were committed by each group in the process. Whereas all rats were able to eventually learn the concurrent discrimination, it can be seen from Figure 13 that the thalamus-lesion group required more trials to meet criterion and made more errors in doing so than did the sham-lesion group. The difference between the groups, however, was statistically significant only when rate of learning was expressed as errors-to-criterion \( t(10) = 1.83, p = 0.046 \), not as trials-to-criterion \( t(10) = 1.30, p = 0.096 \). The failure of the trials-to-criterion measure to reveal a significant group difference was due to one sham-lesion rat that required 560 trials to learn the concurrent-discrimination task compared to the average of 304 trials required by the remaining sham-lesion rats. This rat had achieved a performance of 35 out of 40 correct trials on two consecutive sessions after only 320 learning trials, but it took another 240 trials to improve to the criterion of 36 correct trials.

**Delayed Nonmatching-to-Sample (DNMS)**

Figure 25 illustrates the rate of DNMS acquisition for both groups of rats. The rats in the thalamus-lesion group required, on average, nearly 100 more trials than the rats in the sham-lesion group to reach the criterion of at least 17 correct trials out of 20 on two consecutive DNMS sessions, however, this difference was not statistically significant \( t(10) = 0.46, p = 0.66 \). One of the thalamic-lesioned rats failed to learn the DNMS rule within the maximum number of
Figure 24. Mean number of trials (top) and errors (bottom) to criterion for the control rats (SHAM) and the rats with lesions of the mediodorsal thalamus (MD) on the eight-pair concurrent-object-discrimination task. Error bars represent SEMs.
Concurrent Object Discrimination

Trials to Criterion

Errors to Criterion
Figure 25. Mean number of trials that the control rats (SHAM) and the rats with lesions of the mediodorsal thalamus (MD) required to reach the criterion on the DNMS task at the 4-s delay. Error bars represent SEMs.
DNMS Acquisition

Trials to Criterion

SHAM  MD
trials allotted (i.e., 1500) and thus was not tested at longer delays (however, this animal's data was included in Figure 25).

Figure 26 illustrates DNMS performance across the different retention intervals and list-length conditions. Despite the fact that there was no significant difference between the two groups in the rate of DNMS acquisition at the 4-s delay, the rats in the thalamus-lesion group performed significantly worse than the rats in the sham-lesion group when tested at longer delays. An ANOVA confirmed that this group difference was statistically significant \( F(1, 8) = 17.07, p = 0.003 \). It is apparent from Figure 26 that scores in both groups of rats also declined as the retention interval was increased \( F(3, 24) = 28.69, p < 0.001 \); however, there was no significant interaction between the effect of lesion and the effect of delay \( F(3, 24) = 0.9, p = 0.46 \). Pairwise comparisons later revealed that the thalamus-lesion group was significantly impaired relative to the sham-lesion group at all of the retention delays (all \( p \)'s < 0.05).

**DNMS With Lists**

It can be seen from Figure 27 that when DNMS ability was assessed with lists of different sample objects, scores decreased as the list length increased \( F(2, 16) = 15.05, p < 0.001 \). It is also apparent from this figure that rats with lesions of the mediiodorsal thalamus made fewer correct choices than rats with sham lesions at all of the list length conditions \( F(1, 8) = 10.73, p = 0.011 \). However, there was no significant interaction between group and list length \( F(2, 16) = 0.15, p = 0.98 \). Pairwise comparisons revealed that the difference between the groups at each list-length condition approached, but did not quite achieve, statistical significance \( (0.5 < \text{all } p \text{'s} < 0.1) \).
Figure 26. Mean percent correct for the control rats (SHAM) and rats with lesions of the mediodorsal thalamus (MD) on the DNMS task across different retention delays. Error bars represent $SEM$s.
DNMS Delays

Percent Correct

Delay (sec)

SHAM
MD
Figure 27. Mean percent correct for the control rats (SHAM) and rats with lesions of the mediodorsal thalamus (MD) on the DNMS task with different sample list lengths. Error bars represent SEMs.
DNMS with Lists

Percent Correct

List Length

SHAM
MD
**Order Discrimination**

Figure 28 shows that the scores on the order-discrimination task decreased as the lag decreased \[ F(2, 18) = 5.32, p < 0.05 \]. It can also be seen from this figure that rats in the thalamus-lesion group made fewer correct responses than did rats in the sham-lesion group, and this difference was statistically significant \[ F(1,9) = 5.10, p = 0.05 \]. However, the thalamus-lesioned rats performed significantly worse than the sham-lesioned rats only in the lag-2 condition \( p < 0.05 \).

**DISCUSSION OF EXPERIMENT 3**

The present study examined the effects of damage to the mediodorsal thalamus in rats on the acquisition and performance of a battery of object-memory tasks. Rats with bilateral electrolytic lesions of the mediodorsal thalamus were impaired in the acquisition of a two-choice object discrimination, the reversal of that discrimination, and an eight-pair concurrent object-discrimination task. However, despite their slower initial rates of learning on these tasks, the lesioned rats eventually reached the same stable, high levels of performance that were observed in controls. On the other hand, although rats with lesions of the mediodorsal thalamus were not significantly impaired in the rate at which they learned the DNMS task at a 4-s delay, they performed significantly worse than controls on this task when the retention delay was increased or when the sample list length was increased. Finally, lesions of the mediodorsal thalamus also disrupted normal performance of an order-discrimination task, albeit only at the longest lag condition.
Figure 28. Mean percent correct for the control rats (SHAM) and rats with lesions of the mediodorsal thalamus (MD) on the order-discrimination task. Error bars represent SEMs.
Order Discrimination

Percent Correct

Lag

SHAM
MD
Object Discrimination

The finding that lesioned rats required significantly more trials than controls to learn the simple object-discrimination task is consistent with previous investigations of mediodorsal-thalamic function in rats. Studies in rats have shown that damage to the mediodorsal thalamus can disrupt the performance of a wide range of discrimination tasks, including odor discriminations (Slotnick & Risser, 1990; Staubli, Schottler, & Nejat-Bina, 1987), spatial discriminations (Weiss & Means, 1980), and visual-tactile discriminations (Waring & Means, 1976). In monkeys, however, the effects of mediodorsal-thalamic damage on visual-discrimination learning have proved more variable. Some studies have found acquisition of single discriminations to be normal following lesions of the medial thalamus (Aggleton & Mishkin, 1983b; Zola-Morgan & Squire, 1985), whereas others have found deficits (Gaffan & Murray, 1990; Schulman, 1964).

Gaffan and Murray (1990) have suggested that the mediodorsal thalamus is involved in reward-related processes, such as the formation of associations between discriminative stimuli and the incentive value of the food reward. In support of this hypothesis, Gaffan and Watkins (1991) showed that monkeys with mediodorsal-thalamic lesions are impaired on tasks that require the subject to remember the amount of reward associated with a particular stimulus. The present finding is also consistent with this hypothesis.

Discrimination Reversal

In addition to learning a simple two-choice object-discrimination problem more slowly than controls, rats with lesions of the mediodorsal thalamus also learned the reversal of that
discrimination more slowly. Similar deficits in learning the reversal of spatial discriminations have been reported in rats with medial thalamic damage (e.g., Harrison & Mair, 1996; Kolb, 1977; Krazem et al., 1995; Means, Hershey, Waterhouse, & Lane, 1975; Tigner, 1974).

The reversal-learning impairment displayed by the present rats with mediodorsal thalamic lesions was in part due to a difficulty in suppressing or unlearning the previous object-reward association, a fact indicated by the significantly greater number of discrimination-reversal sessions during which the lesioned rats performed significantly below-chance levels. This observation is consistent with the report of an increase in perseverative errors during the reversal of spatial discriminations by rats with lesions of the mediodorsal thalamus (Kolb, 1977).

Deficits in reversal learning have also been documented in both monkeys (Iversen & Mishkin, 1970; Meunier et al., 1997) and rats (Hannon & Bader, 1974; Wikmark, Divac, & Weiss, 1973) with lesions of the prefrontal cortex, one of the main projection sites of mediodorsal nucleus neurons. Apparently, the mediodorsal thalamic nucleus and the prefrontal cortex form part of a functional system involved in the inhibition of previously-learned responses, a process critical to normal reversal learning.

Eight-Pair Concurrent Object Discrimination

Rats with lesions of the mediodorsal thalamus were impaired in the rate at which they acquired the eight-pair concurrent-object-discrimination task. This finding is consistent with reports of impaired learning of concurrent visual discriminations in Korsakoff patients (e.g., Aggleton et al., 1988; 1992; Gaffan, Aggleton, Gaffan, & Shaw, 1990; Kessler, Irle, & Markowitsch, 1986; Squire et al., 1988). There is, however, an important difference between the
present concurrent-object-discrimination deficit in rats and that previously reported in Korsakoff patients: Despite their slower rate of acquisition on this task, rats with mediodorsal-thalamic lesions were eventually able to reach the same performance levels as controls, whereas Korsakoff amnesics in various studies have rarely approached control levels in their performance of concurrent-discrimination tasks (Aggleton et al., 1988; Kessler et al., 1986; Squire et al., 1988). However, because the Korsakoff patients in these studies were given only a few presentations (i.e., 4 or 5) of each discrimination pair, the possibility remains that they could have eventually learn the discriminations. The present data suggest that the effect of medial-thalamic damage on concurrent-object-discrimination performance might be limited to the initial stages of the learning process (see Hunt et al., 1994).

Although the present finding of impaired concurrent-object discrimination in rats with lesions of the mediodorsal thalamus is consistent with similar impairments observed in Korsakoff patients and other diencephalic amnesics (Aggleton et al., 1988; Squire et al., 1988), the only comparable study in monkeys, one by Parker, Eacott, and Gaffan (1997), did not find a significant deficit. The difference between the present findings and those of Parker et al. could of course reflect a species difference; however, the following two explanations warrant consideration. First, in the present experiment, there was near total bilateral destruction of the mediodorsal nucleus, whereas all of the monkeys in Parker et al.’s study had partial sparing of the magnocellular portion of the nucleus, which receives projections from the rhinal cortex, and near complete sparing of the parvocellular portion of the nucleus. Second, in the present experiment and in comparable studies of concurrent-discrimination learning in human amnesics, each particular object pair was presented five times per session with an intertrial interval of 1 or 2
min, whereas, in Parker et al.'s study, the monkeys were presented with each object pair once per daily session, therefore the intertrial interval for each pair was 24 hr. Because monkeys with medial-temporal lobectomies are impaired on concurrent-discrimination tasks when relatively short intertrial intervals are used (Zola-Morgan & Squire, 1985) but not when each pair of stimuli is presented once per day (Malamut, Saunders, & Mishkin, 1984), it has been proposed that learning of concurrent discriminations with long intertrial intervals involves a different neural system than that involved in learning massed concurrent discriminations (Gaffan & Murray, 1990; Mishkin, Malamut, & Bachevalier, 1984). Evidence for a similar dissociation after medial-thalamic damage comes from Hunt et al.'s (1994) finding that rats with lesions of the mediodorsal nucleus were impaired on a concurrent-object-discrimination task when each object pair was presented either four or eight times per daily session, but not when they were presented once per session.

Task 4: Delayed Nonmatching-to-Sample (DNMS)

Acquisition

Rats with lesions of the mediodorsal thalamus learned the DNMS rule at a normal rate. This is somewhat surprising given that damage to this brain area had been found to impair DNMS acquisition in both monkeys (Zola-Morgan & Squire, 1985) and rats (Mumby et al., 1993). This inconsistency may have resulted from a major difference in experimental design between the current and past studies. The animals in both Mumby et al.'s (1993) and Zola-Morgan and Squire’s (1985) studies began DNMS training after no more than six sessions of object-discrimination testing, whereas the rats in the present experiment completed between 27
and 38 discrimination sessions (object discrimination, discrimination reversal, and concurrent object discrimination) before the commencement of DNMS training.

**Delay Performance**

Although thalamic lesions did not retard learning of the DNMS rule at a 4-s retention delay, they did disrupt DNMS at longer retention delays. This finding is consistent with those of past studies of object recognition in animals with lesions of the mediodorsal thalamus (Aggleton & Mishkin, 1983a; 1983b; Mumby et al., 1993; Zola-Morgan & Squire, 1985). Another similarity between the present results and those of previous studies (e.g., Aggleton & Mishkin, 1982a; 1983b; Mumby et al., 1993) is that the thalamic-lesioned rats performed worse than control rats over a wide range of delays (i.e., 15 to 120 s), not just at long delays. This delay-independent pattern of memory deficits is similar to that observed in Korsakoff patients (e.g., Mair, 1994; Oscar-Berman & Bonner, 1989; Squire et al., 1988).

**DNMS With Lists**

The rats with lesions of the mediodorsal thalamus were also impaired on DNMS when there were three, five, or seven sample objects. The size of the impairment was not greater when more sample objects were presented. Similar findings have been reported in monkeys with medial thalamic lesions (Aggleton & Mishkin, 1983a) and in Korsakoff patients (Aggleton et al., 1988). In addition to requiring the rats to retain more information, the introduction of longer lists of sample objects to the DNMS task extended the interval between the sample presentation of any object in the list and the later presentation of the same object during the test phase. These
results, therefore, are consistent with the observation of the delay-independent DNMS deficit in the same rats.

**Order Discrimination**

Rats with lesions of the mediodorsal thalamus were displayed a significant deficit in only the easiest condition of the order-discrimination task (i.e., lag of two). The lack of a significant impairment on lags of one or zero was likely due to a floor effect; the performance of the control rats approached chance levels as the separation lag between comparison stimuli was decreased (see Figure 28).

The observed deficit in order discrimination is consistent with a report of impaired order discrimination in monkeys with lesions of the medial thalamus (Gower, 1992). It is also consistent with numerous reports of deficits in temporal-order memory in Korsakoff amnesics with presumed diencephalic damage (e.g., Hunkin & Parkin, 1993; Hunkin, Parkin, & Longmore, 1994; Parkin & Hunkin, 1993). However, because Korsakoff patients also display atrophy of the frontal lobes, which play a role in the temporal organization of information (Chiba, Kesner, & Reynolds, 1994; Kesner & Holbrook, 1987; Milner, 1964; Milner, Petrides, & Smith, 1985; Shimamura, Janowsky, & Squire, 1990), it is not clear to what extent their deficits in order discrimination are a consequence of their diencephalic pathology.

Despite the likely contribution of frontal-lobe pathology to the temporal memory deficits of Korsakoff patients, Gower's (1992) results in monkeys and the present finding in rats indicate that damage to the medial thalamus can itself disrupt memory for the temporal order of events. This conclusion is supported by recent reports of impaired temporal discrimination in two
patients following discrete thalamic infarction (Parkin et al., 1994; Shuren, Jacobs, & Heilman, 1997). Nevertheless, the fact that there are major efferent projections from the mediodorsal thalamic nucleus to various regions of the frontal cortex (Akert, 1964; Markowitsch, 1982) suggests that the deficits in temporal-order memory produced by thalamic damage might be caused by disrupting the flow of information from the mediodorsal nucleus to the frontal cortex.

**General Conclusions: Experiment 3**

In general, the profile of object-memory deficits in rats with lesions of the mediodorsal thalamus resembles the profiles that have been reported in monkeys with similar lesions. For example, both the results of the present experiment and those of past monkey studies demonstrate that medial-thalamic damage produces an impairment in object-reward discrimination (Aggleton & Mishkin, 1983b; Gaffan & Murray, 1990), temporal-order discrimination (Gower, 1992), and DNMS performance across various retention delays (Aggleton & Mishkin, 1983a; Zola-Morgan & Squire, 1985) and with different sample list-lengths (Aggleton & Mishkin, 1983b; Parker et al., 1997).

Despite the fact that thalamic-lesioned rats were impaired in the rate at which they were able to acquire the object-discrimination, discrimination-reversal, and concurrent-object-discrimination tasks, they eventually reached the same high level of performance on these tasks as did controls. These findings, together with studies of olfactory-discrimination learning (e.g., Staubli et al., 1987), indicate that lesions of the mediodorsal thalamus lead to a learning deficit that can be overcome with extensive training. It would appear, therefore, that lesions of the
mediodorsal thalamus can disrupt initial learning but that other systems ensure that the animal is still able to learn the task, albeit less efficiently.

To explain how lesions of the mediodorsal thalamus disrupt the initial learning of a number of different tasks, it has been proposed that the mediodorsal nucleus functions to encode aspects of a task into memory (Hunt & Aggleton, 1991; Staubli et al., 1987). Accordingly, the mediodorsal thalamus might play an important role in acquiring new information, but not in its storage or retrieval. This view is consistent with the present finding of a delay-independent deficit in object recognition; it has been argued that when performance on a memory task is comparably affected at both the shortest and longest delays the impairment is likely to be in the encoding of information, not in its retention (Ringo, 1992).

Additional support for the notion that the memory loss following lesions of the mediodorsal thalamus is related to a failure in the encoding of information during the early stages of learning comes from both human and nonhuman animal studies. For example, Winocur (1985) found that rats with mediodorsal-thalamic lesions were impaired on a spatial delayed-alternation task at all intertrial intervals, including a 0-s delay condition where demands on working memory were minimal. By the same token, it has been reported that an amnesic patient with a discrete bilateral lesion to the mediodorsal thalamus was impaired on a short-term memory task, even at very brief delay intervals, and that his performance improved dramatically when stimulus exposure time was increased to allow more study time at original presentation (Winocur et al., 1984).

Other theories postulate that the mediodorsal thalamus forms part of an “event processing” (Gabriel, 1993) or a “stimulus-significance decoding” circuit (Oyoshi, Nishijo,
Asakura, & Ono, 1996). Consistent with a role for the mediodorsal thalamus in encoding stimulus significance are findings demonstrating a differential response rate of thalamic neurons within the mediodorsal nucleus to conditioned stimuli in terms of the reward contingency predicted by the stimuli rather than the physical properties of the stimuli themselves (Oyoshi et al., 1996). In the same study, conditioned stimulus-related neurons were found to change their response patterns during extinction and relearning trials (i.e., a decrease in neuronal firing rate followed by an increase), even though the same physical stimulus was presented repeatedly. This pattern of activity suggests that neurons within the mediodorsal nucleus might play an important role in normal reversal learning and might help explain the perseverative tendencies that have been observed following damage to this brain structure.

The present results are consistent with all of the aforementioned theories of mediodorsal thalamic function; thus, they do not lend support to any particular one of them. They do, however, emphasize that the mediodorsal thalamus plays an important role in a wide variety of memory tasks.
EXPERIMENT 4: AN ANALYSIS OF RETROGRADE MEMORY FOR OBJECTS FOLLOWING LESIONS OF THE MEDIAL TEMPORAL LOBE, MEDIAL DIENCEPHALON, OR BASAL FOREBRAIN IN RATS.

There appear to be two distinct stages of memory storage: short term and long term (see Squire, 1992; Schacter & Tulving, 1994). The study of amnesic patients suggests that the mechanisms underlying these two stages are different: Many amnesic patients experience no deficits in short-term memory, but have difficulty recalling long-term memories laid down before their amnesia-inducing brain trauma (i.e., retrograde amnesia) and in forming new posttraumatic long-term memories (i.e., anterograde amnesia). The fact that retrograde amnesia is often temporally-graded, affecting memories for recent events more than memories for remote events, suggests a disturbance of consolidation (Alvarez & Squire, 1994). Brain-damage-produced retrograde amnesia for objects was the focus of Experiment 4.

Retrograde amnesia has been studied less than anterograde amnesia because of the methodological difficulties inherent in assessing retrograde memory (see Butters & Cermak, 1986; Sanders & Warrington, 1971; Squire, 1992). Studies of retrograde amnesia in human amnesics have been particularly problematic because of the inability of researchers to control or measure the original learning or the intervening experiences. These problems and others have been circumvented by a series of recent studies of brain-damage-produced retrograde amnesia in monkey and rat models (e.g., Astur, Mumby, Weisand, & Sutherland, 1994; Cho et al., 1993; Zola-Morgan & Squire, 1990).
Both monkey and rat studies of retrograde amnesia have focused on the effects of damage to medial-temporal-lobe structures; nevertheless, their results have been difficult to integrate.

On one hand, monkey experiments have typically assessed the effects of large bilateral medial-temporal-lobe lesions (often involving the hippocampus, amygdala, parahippocampal gyrus, and perirhinal and entorhinal cortices) on the retention of object discriminations (Salmon et al., 1985; Zola-Morgan & Squire, 1990). On the other hand, rat experiments have typically assessed the effects of selective hippocampal or rhinal cortex lesions on a variety of tasks other than object discrimination: conditioned fear (Kim & Fanselow, 1992), trace eyeblink conditioning (Kim, Clark, & Thompson, 1995), socially-transmitted food preferences (Winocur, 1990), and spatial discriminations (Cho et al., 1993; Cho & Kesner, 1996; Cho et al., 1995).

The present experiment compared the retrograde amnesia of rats with bilateral lesions of the rhinal cortex, bilateral lesions of the mediodorsal thalamus, or bilateral lesions of the medial septum and diagonal band. Retrograde amnesia has typically been studied in monkeys by measuring retention for object-discrimination problems learned at various times before surgery; Astur et al. (1994) recently adapted this method to study retrograde memory in rats. Astur et al.'s method was adopted in Experiment 4.

Because of the many connections between the rhinal cortex and the mediodorsal nucleus of the thalamus (Deacon et al., 1983), it is widely believed that they are components of the same memory system. This has led to the expectation that damage to either of these structures would produce comparable memory deficits (see Mumby & Pinel, 1994). The amnesia associated with basal-forebrain damage has also been assumed to result from disruption of information processing within medial-temporal-lobe structures due to the strong anatomical (cholinergic)
connections between these two brain areas (Damasio, Graff-Radford, Eslinger, Damasio, & Kassell, 1985; Squire, 1987); and this assumption has led to the suggestion that destruction of the cholinergic projections from the basal forebrain should produce memory impairments equivalent to those produced by lesions of their target tissue within the medial temporal lobe (Ridley & Baker, 1991). The main purpose of Experiment 4 was to test these hypotheses by comparing the retrograde effects on memory for objects of bilateral lesions to the rhinal cortex, the mediodorsal thalamus, and the medial septum and diagonal band.

METHOD

Subjects

The subjects were 32 experimentally naive male Long-Evans rats.

Apparatus

The apparatus was the same as that used in Experiments 1, 2, and 3; it is described in the General Methods section. The 12 stimulus objects were selected from the set of over 500 test objects that were used in the previous experiments in this thesis. These objects were chosen on the basis of being intuitively highly discriminable from one another. The objects were washed daily in a solution of water and chlorine bleach.

Behavioural Procedure

Presurgery Training: Acquisition of Object Discriminations

Following habituation, the rats were trained on five different two-choice object-discrimination problems. Object-discrimination training was identical to that described in the
General Methods section, except that a slightly more stringent learning criterion of at least 27 correct choices out of 30 was employed. In addition, all the rats received at least three discrimination sessions for each object pair. Training on the first object-discrimination problem was designed so that the third testing session occurred 58 days prior to surgery. Subsequent training on discriminations 2, 3, 4, and 5 was similarly arranged so that the third day of testing fell at periods of 37, 16, 9, and 2 days prior to surgery, respectively.

**Surgery**

At time of surgery, the rats were divided into four groups that received either: bilateral aspiration lesions of the perirhinal and entorhinal cortex (n = 6), bilateral electrolytic lesions of the mediodorsal thalamus (n = 8), bilateral electrolytic lesions of the medial septum and diagonal band (n = 8), or a sham surgical procedure (n = 8). The surgical procedures were identical to those described for lesions to the same areas in Experiments 2 and 3. The postoperative treatment was described in the General Methods.

**Postsurgery testing: Reacquisition of object-discrimination problems**

Following recovery, the rats’ ability to perform the five preoperatively-learned object-discrimination problems was tested concurrently with their ability to learn an unfamiliar object-discrimination problem. Each session consisted of 30 trials; 5 trials for each of the five preoperatively-learned discriminations and 5 trials for the new discrimination problem. Within each session, the order of testing for the discrimination problems occurred in the following pseudorandom pattern: discrimination #1, unfamiliar discrimination, discrimination #5, discrimination #4, discrimination #2, and discrimination #3. Testing continued for all problems
until the rat had learned the unfamiliar object discrimination to a criterion of at least 27 correct responses out of the 30 trials on six consecutive testing sessions.

Statistical Analyses

The percentage of correct responses made on each discrimination pair over the first 10 postoperative trials served the measure of retention. The results of a previous study by Astur et al. (1994) revealed that control rats do not display any evidence of learning during the first 10 trials of a new object-discrimination problem. Thus, potentially confounding effects of anterograde learning can be minimized by restricting the retention measure to these first few trials. The significance of differences in retention scores were assessed with repeated measures ANOVA's using group (lesion type) as a between-subjects factor and the duration of the learning-surgery interval as a within-subjects factor. The significance of differences between the groups in the number of trials required to reach criterion on the unfamiliar postoperative discrimination problem was assessed with a single measure ANOVA using group as the between-subjects factor.

RESULTS

The main finding was that the rats with bilateral lesions of the rhinal cortex or bilateral lesions of medial septum and diagonal band displayed a temporally-graded impairment in the postoperative performance of preoperatively-learned object discriminations, with the greatest deficits in savings at the shortest learning-surgery intervals. In contrast, rats with bilateral lesions of the mediodorsal thalamus displayed normal savings of all discrimination problems.
Histological Results

Figure 29 illustrates the location and extent of the lesions in each of the three experimental groups. Although the rhinal-lesion group initially comprised 9 rats, the scores of 3 of these rats were not included in the statistical analysis: Histological analysis revealed substantial bilateral ventral hippocampal damage in one, substantial bilateral damage to temporal association cortex (areas Te2 and Te3) in another; and one died from surgical complications. Of the remaining 6 rhinal-lesioned rats, each had bilateral damage to both the perirhinal and entorhinal cortices that was roughly symmetrical in the two hemispheres; this damage included the perirhinal cortex both ventral and dorsal to the rhinal fissure, as well as the lateral entorhinal cortex (see Figure 29A). In addition, 1 of the rhinal-lesion rats sustained bilateral damage to the posterior extent of the medial entorhinal cortex (see the largest lesion in Figure 29A); 5 sustained slight-to-moderate amounts of damage to ventro-posterior portions of the temporal association cortex (area Te2); 2 sustained a small degree of damage to area Te3; and 1 sustained slight damage to the ventral portions of the hippocampal CA3 and CA1 fields in one hemisphere. None of the extraneous damage was predictive of greater behavioral deficits.

The thalamic lesions were consistent in all rats. In all 9 rats composing the thalamus-lesion group, there was near complete bilateral destruction of the mediodorsal and intermediodorsal nuclei. As well, there was usually bilateral damage to several thalamic nuclei adjacent to the mediodorsal nuclei: the paraventricular, paracentral, paratenial, central medial, and habenular nuclei. Two of the thalamus-lesioned rats also sustained slight unilateral damage to the anteroventral and anterodorsal thalamic nuclei (see the largest lesion in Figure 29B).
Figure 29. Reconstructions of the largest (striped) and smallest (black) rhinal cortex (RH), mediodorsal thalamus (MD), and basal forebrain (BF) lesions. Planes of section are shown in millimeters, relative to bregma. The drawings are adapted from the atlas of Paxinos and Watson (1986).
In the 9 rats with lesions of the basal forebrain, there was consistent bilateral damage to both the medial septum and the diagonal band (see Figure 29C). In most cases, slight to moderate amounts of damage was also observed in the lateral septal nuclei. Seven of the lesions were similar in size and location to the smaller lesion depicted in Figure 29C, and two were more similar to the larger lesion. In six rats, the lesion extended posteriorly into the strial and medial preoptic areas, and in two of these rats, there was damage to the anterior commissure, however this extraneous damage was unrelated to the severity of the performance deficits.

**Behavioural Results**

*Presurgical acquisition of object-discrimination problems*

All the rats readily learned the discrimination problems. During the last sessions of the object-discrimination problems, the rats averaged between 93.1% to 97.9% correct. Although each rat was given a minimum of 90 preoperative trials with each discrimination pair, the mean number of trials required by all rats to reach the learning criterion on object-discriminations 1 through 5 was 75, 78, 45, 132, and 36, respectively; the trials of the criterion session were excluded from the calculation of these measures. Although statistical analysis revealed a significant difference in the rates at which the five discrimination problems were acquired \([F(4,128) = 38.2, p < 0.01]\), trials-to-criterion over the five discrimination problems was comparable for the rats that subsequently underwent rhinal lesions \((M = 65.0)\), thalamic lesions \((M = 75.2)\), septal lesions \((M = 78.0)\), or sham surgery \((M = 72.1)\) \([F(3, 28) = 0.82, p > 0.1]\).
Postsurgical retention of object-discrimination problems

Figure 30 summarizes the mean postoperative retention scores (percent correct on the first 10 trials) for the rats in each of the four groups as a function of the duration of the learning-surgery interval. It is readily apparent that the main difference among the four groups is the poor retention of object discriminations learned 2 days and 9 days prior to surgery by rats in both the rhinal-lesion and medial-septal-lesion groups. These two groups displayed an improvement in performance when the duration of the learning-surgery interval was more than 9 days, whereas the thalamus-lesion and sham-lesion rats displayed progressively poorer performance as the duration of the learning-surgery interval increased.

Analysis of variance on the postsurgery retention scores confirmed the significance of the differences observed in Figure 30. There was a significant main effect of group \( \left[F(3,28) = 6.51, p < 0.005\right] \), a significant effect of interval \( \left[F(4,112) = 6.61, p < 0.001\right] \), and a significant group \( \times \) interval interaction \( \left[F(12,112) = 1.80, p = 0.05\right] \). Tukey’s post hoc tests revealed that both the rhinal-lesion and medial-septal-lesion groups displayed significantly poorer retention relative to the sham-lesion group on the discriminations learned 2 days [rhinal vs. sham, \( p < 0.005\); medial-septal vs. sham, \( p < 0.05\)] and 9 days [rhinal vs. sham, \( p < 0.001\); medial-septal vs. sham, \( p < 0.005\)] prior to surgery. The rhinal-lesioned rats were also impaired with respect to the thalamic-lesioned rats at these first two learning-surgery intervals (both \( p \)'s < 0.05). None of the differences among the four groups for discriminations learned 16, 37 or 58 days before surgery was statistically significant. The retention scores of rhinal group increased significantly as the duration between learning and surgery increased \( \left[F(1,25) = 5.70, p < 0.05\right] \). This pattern was opposite to the normal forgetting curve displayed by the sham-surgery rats whose retention
Figure 30. Postoperative retention scores (measured as mean percent correct over the first 10 postoperative trials) for the object-discrimination problems as a function of learning-surgery interval. Error bars represent SEMs. CON, control group; RH, rhinal-cortex group; MD, mediodorsal-thalamus group; BF, basal-forebrain group.
scores dropped significantly as the learning-surgery interval became longer \([F(1,35) = 7.17, p < 0.05]\).

To test whether the control rats expressed significant learning during the first 10 postoperative trials of the novel object-discrimination problem, a one-sample t-test was performed. The control rats, as expected, did not perform significantly above chance values over this period \((M = 52.5\% ; t = 0.68, p = 0.52)\).

In addition to measuring retention of the preoperatively-learned discrimination problems over the first 10 postoperative trials, rats were also assessed for their ability to reacquire these discriminations to criterion and to acquire an unfamiliar object discrimination. On average, rhinal-lesion rats required 32.3 trials to relearn each of the five preoperative discriminations, whereas the averages for thalamus-lesion, medial-septal-lesion, and sham-lesion rats were 10.6, 10.8, and 9.3 trials, respectively. An ANOVA revealed that this group effect was significant \([F(3,28) = 11.5, p < 0.001]\), and post hoc comparisons revealed the rhinal-lesion group to be significantly impaired with respect to all three other groups at relearning each of the two discriminations acquired closest to the time of surgery (all \(p\)'s < 0.05). None of the other pairwise comparisons among the four groups for any of the five preoperatively-learned discriminations was significant.

Rats in the rhinal-lesion group required more trials \((M = 55.0)\) than rats in the thalamus-lesion \((M = 30.6)\), medial-septal-lesion \((M = 15.6)\), and sham-lesion \((M = 38.6)\) groups to reach criterion on the unfamiliar discrimination; an ANOVA revealed a significant group effect \([F(2,24) = 4.91, p < 0.01]\), and post hoc comparisons of this effect revealed that rhinal-lesioned
rats required significantly more trials to learn the new discrimination than did the medial-septal-lesioned rats, but not the thalamic-lesioned or sham-lesioned rats.

DISCUSSION OF EXPERIMENT 4

The main finding of Experiment 4 was that rats with bilateral lesions of either the rhinal cortex or medial septum and diagonal band displayed significantly fewer savings than did control rats for object-discrimination problems learned 2 or 9 days before surgery, but not 16 or more days before surgery. In contrast, rats with bilateral electrolytic lesions of the mediodorsal thalamus displayed no significant impairment in performance at any of the learning-surgery intervals.

The impairment in retrograde memory displayed by the rats with rhinal cortex lesions in the present experiment is consistent with previous reports of retrograde amnesia for objects in monkeys (Gaffan, 1983; Salmon et al., 1985; Zola-Morgan & Squire, 1990) and humans (Barr, Goldberg, Wassertein, & Novelty, 1990; Cermak & O’Connor, 1983; Scoville & Milner, 1957) following bilateral medial-temporal-lobe damage. Most studies of the effects of medial-temporal-lobe damage on retrograde object memory in humans and monkeys have involved damage to both the hippocampus and adjacent cortical tissue; nevertheless, it has usually been concluded that hippocampal damage is the critical cause of the retrograde amnesia. However, the observation of retrograde amnesia for objects in rats with lesions restricted to perirhinal and entorhinal cortex clearly shows that medial-temporal-lobe lesions do not have to impinge on the hippocampus to produce retrograde amnesia. A similar conclusion was reached by Wiig, Bear, and Cooper (1996).
The temporally-graded nature of the retrograde impairment displayed by the rats with rhinal cortex lesions suggests that approximately 2 weeks (i.e., 16 days) is required before memory for a two-choice object-discrimination problem no longer depends on the integrity of the rhinal cortex. This result is comparable to those of Wiig et al. (1996) and Zola-Morgan and Squire (1990): Both found significant retrograde memory impairments covering the 4 weeks prior to surgery—Wiig et al., following perirhinal cortex lesions in rats, and Zola-Morgan and Squire, following combined entorhinal, parahippocampal, and hippocampal lesions in monkeys. Accordingly, the present results offer further evidence in support of the proposal that medial-temporal-lobe structures serve as a temporary repository of memories while they are being consolidated (e.g., Alvarez & Squire, 1994; Squire, Cohen & Nadel, 1984; however, for an alternative view see Nadel & Moscovitch, 1997).

The present observation of retrograde object-discriminations deficits following bilateral lesions of the medial septum and diagonal band is the first to demonstrate that basal-forebrain damage in laboratory animals can produce a significant period of retrograde amnesia. In the only other study to investigate the effect of basal-forebrain damage on retrograde amnesia in laboratory animals, Ridley et al. (1988) failed to demonstrate retrograde memory loss for preoperatively-learned object discriminations in marmosets following lesions of the diagonal band. However, in Ridley et al.'s study, even though no significant differences were found between lesioned animals and controls in the number of trials they required to relearn each of two preoperatively-acquired object discriminations to criterion, the animals with basal-forebrain damage required on average more than twice the number of trials than did the controls.
The pattern of retention deficits observed in rats with lesions of the medial septum and diagonal band was identical to that seen in rats with lesions of the rhinal cortex: Both groups were impaired on the postsurgical performance of object discriminations learned just prior to surgery, but not on those learned more remotely, and there were no significant differences between the two groups at any of the learning-surgery intervals. This result is suggestive of the fact that the effects of lesions to either the basal forebrain or rhinal cortex on the consolidation of object memories may be linked, perhaps by virtue of the cholinergic innervation of medial-temporal-lobe structures by the medial septum and diagonal band. Some support for this hypothesis comes from the recent finding that the formation of new stimulus memories in monkeys during visual recognition can be disrupted by cholinergic blockade directly in the perirhinal cortex (Tang, Mishkin, & Aigner, 1997).

Rats in all four groups required significantly more trials to learn discrimination pair 4 than any of the other discrimination pairs. It is unlikely that this difference influenced the observed gradient of retrograde effects because neither rhinal-lesioned nor septal-lesioned rats displayed deficits in relearning this particularly difficult task.

In contrast to the temporally-graded deficits of rats with lesions of the rhinal cortex or basal forebrain, rats with lesions of the mediodorsal thalamus displayed no significant retrograde deficits. This result is somewhat surprising given that severe retrograde amnesia is frequently observed in patients with medial-diencephalic damage (see Parkin, 1984 for a review). However, the present finding is consistent with previous studies of medial-diencephalic retrograde amnesia in laboratory animals. Mumby, Cameli, and Glenn (1997) found that medial-thalamic damage produced by pyrithiamine-induced thiamine deficiency in rats failed to result in any retrograde
memory loss for preoperatively-learned object-discrimination problems; Langlais, Mandel, and Mair (1992) found no evidence of retrograde amnesia for a Morris water maze task learned prior to pyrithiamine treatment in rats; and Winocur (1990) found that lesions of the hippocampus, but not lesions of the mediodorsal thalamus, in rats produced temporally-graded retrograde amnesia for a socially-transmitted food preference.

When a lesion fails to produce an effect—in this case, the mediodorsal-thalamus lesion failed to produce retrograde object-recognition deficits—it is important to consider the adequacy of the lesions. Perhaps the thalamic lesions were too small to have significant behavioural effects. Two lines of evidence suggest otherwise. First, the histological analysis indicated that in all thalamus-lesion rats there was near complete bilateral destruction of the mediodorsal nucleus, as well as moderate amounts of bilateral damage to several adjacent thalamic nuclei. Second, comparable lesions in Experiment 3 were found to impair delayed nonmatching-to-sample (DNMS) performance.

Together with the results of past studies, the current finding that damage to the rhinal cortex, but not the mediodorsal thalamus, produces retrograde amnesia for preoperatively-learned object discriminations suggests that these two brain regions make different contributions to the mnemonic processing of new information. Although both the rhinal cortex and mediodorsal thalamus seem to be involved in recognition memory for objects—as suggested by the anterograde impairments in DNMS that result from lesions of either structure (e.g., Meunier et al., 1993; Mumby & Pinel, 1994; Mumby et al., 1993; Zola-Morgan & Squire, 1985; Zola-Morgan et al., 1989) (also see Experiments 2 and 3)—the current results indicate that they are not equally involved in the consolidation of long-term object memories.
GENERAL DISCUSSION

The primary purpose of the present research was to clarify a fundamental aspect of brain-damage-produced amnesia: Are the amnesic syndromes associated with damage to different brain areas similar or are they qualitatively distinct? More specifically, the present research was intended to compare the effects of selective damage to the medial temporal lobe, medial diencephalon, or basal forebrain on the ability of rats to acquire, retain, or express information about objects. Accordingly, the nature and extent of the anterograde and retrograde object-memory deficits produced by separate lesions of these three brain areas was assessed in rats. The General Discussion begins with a brief summary of findings—see Table 1. Then, the implications of the results are discussed in the following five sections: (1) a comparison of the profiles of object-memory deficits in rats and monkeys with similar brain damage, (2) differences in the object-memory profiles associated with damage to the medial temporal lobe, medial diencephalon, and basal forebrain in rats, (3) theories regarding the contribution of individual brain structures to memory function, (4) relevance of the results to current theories of memory consolidation, and finally (5) a summary of the major conclusions and future directions of this work.

SUMMARY OF FINDINGS

This thesis comprises four experiments. The major findings of each of these experiments are summarized in the following section.
Table 1. Profiles of anterograde and retrograde object-memory deficits in rats with lesions to the hippocampus (HPC), amygdala (AM), rhinal cortex (RH), basal forebrain (BF), or mediodorsal thalamus (MD).
<table>
<thead>
<tr>
<th>Lesion Site</th>
<th>Anterograde Memory</th>
<th>Retrograde Memory</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HPC</strong></td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td><strong>AM</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>RH</strong></td>
<td>+</td>
<td>+†</td>
</tr>
<tr>
<td><strong>BF</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>MD</strong></td>
<td>+</td>
<td>+†</td>
</tr>
</tbody>
</table>

*HPC*, Hippocampus-lesion group; *AM*, Amygdala-lesion group; *RH*, Rhinal-cortex-lesion group; *BF*, Basal-forebrain-lesion group; *MD*, Mediodorsal-thalamus-lesion group; +, significant lesion-induced impairment with respect to sham-surgery controls; 0, nonsignificant effect; ND, no data; † Although the hippocampus-lesion group was not significantly impaired with respect to the parietal-cortex control group at the 120-s delay, they were impaired with respect to the sham-surgery control group; * Result from Mumby et al. (1994); ‡ Impairment in Stage II of reversal learning; § All but one rat in the basal-forebrain group failed to reach criterion on DNMS at a 4-s delay (performance after the maximum number of trials averaged 70.5%); † Impairment in Stage I of reversal learning.
Experiment 1

Experiment 1 demonstrated, for the first time, that the mnemonic effects of damage to the hippocampus and amygdala can be dissociated in rats with a battery of anterograde object-memory tasks that resemble the tasks that have been used to test memory for objects in human and nonhuman primates: Rats with damage to the hippocampus required significantly more trials than controls to learn the simple object-discrimination task, whereas rats with damage to the amygdala did not; in contrast, amygdalar damage, but not hippocampal damage, retarded the acquisition of the DNMS task at a 4-s delay. Both lesions produced an impairment in the rate at which rats were able to acquire an eight-pair concurrent-object-discrimination task, but rats with hippocampal damage were more severely impaired than rats with amygdalar damage. In contrast, neither lesion disrupted discrimination reversal, order discrimination, or DNMS performance at retention delays of 15, 30, 60, and 120 s or with lists of three, five, and seven sample objects.

In agreement with the results of similar experiments on monkeys (Alvarez et al., 1995; Mahut, 1971; Zola-Morgan et al., 1989) the results of Experiment 1 indicated that neither the hippocampus nor the amygdala is essential for the normal anterograde performance of object-memory tasks. Although rats with lesions of the hippocampus or amygdala were impaired in the rate at which some of these tasks were acquired, they were able to learn all tasks to the same level as controls, and once the tasks were learned, they did not display any impairments if the mnemonic demands of the task were increased.

Several of the findings of Experiment 1 were original contributions with respect to the effects of hippocampal or amygdalar damage in rats on particular measures of anterograde memory: for example, the lack of a significant impairment of object-discrimination-reversal and
order-discrimination tasks, and of DNMS with lists. In addition, Experiment 1 demonstrated, for the first time, that extensive pretraining was not responsible for the mild DNMS deficits that were previously observed in rats with hippocampal or amygdalar lesions tested on a similar DNMS task (Mumby et al., 1992).

Experiment 2

Experiment 2 confirmed a critical role for the rhinal cortex in DNMS: Although unretrained rats with bilateral rhinal-cortex ablation were unimpaired in the acquisition of the DNMS rule at a brief delay, DNMS performance was disrupted in a delay-dependent manner when the retention interval was subsequently increased. A similar pattern of results has previously been reported in rhinal-lesioned rats that had received extensive presurgical DNMS training (Mumby & Pinel, 1994). In addition, Experiment 2 provided new findings indicating that the mnemonic impairment produced by lesions of the rhinal cortex in rats extends beyond a deficit in DNMS: Rhinal-lesioned rats were also impaired on object discrimination, discrimination reversal, concurrent object discrimination, order discrimination, and DNMS performance when lists of three or more sample objects had to be remembered concurrently. In effect, Experiment 2 illustrated that rhinal cortex damage in unretrained rats produces deficits on many of the same tasks that have been shown to be sensitive both to human amnesia and to the amnesia produced by large medial-temporal-lobe lesions in nonhuman primates.

Experiment 2 assessed, for the first time, the effects of basal forebrain lesions in rats on the acquisition and performance of a battery of anterograde object-memory tasks. The results indicated that the deficits produced by basal-forebrain damage were different than those
produced by rhinal-cortex damage (see Table 1): Rats with lesions of the medial septum and diagonal band were unimpaired in the rates at which they learned a simple object discrimination, the reversal of that discrimination, or a concurrent object discrimination; but they were unable to learn the DNMS rule to criterion at a 4-s delay—a pattern of deficits directly opposite to that observed following lesions of the rhinal cortex.

Given that basal forebrain lesions prevented normal acquisition of the DNMS rule in Experiment 2, the subsequent DNMS performance of the basal-forebrain-lesioned rats was understandably impaired. However, by exposing rats to extensive presurgery DNMS training in Experiment 2A, it was demonstrated that damage to the medial septum and diagonal band disrupts DNMS even in lesioned rats that are eventually able to reacquire the nonmatching-rule to a stringent criterion at a 4-s delay. Nevertheless, rats with basal-forebrain damage in Experiment 2A took considerably longer than control rats to reacquire the DNMS rule following surgery, and their impairment in choice accuracy during mixed-delay testing was delay-independent, occurring equivalently at all delays, including the shortest (i.e., 4-s) one.

**Experiment 3**

The results of Experiment 3 confirmed that bilateral lesions of the mediodorsal thalamus produce DNMS deficits in rats. Experiment 3 also provided new findings illustrating that the profile of deficits displayed by rats with lesions of the mediodorsal thalamus on a battery of anterograde object-memory tasks is similar to that displayed by rats with lesions of the rhinal cortex (see Experiment 2; Table 1): Thalamic-lesioned rats were impaired in the rate at which they learned the object-discrimination, discrimination-reversal, and concurrent-object-
discrimination tasks to criterion; they displayed a mild, but statistically significant, deficit on the order-discrimination task; and despite a lack of impairment in initial acquisition of the DNMS rule, they performed significantly worse than controls on DNMS testing with lists of three or more sample objects or with delays of 15 s or greater. However, in contrast to the DNMS deficit observed following lesions of the rhinal cortex, the deficit produced by lesions of the mediodorsal thalamus was delay-independent (i.e., the impairment did not become progressively greater with increasing retention intervals). In addition, Experiment 3 demonstrated a perseverative tendency in the thalamic-lesioned rats on the discrimination-reversal task, an effect that was not observed following damage to either the medial temporal lobe structures or the basal forebrain.

Experiment 4

In contrast to the first three experiments, Experiment 4 focused on retrograde, rather than anterograde, object-memory in rats. Experiment 4 was the first to systematically compare the retrograde effects on memory for objects of damage to the medial temporal lobe, medial diencephalon, and basal forebrain.

Retrograde memory for objects was impaired following lesions of the rhinal cortex or the basal forebrain (i.e., the medial septum and diagonal band), but not the mediodorsal thalamus. The retrograde impairment was temporally-graded in both the rhinal and basal-forebrain-lesion groups--relative to controls, they displayed reduced savings for object-discrimination problems learned 2 or 9 days prior to surgery but not for problems learned 16, 37, or 58 days prior to surgery. In effect, the deficits in retrograde memory for object-discrimination
problems was similar to those seen in monkeys following large medial-temporal-lobe lesions (Zola-Morgan & Squire, 1990).

Considering the similarities between the anterograde object-memory deficits that were observed in rhinal-lesioned and thalamic-lesioned rats (see Table 1), it is remarkable that these two lesions had such different effects on retrograde object memory. Whereas mediadorsal-thalamic damage did not affect the normal retention of preoperatively-learned discrimination problems, rhinal-cortex damage produced a pronounced period of retrograde amnesia.

A COMPARISON OF THE PROFILES OF OBJECT-MEMORY DEFICITS IN RATS AND MONKEYS WITH SIMILAR BRAIN DAMAGE

In evaluating the effects of any instance of brain damage, it is essential to consider the profile of performance on a number of tests: Any individual test can be failed for a variety of reasons. This principle has important implications for the comparative study of brain-damage-produced amnesia. Many rat and monkey studies of brain-damage-produced amnesia have focused on DNMS—indeed, Aggleton and Shaw (1996) have recently described the DNMS task as the “behavioural linchpin” of animal models of anterograde amnesia. Rats, monkeys, and humans with damage to the medial temporal lobe or medial diencephalon all display DNMS deficits, and it is often assumed that they have the same cognitive impairment; however, it is only when the same profile of deficits is observed across several tasks that it is reasonable to assume that memory is affected in the same way in different species (Ridley & Baker, 1991).

In the present experiments, rats with selective brain lesions were tested on a battery of object-memory tasks similar to those that have been used in many monkey studies, thus it has
become possible to compare the nature of the performance deficits produced by damage to similar brain areas in these two species. The similarity in the object-memory profiles in rats and monkeys with damage to the medial temporal lobes, medial diencephalon, or basal forebrain is discussed in this section.

**Hippocampus or Amygdala**

The present results indicated that the functions of the hippocampus or amygdala in rats are not necessary for normal performance of any of the current anterograde object-memory tasks. Although deficits were observed in the rate at which rats with damage to the hippocampus or amygdala mastered certain tasks, their ability to perform the tasks once acquired was little affected by the lesions. This finding is consistent with recent studies of hippocampal or amygdalar lesions in monkeys in which the cortical tissue adjacent to these structures has largely been spared (Alvarez et al., 1995; Murray & Mishkin, 1996; O’Boyle et al., 1993; Zola-Morgan et al., 1989a). These studies have shown that performance on simple and concurrent object-discrimination tasks, as well as on the DNMS task at various retention delays or with lists of sample objects, is largely spared following selective lesions of the hippocampus or amygdala in monkeys. However, future monkey studies are required to determine whether circumscribed hippocampal or amygdalar damage spares object-reversal learning and order-discrimination performance in much the same way that it does in rats. In addition, whereas Mumby and colleagues (Astur, Mumby, & Sutherland, 1994; Mumby et al., 1994; Francis, Glenn, & Mumby, 1996) have repeatedly shown that damage limited to the hippocampus fails to disrupt retrograde memory for object-discrimination problems in rats, it is not yet known if such a selective lesion
in monkeys would spare the retrograde object-memories that have been shown to be disrupted following extensive medial-temporal-lobe damage in that species (Salmon et al., 1987; Zola-Morgan & Squire, 1990).

**Rhinal Cortex**

In the present experiments, lesions of the rhinal cortex produced in the rats a significant impairment in the performance of each of the anterograde object-memory tasks. In addition, they produced a time-dependent impairment in retrograde memory for objects. These findings are similar to those widely reported in monkeys (Buckley & Gaffan, 1997; 1998; Eacott et al., 1994; Meunier et al., 1993; Thornton et al., 1997; Zola-Morgan et al., 1989c). Consequently, the suggestion that the rhinal cortex is a critical component of a system for storing knowledge about objects in monkeys (Eacott et al., 1994; Murray, 1996) seems to apply equally to rats. However, despite the fact that the separate contributions of the entorhinal and perirhinal cortices to object-recognition memory have begun to be elucidated in the monkey (Meunier et al., 1993), the relative importance of each of these subcomponents of the rhinal cortex to similar mnemonic processes in the rat remains uncertain.

**Thalamus**

In the present experiments, many of the anterograde deficits observed in rats with lesions of the mediodorsal thalamus have been reported following similar damage in monkeys. For example, monkeys with medial thalamic lesions are impaired in visual-discrimination learning (Aggleton & Mishkin, 1983b; Gaffan & Murray, 1990), temporal-order discrimination (Gower,
1992), and DNMS performance across various retention delays and with different sample list lengths (Aggleton & Mishkin, 1983a; 1983b; Parker et al., 1997; Zola-Morgan & Squire, 1985). Unfortunately, the retrograde effects of mediodorsal thalamic damage have yet to be assessed in monkeys; thus, whether medial-thalamic damage in monkeys spares retrograde object memories in much the same way that it does in rats remains to be seen.

**Basal Forebrain**

The profile of object-memory deficits in rats with damage to the basal forebrain is difficult to compare to that in monkeys with similar damage because of the inconsistencies in the monkey literature. For example, although the DNMS deficits observed in basal-forebrain-lesioned rats in Experiments 2 and 2A are consistent with some reports of normal DNMS performance in monkeys with basal-forebrain damage (e.g., Aigner et al., 1991; Irle & Markowitsch, 1987), they are inconsistent with others (e.g., Aigner et al., 1987; Voytko et al., 1994). One of the problems in comparing the results of different basal-forebrain-lesion studies, both between and within species, is that there is substantial variability in the extent and location of the forebrain lesions produced in various studies and different basal-forebrain structures seem to serve different functions (Everitt & Robbins, 1997; Olton et al., 1988). Furthermore, differences also exist in the lesioning method; whereas in some studies the basal forebrain has been lesioned electrolytically (e.g., Hepler et al., 1985; Kelsey & Vargas, 1993; Numan, 1991), in others it has been lesioned with neurotoxins relatively selective for cholinergic cells (e.g., Baxter et al., 1995; McAlonan et al., 1995; Walsh et al., 1996).
Despite certain differences in the nature of basal-forebrain damage, and inconsistencies in the monkey literature, the present results and those of past studies in monkeys with lesions of the basal forebrain converge in important ways. For example, the fact that rats with lesions of the medial septum and diagonal band were unimpaired in the acquisition of several object-reward-association tasks (i.e., object discrimination, discrimination reversal, and concurrent object discrimination) is comparable to the lack of effect reported on similar tasks in monkeys following combined damage to the medial septum, diagonal band, and nucleus basalis (Voytko et al., 1994). Furthermore, when a DNMS impairment has been reported in monkeys following damage to the medial septum and diagonal band, this impairment, like that in rats, has been delay-independent and has also involved a severe deficit in task acquisition, suggesting that the impairment is not totally mnemonic (Aigner et al., 1991). Given some of these similarities between rat and monkey studies of basal-forebrain damage, it will be interesting to see if lesions to this brain region in monkeys cause a significant loss of retrograde memory for objects, as they do in rats.

Conclusion: Rat and Monkey Object-Memory Profiles

Overall, the concordance between the object-memory profiles of rats and monkeys with damage to the classic memory areas of the brain is impressive. This concordance illustrates the potential of the comparative approach to the study of the neuroanatomy of brain-damage-produced amnesia.

The concordance between the object-memory profiles of monkeys and rats with brain lesions is all the more remarkable considering that differences in the size and configuration of rat
and monkey brains makes it virtually impossible to make identical brain lesions in the two “species.” For example, in monkeys, the hippocampus has, until recently, usually been removed by aspiration via the inferior surface of the brain, thus destroying substantial amounts of medial temporal cortex; in contrast, in rats, the hippocampus is usually removed by aspiration from the superior surface of the brain, thus destroying small amounts of parietal cortex. Similarly, it is virtually impossible to create identical tests for the two species because of their major differences in body types. For example, although the rat and monkey object DNMS tasks are comparable in major respects, there are obvious differences in both the nature of the testing apparatuses and in the motor responses involved in normal task performance.

DIFFERENCES IN OBJECT-MEMORY PROFILES ASSOCIATED WITH DAMAGE TO THE MEDIAL TEMPORAL LOBES, MEDIAL DIENCEPHALON, AND BASAL FOREBRAIN IN RATS

The importance of using multiple behavioural tests to evaluate the effects of any instance of brain damage is underscored by the fact that, within the same species, animals with different lesions may be impaired on the same task for different reasons. For example, lesions to the three brain areas most commonly implicated in cases of human memory loss—the medial temporal lobe, medial diencephalon, and basal forebrain—have all been shown to produce DNMS deficits in laboratory animals, and the impairments produced by damage to these respective brain regions have often been assumed to reflect a common underlying functional deficit (see Mumby & Pinel, 1994; Zola-Morgan & Squire, 1993). However, it is only by considering the performance on a
number of different tasks that a reasonable assessment of the contribution of that brain area to memory function can be made.

It is evident from Table 1 that the profiles of object-memory deficits produced by damage to selective medial-temporal-lobe, medial-diencephalic, or basal-forebrain structures differ in several respects. The following are three of these differences that provide particularly important insights into the nature of brain-damage-produced amnesia. The differences are discussed with respect to relevant observations in amnesic patients.

**Different Effects of Rhinal and Thalamic Lesions on Retrograde Memory**

Despite similarities between the effects of rhinal cortex and mediodorsal thalamus lesions on tests of anterograde memory in Experiments 2 and 3, a clear dissociation between these two groups emerged when retrograde memory was assessed in Experiment 4: Rats with rhinal cortex damage were severely impaired in their retention of object-discrimination pairs learned up to 9 days before surgery but not thereafter, whereas rats with mediodorsal thalamic damage were unimpaired at any of the learning-surgery intervals. These results suggest that selective damage to the same medial-temporal-lobe structure can cause both anterograde and retrograde amnesia for objects, but that damage to the region of the medial diencephalon that produces deficits in anterograde object-memory does not cause a significant loss of similar retrograde memories. Intact retrograde memory following diencephalic lesions, in the presence of an anterograde deficit, has previously been reported in rats tested on a spatial learning task (Langlais et al., 1992).
The finding that rats with lesions of the mediodorsal thalamus are impaired on several measures of anterograde object memory, but show normal retrograde memory for objects, confirms the findings of several recent human studies that have found a similar dissociation in patients with focal diencephalic pathology (e.g., Dusoir et al., 1990; Kapur, Thompson, Cook, Lang, & Brice, 1996; Parkin et al., 1994; Winocur et al., 1984). In doing so, they add to the weight of evidence that anterograde and retrograde amnesia are dissociable (Kapur, Millar, Abbott, & Carter, 1998).

Kopelman (1997) recently compared the memory abilities of amnesic patients with various kinds of pathology. He found that although Korsakoff patients and patients with temporal-lobe pathology had a severe and extensive retrograde amnesia, two patients who had focal lesions to their diencephalon following irradiation for pituitary tumours had normal retrograde memory. This finding suggests that the retrograde amnesia associated with Korsakoff's disease might be caused by damage to structures outside the medial diencephalon, perhaps in the temporal lobe or frontal cortex (Kopelman, 1995; Langlais, 1992), and the present finding that rats with mediodorsal-thalamic lesions have no retrograde deficits in object recognition confirms this view.

Differential Effects of Lesions on DNMS Tasks: Lack of a Hippocampal Effect

Another key difference among the object-memory profiles illustrated in Table 1 is that lesions to the various structures implicated in human brain-damage-produced amnesia did not all cause a significant impairment in DNMS: Whereas bilateral damage to the rhinal cortex, mediodorsal thalamus, or basal forebrain resulted in DNMS deficits across several different
retention delays and sample list lengths, bilateral lesions of the hippocampus had little effect on
DNMS performance. This lack of impairment following selective hippocampal damage is
consistent with recent monkey DNMS studies (e.g., Murray & Mishkin, 1996; O’Boyle et al.,
1993).

Although the DNMS task has been the favoured method of studying episodic (or
declarative) memory in experimental animals, the present failure to observe deficits in this task
does not exclude the possibility that hippocampal damage makes an important contribution to the
memory deficits observed in human amnesics with widespread medial-temporal-lobe pathology.
Indeed, damage to the hippocampal formation is likely to play a key role in some of the
mnemonic impairments experienced by these patients, and this suggestion is supported by
evidence from monkey and rat studies in which hippocampal lesions have been shown to disrupt
the performance of other types of episodic memory tasks, such as delayed nonmatching-to-
position (e.g., Aggleton et al., 1992; Kesner et al., 1993) or scene-specific memory (e.g., Gaffan,

A parallel can be drawn between the DNMS results of the current experiments and
findings from the human amnesia literature that relate to recognition memory. Aggleton and
Shaw (1996) recently performed a meta-analysis on 33 neuropsychological studies reporting the
performance of amnesic subjects on the Recognition Memory Test—the Recognition Memory
Test is a test of delayed matching-to-sample with words or unfamiliar faces as stimuli. They
found that human amnesics with damage limited to the hippocampus, fornix, or mammillary
bodies performed normally on this test, despite being severely impaired on measures of delayed
recall, whereas all other amnesics (e.g., Korsakoff amnesics, thalamic infarct amnesics,
postencephalitics, anterior communicating artery aneurysm amnesics) were severely impaired on the Recognition Memory Test and the recall test. Aggleton and Shaw concluded that damage to the hippocampus (or its main diencephalic projection site) is sufficient to induce a severe recall deficit in amnesia, but that a deficit in recognition must arise from pathology in other regions. Their conclusion that hippocampal damage produces recall deficits has been questioned on the grounds that the patients with hippocampal damage may have had extrahippocampal pathology that could have produced the recall deficits (see Gaffan, 1997). In any case, Aggleton and Shaw's findings are consistent with the present set of results that damage to the rhinal cortex, medial thalamus, or basal forebrain, but not the hippocampus, produces significant impairments in DNMS.

**Different Profiles of DNMS Deficits**

Another meaningful difference in the object-memory profiles of rats with lesions to the medial temporal lobe, medial diencephalon, or basal forebrain relates to the nature of the DNMS impairment produced by damage to these three brain areas: Whereas lesions of the rhinal cortex, mediodorsal thalamus, or basal forebrain all caused deficits in DNMS performance at different retention delays and with different sample list lengths, only basal-forebrain damage impaired the initial acquisition of the DNMS rule at a 4-s delay. In fact, all but one of the basal-forebrain-lesioned rats was unable to reach criterion on this task; this occurred despite their normal rate of acquisition on the object-discrimination, discrimination-reversal, and concurrent-discrimination tasks. In addition, basal forebrain lesions in Experiment 2A were found to impair DNMS
reacquisition in rats that ad received extensive presurgery training on this task; and following reacquisition, DNMS performance was disrupted even at the shortest (i.e., 4-s) delay.

Together, the results of Experiments 2 and 2A suggest that the effects of basal-forebrain damage on DNMS are likely to at least partially reflect dysfunction in some nonmnemonic process. For example the severe deficit in task acquisition together with the delay-independent deficit in DNMS performance suggest that rats with basal-forebrain lesions have difficulty in acquiring specific nonmnemonic skills that are necessary to reliably perform the task. There is recent support for the notion that this nonmnemonic skill may be related to attention (see Baxter et al., 1997; Voytko, 1996). In this respect, it is worth noting that some human patients with damage to the basal forebrain experience attentional deficits (Irle, Wowra, Kunert, & Kunze, 1992; Laiacona et al., 1989; Teissier du Cros & Lhermitte, 1984); however, that these attentional deficits disrupt performance on tests of memory has yet to be proven.

In contrast to the deficit displayed by rats with basal-forebrain damage, rats with lesions of the rhinal cortex or mediiodorsal thalamus were not impaired in DNMS acquisition at the 4-s delay, and this suggested that the subsequent performance deficits in both of these groups were likely due to a mnemonic dysfunction. However, differences were observed in the nature of the DNMS impairment in rhinal-lesioned and thalamic-lesioned rats when tested at the longer retention intervals: Rats with damage to the rhinal cortex showed evidence of an accelerated loss of recognition memory (i.e., their DNMS impairment was delay-dependent), but rats with damage to the mediiodorsal thalamus did not. This difference raises the possibility that the DNMS deficits in these two groups reflect the disruption of different aspects of mnemonic processing. Whereas an accelerated rate of forgetting may be indicative of a deficit in the ability
to retain information over time, a fixed rate of memory loss suggests that the effects of the lesion are generally on encoding or retrieval (Ringo, 1991).

Although the literature on the rate of forgetting in human brain-damage-produced amnesia is controversial (see Kopelman, 1997; Mayes, 1988), there have been numerous suggestions that the encoding operation in memory may take place in a different brain location from storage (Mayes & Downes, 1997; Metcalfe, 1997; Squire, 1981). The present results indirectly support the notion that medial-thalamic damage may affect recognition memory performance by disrupting the initial encoding of stimulus information (Winocur et al., 1984; Winocur, 1985), whereas rhinal-cortex damage may affect recognition memory by disrupting the storage or consolidation of new information (Eichenbaum et al., 1994; Squire & Zola, 1997).

Conclusion: Differences in Object-Memory Profiles

Taken together, the results of this thesis suggest that despite the extensive anatomical interconnections among the medial temporal lobe, medial diencephalon, and basal forebrain, selective damage to these respective brain regions in rats results in distinct profiles of performance deficits across a variety of object-memory tasks. They also illustrate that even within a particular region such as the medial temporal lobe there is considerable functional heterogeneity; that is, the individual structures in a region make qualitatively different contributions to memory function.
CONTRIBUTION OF MEDIAL-TEMPORAL-LOBE, MEDIAL-DIENCEPHALIC, AND BASAL-FOREBRAIN STRUCTURES TO MNEMONIC PROCESSING: FUNCTIONAL THEORIES

Existing theories regarding the nature of the contributions that the hippocampus, amygdala, rhinal cortex, medial septum and diagonal band, and mediodorsal thalamus make to mnemonic processing are described in this section. The relevance of these theories to the present data is discussed.

Hippocampus

The results of the present experiments are consistent with the hypothesis that the hippocampus does not play a critical role in object-recognition memory (see Duva et al., 1998): hippocampal-lesioned rats acquired the DNMS rule at a normal rate and were unimpaired on DNMS testing with retention delays of up to 120 s and with lists of three or more sample objects. In addition, hippocampal damage failed to produce a significant impairment in the ability of rats to judge the relative recency with which two objects had been presented. These findings are in accordance with the most recent evidence from lesion studies in monkeys (Aggleton et al. 1986; Gaffan et al., 1984; Murray & Mishkin, 1996; O'Boyle et al., 1993). Moreover, the failure of electrophysiological studies to find hippocampal neurons that respond differently to novel and familiar objects suggests that representation of individual items are not directly maintained in the hippocampus (Riches et al., 1991; Zhu, McCabe, Aggleton, & Brown, 1997).

There are numerous theories of the specific mnemonic functions of the hippocampus (e.g., Eichenbaum et al., 1994; Hirsh, 1974; Jarrard, 1993; Olton et al., 1979; Rawlins, 1985;
Sutherland & Rudy, 1989); the broader question of whether the hippocampus is a general memory structure or one with a more limited function will be addressed here. One theory (Cohen & Squire, 1980; Squire, 1992) posits that the hippocampus is critically involved in mediating “declarative memory.” This general category of memory refers to the capacity for conscious recollections about facts and events, and it is typically assessed by tests of recall, recognition, or cued recall (Squire & Zola, 1997). Object-recognition memory tasks in laboratory animals are believed to tap into mnemonic processes analogous to human declarative memory. This idea is supported by the fact that human amnesics perform poorly on DNMS (Aggleton et al., 1988; Squire et al., 1988). However, in light of the growing evidence from both rat and monkey studies that the hippocampus is not critically involved in object-recognition, its consideration as a general “declarative memory structure” must be reappraised.

Recent evidence is consistent with a more specialized role for the hippocampus in memory. For example, there is considerable support for the suggestion that the hippocampus is critically involved in spatial memory. It has long been known that hippocampal damage in rats produces severe impairments on a variety of spatial memory tasks (e.g., Aggleton et al., 1986; Jarrard, 1993; O'Keefe & Nadel, 1978), and similar results have also been obtained in monkeys (Gaffan & Harrison, 1989; Murray, Davidson, Gaffan, Olton, & Suomi, 1989; Parkinson, Murray, & Mishkin, 1988). Accordingly, Nadel (1991; 1992) has argued that the hippocampus may act as a “spatial module” in terms of memory processing. Support for the hippocampus’ involvement in spatial memory processes also comes from the study of non-mammallian species. For example, Sherry and colleagues (see Sherry, Jacobs, & Gaulin, 1992) found that food-caching birds, which must remember the location of hundreds of food caches scattered around
their territory, have a larger hippocampus than non-food-caching birds (Sherry et al., 1989). Moreover, lesions to the hippocampus and area parahippocampalis in pigeons result in impairments in spatial behaviour, most notably in their homing abilities (Bingman, 1993; Bingman, Bagnoli, Ioale, & Casini, 1984).

Although there is general consensus that the hippocampus plays a role in spatially-guided behaviour, some have argued that the processing of spatial information might be only one aspect of a larger functional role for the hippocampus in memory. For example, Parker and Gaffan (1997a) have proposed that the hippocampus, mammillary bodies, and anterior thalamus, form part of a circuit critical for integrating information about objects and their positions in space, and that this system can be dissociated from that involved in object identification. This hypothesis stems from findings indicating that monkeys with transection of the fornix (or with lesions of the mammillary bodies or anterior thalamus) are severely impaired on an object-in-place memory task, which requires the spatial array of elements in a complex scene to be discriminated (Gaffan, 1994; Parker & Gaffan, 1997a, 1997b). Gaffan (1997) has coined the term “scene-specific memory” to refer to the mnemonic process believed to be tapped into by the object-in-place task and has suggested that this form of memory is analogous to human episodic memory in which the to-be-remembered item or event is set in its own unique time and place. As such, lack of impairment in DNMS following either fornix transection or hippocampal ablation is explained by the fact that performance on this task is always tested within a single constant background scene. In this respect, both Aggleton (1997) and Gaffan (1997) have proposed that the standard DNMS task, as given to monkeys or rats, is essentially a test of familiarity that can
be solved in the absence of normal scene-specific memory and hence, in the absence of the hippocampus.

Another influential theory of hippocampal function suggests that the hippocampus is critical for the normal formation of conditional or contextual associations (see Hirsh, 1974; Jarrard, 1993). For example, Whishaw and Tomie (1991) demonstrated that hippocampal-lesioned rats were impaired on a conditional-discrimination task in which the odour of a string signaled whether pulling a thick or thin string produced a reward, whereas the same animals had no trouble learning simple discriminations guided by the same cues. Another example is Penick and Solomon's (1991) demonstration that classically conditioned eyeblink responses are context dependent in normal rabbits but that rabbits with damage to the hippocampus fail to show this context dependency. Although these and other similar findings have often been taken as an indication that the hippocampus plays is critical to conditional and contextual learning, there have also been reports demonstrating that animals with hippocampal damage show abnormally strong dependence on contextual cues (e.g., Winocur & Olds, 1978; Winocur, 1997). Rather than interfering with the ability to use contextual information per se, it may be that the fundamental deficit produced by hippocampal damage is related to the major associative processing demands that are inherent to many, but not all, conditional or contextual tasks (see Eichenbaum et al., 1994; Winocur, 1997).

Amygdala

Although the amygdala was once thought to be involved in the mediation of object-recognition memory, primarily on the basis of studies in monkeys, there is now almost universal
consensus that one must look to structures other than the amygdala to account for the severe memory impairment that follows large lesions of the medial temporal lobe (Mishkin & Murray, 1994; Murray, 1992; 1996; Steckler, Drinkenburg, Saghal, & Aggleton, 1998; Zola-Morgan et al., 1989). The finding from Experiment 1 that DNMS performance in rats with amygdalar lesions was unaffected at all the delays and sample list lengths offers further support for this conclusion. Moreover, amygdalar damage in these rats also failed to produce an impairment in recency memory, as indicated by the lack of a deficit on the order-discrimination task.

In contrast to the general lack of effect of amygdala lesions on DNMS at various retention delays and sample list lengths, amygdala damage in Experiment 1 did produce an impairment in the rate at which rats were able to learn both the DNMS rule and a concurrent-object-discrimination task. Three possible interpretations of these deficits warrant consideration. First, it has been suggested that the amygdala damage disrupts reward-related processes essential to normal task acquisition (Freeman & Kramarcy, 1974; Kemble & Beckman, 1970; Peinado-Manzano, 1988), and this might account for the present discrimination-learning deficit. However, this hypothesis cannot account for the impairment in DNMS acquisition because DNMS acquisition involves the learning of a conditional response rule rather than specific object-reward associations. Second, the deficits caused by amygdalar lesions in Experiment 1 may have resulted from the extraneous entorhinal damage observed in several subjects (see Figure 2). However, this hypothesis seems unlikely, given that the rats with combined entorhinal and perirhinal cortex lesions in Experiment 2 were able to acquire the DNMS task at a normal rate (despite subsequently being impaired at longer retention delays). Third, the observed deficit in DNMS acquisition and discrimination learning may have resulted from a disruption of
attentional processes. In view of the existing evidence, it is the attentional-deficit interpretation of the impairments produced by amygdalar lesions in Experiment 1 that warrants the most consideration.

Evidence that the amygdala plays an important role in attention comes from both human and nonhuman animal studies (see Davis, 1994; Gallagher & Chiba, 1996). For example, electrical stimulation of sites in the central nucleus of the amygdala in rabbits that produce bradycardia also produce low-voltage fast EEG activity (Kapp et al., 1990); and low-voltage fast EEG activity, which is considered a state of cortical readiness for processing sensory information (Steriade & McCarley, 1990), is acquired during Pavlovian aversive conditioning at the same rate as conditioned bradycardia (Yehle et al., 1967). This has led Davis (1994) to suggest that the rapid development of conditioned bradycardia during aversive conditioning, which is critically dependent on the amygdala, may not simple be a marker of an emotional state of fear, but instead a more general process reflecting an increase in attention. Additional support for a role for the amygdala in attentional processing comes from the finding that an attention or orienting reflex is the most common response elicited by electrical stimulation of the amygdala in cats (Ursin & Kaada, 1960). Similarly, in humans, the recording of stimulus-evoked electrical activity in the amygdala of epileptic patients has shown a prominent negative-positive component occurring roughly 200-300 ms after stimulus onset that is much larger when elicited by a stimulus to which the subject is asked to attend (Halgren, 1992). Halgren (1992) summarizes the cognitive conditions that evoke this component of electrical brain activity as being stimuli that are novel or signals for behavioural tasks. These and other observations have led Kapp et al. (1992) to
hypothesize that the amygdala functions, in part, “in the acquisition of an increased state of nonspecific attention ... which functions to enhance sensory processing.”

Although the available evidence indicates that the amygdala is unlikely to be directly involved in the mnemonic processes underlying object recognition, it certainly does not preclude an important role for the amygdala in other forms of information storage. Whereas selective damage to the amygdala in laboratory animals does not result in the type of mnemonic impairment characteristic of brain-damage-produced amnesia, the amygdala has long been known to be involved in the production of emotional behaviour (Kluver & Bucy, 1937), and it is believed to play an essential part in not only the storage of emotional memory but also in modulating the storage and strength of declarative memories (Davis, 1992; LeDoux, 1992).

Rhinal Cortex

It has been suggested that the rhinal cortex, which comprises entorhinal and perirhinal cortices, is the medial temporal lobe region critical for object-recognition memory in both monkeys and rats (Duva et al., 1998; Murray, 1996; Steckler, 1998), and the results of this thesis support this conclusion. In Experiment 2, lesions of the rhinal cortex were shown to impair DNMS performance at all the retention delays and sample list lengths. The finding that rats with rhinal cortex damage were impaired at delays of 15 s or longer, but were not impaired in DNMS acquisition at a 4-s delay, indicates that their DNMS deficits did not result from sensory, motor, or motivational deficits. Moreover, the fact that their DNMS deficit became greater as the retention delay was increased (i.e., that the deficit was delay-dependent) is strong evidence that the impairment was mnemonic. Similar delay-dependent deficits have been reported in monkeys...
following rhinal cortex ablation (Meunier et al., 1993; Zola-Morgan et al., 1989) and in rats following combined lesions of the rhinal cortex and amygdala (Mumby & Pinel, 1994).

In addition to producing an impairment in object recognition, rhinal cortex lesions produce specific olfactory (Otto & Eichenbaum, 1992) and tactual (Suzuki et al., 1993) recognition deficits. The rhinal cortex might, therefore, be part of neural circuit critical for stimulus recognition in general (Mishkin & Murray, 1994).

Eichenbaum et al. (1994) have proposed that the rhinal and parahippocampal cortices act as a “temporary memory buffer.” According to their model, current representations of stimulus items in the neocortex could be matched with recently stored representations in the rhinal cortex as a way of mediating normal performance in recognition memory paradigms. Support for this notion comes from electrophysiological studies showing that some rhinal neurons signal the relative familiarity of stimuli (Zhu, Brown, & Aggleton, 1995). Eichenbaum et al.'s theory of rhinal cortex function is an elaboration of earlier suggestions that the rhinal cortex forms part of a temporary medial-temporal-lobe memory system, upon which the storage or retrieval of information is initially dependent, but whose contribution diminishes as consolidation proceeds until the neocortex alone is capable of sustaining the memory trace and mediating its retrieval (e.g., Squire & Zola-Morgan, 1991). The finding that rhinal cortex lesions in Experiment 4 produced a temporally-graded retrograde amnesia for objects is in agreement with such theories. A possible role for the rhinal cortex in memory consolidation will be examined in more detail in the following section.

Although the rhinal cortex may act as a temporary memory buffer to support normal stimulus recognition, Eacott et al. (1994) suggested a broader role in memory for this brain
region. They proposed that "...the function of the rhinal cortex in recognition memory is part of a wider function in processing visual stimuli, both in judgments of visual identity... and in learning to associate particular stimuli with reward and nonreward." The fact that rhinal-lesioned rats in Experiment 2 were impaired not only on tasks that assessed object familiarity (i.e., DNMS) and object recency (i.e., order discrimination) but also on tasks of object-reward association (i.e., object discrimination, discrimination reversal, and concurrent object discrimination) is consistent with a general role for the rhinal cortex in learning and storing knowledge about objects. Both Eacott et al. (1994) and Murray (1996) have proposed that the cognitive deficits associated with rhinal cortex ablation in nonhuman animals might share similarities with some aspects of the semantic memory impairment seen in human patients with lesions of the temporal cortex (Hodges et al., 1992; Warrington, 1975).

**Medial Septum and Diagonal Band**

In Experiments 2 and 2A, lesions of the medial septum and diagonal band in rats produced severe impairments in DNMS. This finding is consistent with the DNMS deficits observed by Aigner et al (1991) in monkeys with combined lesions of the medial septum, diagonal band, and nucleus basalis and with numerous reports of impaired spatial-recognition memory in rats following basal-forebrain lesions (Everitt & Robbins, 1997; Steckler, Saghal, Aggleton, & Drinkenburg, 1998).

Because the medial septum and diagonal band send extensive cholinergic projections to medial-temporal-lobe structures, lesions to this region of the basal forebrain are often assumed to result in amnesic deficits by disrupting the cholinergic modulation of the medial temporal lobe
(e.g., Mayes & Downes, 1997). However, the DNMS impairment produced by lesions of the rhinal cortex differs in key respects from that produced by lesions of the medial septum and diagonal band, thus suggesting that the function of the two areas is not closely related. In particular, the severe impairment in acquisition (Experiment 2) or reacquisition (Experiment 2A) of the nonmatching rule, and the delay-independent nature of the DNMS deficit, are not characteristic of the DNMS deficits observed following lesions of the rhinal cortex.

The notion that the basal forebrain may serve functions that can influence performance on measures of memory, but are not specifically mnemonic in nature, has received support from studies of spatial recognition in the rat. Lesions of the medial septum, the diagonal band, or both have been shown to impair water-maze and radial-arm-maze delayed nonmatching-to-position (Baxter et al., 1995; McAlonan et al., 1995; Walsh et al., 1996), but the fact that the impairments were delay-independent suggests that they may not have been primarily mnemonic (Steckler et al., 1998b). Steckler et al. (1998b) have suggested that the basal forebrain may control motivational processes critical for the successful performance of many tasks, including the aforementioned memory tasks. However, this suggestion does not explain why rats with lesions of the medial septum and diagonal band in Experiment 2 were impaired on the DNMS task but not on the discrimination tasks, which involved the same operant response and were motivated by the same food reward.

An alternative explanation to account for the deficits of basal forebrain lesions on spatial recognition tasks was proposed by Baxter et al. (1995). They suggested that the deficits might result from a mild impairment in attentional processing during the information trial rather than an impairment of memory for the location on the retention trial. Indeed, Johnson and Kesner (1994)
had proposed that cholinergic input to the rhinal cortex from the diagonal band serves as an
attention modulator, altering rhinal cortex function when important information is being
presented. In support of the theory that the cholinergic neurons of the medial septum and
diagonal band may play a more important role in attention than in memory, Gallagher (1997)
reported that immunotoxic lesions of both of these basal forebrain structures impaired the
performance of an attentional task but spared the learning of a standard spatial water-maze
memory task. Similarly, combined lesions of the medial septum, diagonal band, and nucleus
basalis have also been found to disrupt attentional focusing in monkeys in the absence of any
memory impairment (Voytko et al., 1994).

In contrast to attentional-processing hypotheses of basal forebrain function, Everitt and
Robbins (1997) suggested that the delay-independent deficits that are often observed on
recognition tasks following basal forebrain damage might best be explained as an inability to
utilize response rules required for correct performance—the vertical limb of the diagonal band
projects to the prefrontal cortex (Gaykema et al., 1990; Krettek & Price, 1977), which plays a
role in motor planning and response selection (Seamans, Floresco, Phillips, 1995; Winocur,
1991). The observed impairments in the acquisition or reacquisition of the DNMS task by basal-
forebrain-lesioned rats (Experiments 2 and 2A) could reflect such a deficit.

Specific roles for the medial septum and diagonal band in attention or response selection
does not preclude their involvement in aspects of learning and memory. Similarly, the delay-
independent nature of the DNMS deficit in basal-forebrain-lesioned rats does not exclude a
memory interpretation either. It remains possible that this deficit reflects a severe disruption of
memory resulting in impaired performance at delays as brief as 4 s. Indeed, the finding from
Experiment 4 that combined lesions in this region of the basal forebrain can produce a retrograde amnesic deficit for object information indicates that the medial septum and diagonal band participate in memory consolidation, perhaps by modulating neuronal activity in both rhinal cortex and higher order sensory areas.

**Mediodorsal Thalamus**

The issue of whether damage limited to the mediodorsal thalamus causes amnesia in humans remains controversial (see Kritchevsky, Graf-Radford, & Damasio, 1987; Markowitsch, 1982; McEntee, Biber, Perl, & Benson, 1976; Victor et al., 1971); however, lesions of the mediodorsal thalamus impairs the performance of nonhuman primates on both recognition and associative memory tasks (Aggleton & Mishkin, 1983; Gaffan & Murray, 1990; Gaffan & Watkins, 1991; Parker et al., 1997; Zola-Morgan & Squire, 1985). The results of this thesis are consistent with these findings: In Experiment 3, rats with lesions of the mediodorsal thalamus displayed deficits in DNMS, temporal order discrimination, simple and concurrent object discrimination, and object discrimination reversal.

Memory deficits associated with diencephalic lesions have often been interpreted in terms of disconnection of limbic-diencephalic pathways critical to normal mnemonic functioning (e.g., Delay & Brion, 1969). One such pathway that is believed to underlie spatial memory processing in the rat (Steckler et al., 1998a) and scene-specific memory in the monkey (Parker & Gaffan, 1997) involves the hippocampus, mammillary bodies, and anterior thalamic nucleus. However, it appears that this circuit does not play an important role in object-recognition memory (Aggleton et al., 1990; 1995; Murray, 1996; Zola-Morgan et al., 1989c). Instead, object
recognition is thought to be subserved by a neural circuit that includes the visual association
cortex, rhinal cortex, and mediodorsal thalamic nucleus (Mishkin & Murray, 1994; Steckler et
al., 1998a). Both of these neural networks are also likely to be affected by reciprocal connections
with the prefrontal cortex and cholinergic modulation from the basal forebrain.

The location of the mediodorsal thalamus and rhinal cortex in the same functional circuit
suggests that separate lesions of these structures should produce similar profiles of mnemonic
impairment. The profiles would not be expected to be identical because it is likely that
progression from one component of a neural system to another would be coextensive with some
significant change in the nature of information processing (Aggleton & Sahgal, 1993; Parkin &
Hunkin, 1997). The similarity of impairment profiles produced by lesions of the rhinal cortex
and mediodorsal thalamus seems to hold true in monkeys (Eacott et al., 1994; Parker et al.,
1997), and the present research revealed similar patterns of anterograde object-memory deficits
in rats with lesions of these two brain areas (see Table 1).

One observed difference between the effects of rhinal-cortex lesions (Experiment 2) and
mediodorsal-thalamic lesions (Experiment 3) was that thalamic lesions, but not rhinal lesions,
produced in the rats a tendency to perseverate on the discrimination-reversal task. Two
hypotheses might account for the perseverative effects of mediodorsal thalamic lesions: First,
Hunt et al. (1994) suggested that lesions of the mediodorsal thalamus might disrupt initial
learning by producing an animal that is more inflexible, and thus an acquisition deficit may
appear in lesioned animals if they have a prior bias counter to the correct response. Second, both
Winocur (1985) and Staubli et al. (1987) suggested that lesions of the mediodorsal thalamus
might disrupt the encoding aspects of a task, and thus lesioned animals may have difficulty
learning to respond to reward. Both of these hypotheses stress the special role of the mediodorsal nucleus in initial learning, thus both can explain why the rats with medial thalamic lesions in Experiment 3 were equally impaired on DNMS at all retention intervals. In contrast, the delay-dependent deficit in DNMS displayed by rats with rhinal cortex damage, is more likely to reflect an impairment in the retention or storage of stimulus information.

Another observed difference between the effects of lesions to the mediodorsal thalamus and lesions to the rhinal cortex was that rhinal-cortex lesions produced a temporally graded retrograde amnesia for objects, whereas mediodorsal-thalamic lesions did not. This observation is also consistent with the hypothesis that the impairment associated with mediodorsal-thalamic damage reflects a fundamental problem in acquiring new information whereas the impairment associated with rhinal-cortex damage reflects a deficit in the storage or consolidation of newly acquired information.

RETROGRADE AMNESIA AND MEMORY CONSOLIDATION

One of the most influential theories of medial-temporal-lobe function posits that structures within this brain region are critically involved in the initial storage and recovery of new declarative information but that their contribution diminishes with time, as they direct the gradual establishment of more permanent representations in neocortex (Alvarez & Squire, 1994; Squire, 1992; Squire & Alvarez, 1995). This gradual reorganization of memory storage from a short-term to a long-term repository is the putative process known as memory consolidation.

Theories of medial-temporal-lobe involvement in memory consolidation stem largely from observations of temporally-graded retrograde amnesia in patients with damage to the
hippocampus and adjacent rhinal and parahippocampal cortices (e.g., Cermak & O'Connor, 1983; Rempel-Clower, Zola-Morgan, Squire, & Amaral, 1996; Scoville & Milner, 1957). Similar observations have been made in experimental animals with medial-temporal-lobe lesions (Cho et al., 1993; Winocur, 1990; Zola-Morgan & Squire, 1990).

The observation in Experiment 4 that lesions of the rhinal cortex significantly impaired the retention of object-discrimination problems learned 2 or 9 days, but not 16, 37, or 58 days, before surgery is consistent with the idea that the medial temporal lobe is critically involved in consolidation. Similarly, Cho et al. (1993) reported a temporally-graded deficit in the retention of preoperatively-acquired spatial discriminations following neurotoxic lesions of the entorhinal cortex. These findings illustrate that medial-temporal-lobe lesions need not include damage to the hippocampus in order for retrograde amnesia to occur. Conversely, the demonstration that hippocampal lesions in rats can produce temporally-graded retrograde amnesia for spatial locations, while sparing retrograde memory for object discriminations, suggests that involvement of the hippocampus in memory consolidation may be limited to certain kinds of information (Mumby et al., 1994).

Alvarez and Squire (1994) have suggested that the key event in consolidation is “the gradual binding together of the multiple, anatomically disparate cortical regions that together store the representation of a whole event.” This binding process is believed to depend upon the reactivation of neocortical sites that constitute the representation via reciprocal connections with the rhinal and parahippocampal cortices. The importance of the feedback connections from rhinal cortex to neocortical association areas is underscored by the retrograde effects of rhinal cortex lesions on memory, but other brain regions might also contribute to the binding together of different aspects of a memory trace.
Preliminary evidence that the basal forebrain might influence the consolidation of new object memories comes from the finding in Experiment 4 that damage to the medial septum and diagonal band resulted in a temporally-graded amnesic deficit similar to that seen following ablation of the rhinal cortex. Mishkin and Murray (1994) have proposed that the basal forebrain, by virtue of its reciprocal connections with medial temporal-lobe structures and efferent projections to sensory neocortex, may modulate the function of a putative neural circuit devoted to object recognition, and it is possible that these same projections might be involved in the long-term storage of similar stimulus information.

Most theories of memory consolidation have difficulty accounting for cases of retrograde amnesia with no apparent temporal gradient (see Damasio et al., 1985; Warrington & Duchen, 1992): One exception is the recent theory of Nadel and Moscovitch (1997). Nadel and Moscovitch (1997) propose that the hippocampus and related medial-temporal-lobe structures play a role in the activation of all episodic memories, even remote ones. They argue that episodic memories are stored in neuronal ensembles comprising both medial-temporal-lobe and neocortical circuits and that older episodic memories are associated with a greater number of distributed traces. They suggest that as the number of traces, and access routes to them, increases, the activation of memories becomes easier. Thus, "newly acquired traces would be particularly vulnerable, but older memories, which are multiply represented, would be able to withstand the loss of more (medial-temporal-lobe) tissue" (Nadel & Moscovitch, 1996). Accordingly, the length of the period of retrograde memory loss is seen to be dependent upon the size of the lesion to the medial temporal lobe: the greater the lesion, the more extensive the retrograde amnesia. By Nadel and Moscovitch's theory, the ungraded retrograde amnesia that has been observed in some experimental animal studies (e.g., Salmon et al., 1987) may be a
consequence of extensive damage to the medial-temporal-lobe memory system in those animals; lesions that affect the hippocampus, amygdala, and large portions of their adjacent cortical structures would be likely to eliminate the majority of traces for both older and newer memories. In contrast, the temporal gradient seen in Experiment 4 and in other animal studies of medial-temporal-lobe damage (e.g., Cho et al., 1993; Zola-Morgan & Squire, 1990) might reflect the more limited nature of the lesions in these studies, and hence the greater likelihood that some of the memory traces for more remote episodes have survived. Be that as it may, Thornton et al. (1997) recently reported an ungraded loss of retrograde memory in monkeys following relatively small rhinal cortex lesions.

Ultimately, it may prove to be the case that both Alvarez and Squire’s (1994) and Nadel and Moscovitch’s (1997) models of memory consolidation correctly explain different aspects of retrograde memory loss. As Kapur (1997) has recently suggested, “it is probably more meaningful to ask questions relating to specific retrograde memory deficits rather than to try to develop an all-encompassing theory of retrograde amnesia,” as retrograde amnesia is likely to comprise a heterogeneous range of functional deficits.

GENERAL CONCLUSIONS AND FUTURE DIRECTIONS

The results of the present experiments clearly establish that different syndromes of amnesia result from damage to the various memory structures of the brain. The mnemonic effects of damage to the medial temporal lobe, medial diencephalon, and basal forebrain in rats were dissociated by a battery of anterograde and retrograde object-memory tasks. The findings also confirmed that medial-temporal-lobe structures themselves make different contributions to memory. Finally, the results illustrated that memory for objects can be tested in much the same
way in rats as it is in humans and nonhuman primates: The similarities between the present findings and those of studies in monkeys and humans underscores the usefulness of rodent models of brain-damage-produced amnesia in furthering our understanding of the neuroanatomical basis of learning and memory.

Many new findings were reported in this thesis. The following are four of the most important. First, it was shown that the previous report of only a mild DNMS impairment in rats with hippocampal or amygdalar lesions when tested on the same paradigm used in the present study (i.e., Mumby et al., 1992) was not entirely attributable to the extensive presurgery training that they received: Following lesions of the hippocampus or amygdala in Experiment 1, rats that received no presurgery training were unimpaired on DNMS with lists of three or more sample objects and displayed little impairment even at the longest (i.e., 120-s) retention delay. Second, it was shown that lesions of the rhinal cortex and mediodorsal thalamus in rats produce similar profiles of anterograde object-memory deficits: Experiments 2 and 3 demonstrated that the mnemonic impairments produced by damage to these respective structures extends beyond a deficit in DNMS to include deficits in temporal order discrimination, both simple and concurrent object discrimination, and object discrimination reversal. Third, Experiments 2 and 2A demonstrated that basal-forebrain damage in rats severely impairs both DNMS acquisition at brief retention intervals and DNMS performance at long retention intervals but that it spares the normal learning of object-reward association tasks (i.e., object discrimination, discrimination reversal, and eight-pair concurrent object discrimination). Fourth, it was shown in Experiment 4 that lesions of the rhinal cortex or basal forebrain, but not the mediodorsal thalamus, produce temporally-graded retrograde amnesia for object-discrimination problems. Accordingly, although there are many similarities between the anterograde effects of rhinal cortex and
mediodorsal thalamic damage on the performance of tests of object-memory, their effects on retrograde memory can clearly be dissociated.

Converging operations was the underlying theme of this thesis. The convergence of clinical studies of human amnesics with monkey and rat studies of experimentally-induced amnesia is now leading to a clearer understanding of the effects of damage to various brain areas on memory. The understanding of brain-damage-produced amnesia should increase even more with the recent development of computational models that allow the specific delineation of profiles of impairment that can be expected when particular memory components are damaged (e.g., Metcalfe, 1997). But the understanding of the effects of brain damage is not the entire story of memory. Functional neuroimaging studies provide another means of testing hypotheses about syndromes of amnesia, which can be used in conjunction with examining the effects of focal lesions on animals and human patients. To address fundamental theoretical issues of amnesia, not only must the precise loci of critical damage be determined, but functional changes in remaining brain areas must also be assessed. For example, functional changes at sites remote from the lesion have been demonstrated in stroke patients (Baron, 1989; Szelies, Herzolz, Pawlik, Karbe, Hebold, & Heiss, 1991) and both Paller et al. (1997) and Fazio et al. (1992) have recently reported widespread declines in glucose metabolism in areas quite distal to the site of pathology in amnesic patients, including frontal, parietal, and cingulate cortices. Thus, clinical-pathological correlations associating particular patterns of brain damage with memory dysfunction might be misleading if altered functioning of other brain areas is not taken into account. These findings underscore the notion that the key to our understanding of the neural basis of memory and amnesia is almost certainly to be found through a combination of many different approaches.
References


Kolb, B., Pittman, K., Sutherland, R. J., & Wishaw, I. Q. (1982). Dissociation of the contributions of the prefrontal cortex and dorsomedial thalamic nucleus to spatially guided behavior in the rat. *Behavioural Brain Research, 6*, 365-378.


Kopelman, M. D. (1997). Comments on Mayes and Downes: “What do theories of the functional deficit(s) underlying amnesia have to explain?” *Memory, 5*, 105-114.


