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The effects of primary olfactory cortical and thalamic lesions on olfactory continuous non-matching to sample and discrimination in the rat

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THE EFFECTS OF PRIMARY OLFACTORY CORTICAL AND THALAMIC LESIONS ON OLFACTORY CONTINUOUS NON-MATCHING TO SAMPLE AND DISCRIMINATION IN THE RAT

BY

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DISSERTATION

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This dissertation has been examined and approved.

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April 8, 1996
Date

DEDICATION

I dedicate this dissertation to my parents, Linben Zhang and Xixang Sun, who have always been understanding and supporting. To George Wang, whom I cannot live without (or with?).

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ABSTRACT

THE EFFECTS OF PRIMARY OLFACTORY CORTICAL AND THALAMIC LESIONS ON THE OLFACTORY CONTINUOUS DELAYED NON-MATCHING TO SAMPLE AND DISCRIMINATION IN THE RAT

By

Yueping Zhang
University of New Hampshire, May, 1996
Dissertation Advisor: Robert G. Mair

Fourty two male rats were pretrained on the olfactory continuous delayed non-matching to sample (CDNMTS) task. They were then matched for performance and randomly assigned to one of the following six treatment groups: excitotoxic lesions of pyriform cortex, later entorhinal cortex, lateral internal medullary lamina (L-IML), mediodorsal nucleus (MDn), nonspecific nuclei, and sham control. After recovery from surgery, the rats were retrained on the olfactory CDNMTS. Delay effects were examined by manipulating retention intervals (RI), with five RIs (4, 6,9,13.5, and 20.25 s) randomly mixed within each session. The number of odor stimuli used in each session varied from 8 to 2. All the rats were then trained on olfactory discrimination task, a task with similar procedural requirements as olfactory CDNMTS except that the stimulus-response contingency was fixed.

Only L-IML and pyriform groups were impaired on the olfactory CDNMTS. Increasing RIs or reducing number of odor stimuli used in each session significantly decreased performance accuracy for all the rats. There was no

differential effect.

All subjects learned the two-odor discrimination task at equivalent rates. The normal performance of discrimination task, indicated that the olfactory CDNMTS deficits could not be attributed to olfactory sensory dysfunction, to difficulties in learning the procedural aspects of the task, or to an inability to suppress responding.

The present findings demonstrate that excitotoxic lesions of L-IML disrupt olfactory working memory but not reference memory, which is consistent with previous studies of radiofrequency lesions of L-IML. Pyriform cortex, a major primary olfactory cortex, apparently is not necessary for olfactory discrimination, although it is critical for olfactory CDNMTS. Taken together, it suggests that either pyriform cortex alone is critical for olfactory memory or there exist parallel pathways for olfactory memory processing.

INTRODUCTION

Korsakoff syndrome is a neurologic disorder characterized by severe memory impairment. Pathological analyses have emphasized the consistent involvement of the medial thalamus and the mammillary bodies in this disease (Victor, Adams & Collins 1989; Mair, Warrington, & Weiskrantz, 1979; Mayes, et al., 1988), although there is no agreement on the precise neurological basis of its amnesic symptoms. Korsakoff patients were also reported to be impaired on several measures of odor perception, including odor recognition memory (Mair, Capra, et al., 1980), psychophysical scaling of odor intensity (Jones et al., 1975; Jones et al., 1978), and matching odorants with labels (Mair, Doty, et al., 1986). Although olfactory deficits are as consistent as the amnesic symptoms among Korsakoff patients, they have received relatively little research attention.

Jones, Moskowitz, Butters and Glosser (1975) interpreted the olfactory deficits experienced by Korsakoff's patients as impaired olfactory sensitivity, and suggested that this primary sensory impairment may in part explain the olfactory deficits observed. Mair, Capra, McEntee, & Engen (1980) argued against this sensitivity theory. They demonstrated that Korsakoff's patients were not impaired in their ability to detect weak odorants at the so-called threshold level even though they were unable to perform an odor recognition memory

task. Many procedures used to measure olfactory recognition and discrimination include a delay imposed between presentation of discriminative stimuli. Mair and colleagues (1986; Mair and Flint, 1992) have argued that impairments observed on these tasks may result from cognitive deficits related to memory or attentional processes, but not from an impairment in primary olfactory sensory function.

From an anatomical point of view, the olfactory system is special in that the olfactory bulb projects directly to a number of areas, such as the pyriform and the lateral entorhinal cortex, that are cortical in nature. In other sensory systems, ascending information is relayed in the thalamus before it enters the cortex. These cortical areas that receive direct input from the olfactory bulb in turn connect with the hippocampus and the dorsomedial thalamic nucleus (MDn) of the thalamus, two structures that have long been implicated in memory. The MDn of thalamus is one of the common sites affected by Korsakoff disease. Thus, the anatomical substrate of olfaction is intimately related to the brain areas that appear to be most relevant to memory processing.

Taken together, it is possible that the olfactory and memory disorders associated with Korsakoff's syndrome share a common pathologic basis or mechanism, as suggested by Mair and others (1986; 1992). Although it is well documented that both memory and olfactory deficits are common signs of Korsakoff's

disease, there is little agreement as to what neural structure(s) or pathway(s) are responsible for the memory and olfactory impairments. The nature of the olfactory impairment and its relationship with the memory deficits are also not fully understood. Data from animal studies regarding these issues are inconsistent at the best. Further studies will be needed to determine the nature and pathological basis of olfactory deficits in Korsakoff's disease.

The present dissertation was conducted to determine the effects of lesions in primary olfactory cortical and thalamic areas on olfactory discrimination and memory in the rat. The cortical lesions were placed in the pyriform and lateral entorhinal cortex. The pyriform cortex is the largest primary olfactory cortex, and the lateral entorhinal cortex is the primary source of olfactory afferents to the hippocampus. The thalamic lesions were placed in three sites: the lateral internal medullary lamina (L-IML), MDn, and non-specific nuclei. The L-IML site has been implicated as critical for memory impairments in animal models of Korsakoff disease. The MDn and non-specific nuclei are the major neural structures affected by the lesions of the L-IML site.

In order to establish the rationale behind the choice of lesion sites and the selection of tasks in this study, it is necessary to review briefly the anatomy and function of olfactory system. Because the ultimate goal of this investigation is to advance the understanding of human

Korsakoff syndrome, literature on human Korsakoff syndrome and relevant animal studies were also reviewed. This paper is organized in the following orders: first, the anatomy of olfactory system is described. Second, the functional roles of the major neural structures in the olfactory system are discussed. Third, human Korsakoff's syndrome is reviewed. Fourth, animal model of Korsakoff's disease and a series of studies that have been conducted in this laboratory are summarized. Fifth, the still controversial issue of the role of MDn in memory is discussed. And finally, the current investigation and its contribution to the understanding of diencephalic amnesia is discussed in detail.

The Anatomy of Rodent Olfactory System

The anatomical consideration of olfactory system will be described in a general rather than detailed fashion. Although comparison is made between the olfactory system of the rat and the primate, the focus of the following review is on the rat.

Unlike other sensory systems which relay information indirectly to cortex via transthalamic pathways, the olfactory bulb projects directly to a number of paleocortical areas. These areas include the pyriform cortex, anterior olfactory nucleus, olfactory tubercle, anterior cortical nuclei of amygdala, periamygdaloid cortex and the lateral entorhinal cortex (Haberly, 1985; Price, 1985). Together, they are usually considered as the primary olfactory cortex due to

their direct afferent inputs from the olfactory bulb. Olfactory information, then, travels from the primary olfactory cortex to the following areas: the neocortical areas in the dorsal bank of the rhinal sulcus, the mediodorsal nucleus (MDn) of thalamus, hypothalamus, hippocampus and dentate gyrus, and the deep nuclei of the amygdala (Haberly, 1985; Price, 1985).

The largest primary olfactory cortex is the pyriform cortex (also referred to as piriform or prepyriform cortex). It receives inputs from brain stem, thalamus, hypothalamus and basal forebrain, in addition to afferent fibers from the olfactory bulb and other olfactory cortical areas. The pyriform cortex projects directly to neocortical areas in the dorsal bank of the rhinal sulcus, and MDn in thalamus. (Haberly, 1985; Price & Slotnick 1983). The neocortical areas that receive fibers directly from the pyriform cortex are the ventral agranular insular area, and the lateral and ventrolateral orbital areas, all boarding on the dorsal bank of the rhinal sulcus. Agranular insular area receives fibers from cells throughout the pyriform cortex and periamygdaloid cortex, and lighter inputs from other area such as the lateral entorhinal cortex. The lateral and ventrolateral orbital areas receive projections from only the medial part of the anterior pyriform cortex (Haberly, 1985; Price, 1985). The projections of pyriform to the three neocortical areas are carried by relatively large numbers of cells in the

superficial layers of the pyriform cortex (Price, Carmichael, et al., 1991).

Powell et al., (1965) first identified the existence of a thalamic component of the olfactory projection, which was verified by many subsequent anatomic studies. The MDn in the rat can be divided into medial, central, lateral and paralamillar segments on the basis of its structure and axonal connections. Experiments using anterograde and retrograde axonal tracers, as well as electrophysiological recording of unit activity have demonstrated that the central segment of the MDn, but not the medial or lateral segments, receives inputs from pyriform cortex (Heimer, 1972; Groenewegen, 1988). In addition to pyriform cortex, the MDn also receives projections from other primary olfactory cortical areas, such as the olfactory tubercle, anterior cortical amygdaloid nucleus, periamygdaloid cortex and the lateral entorhinal cortex (Price, 1985; Price, Carmichael, et al., 1991). Although the MDn receives inputs from several areas of the primary olfactory cortex, the olfactory information is restricted to only one segment of the MDn, and the projections are from only a few cells in the olfactory cortex (Price, 1985).

The neocortical areas and the central segment of MDn, both of which receive direct projections from primary olfactory cortex, are reciprocally connected (Groenewegen, 1988; Heimer, 1972; Leonard, 1972; Price, et al., 1991).

Therefore, there exist a circuit among the pyriform cortex, the MDn of thalamus and the neocortex in orbital and insular areas. Since the MDn receives olfactory inputs and in turn projects to the olfactory-related neocortex, it appears thalamus may function as a relay for olfactory information entering the cortex, in a way similar to other sensory systems. However, the direct projections from the primary olfactory cortex to the neocortical areas are much more prominent than that of the MDn, the latter are carried by relatively small number of cells. Price (1985) demonstrated that the latency of electrophysiological responses in the cortex dorsal to the rhinal sulcus is the same as, or less than the latency of response in the thalamus following olfactory bulb stimulation. This suggests that olfactory information can be transmitted to neocortex without going through the transthalamic pathway. Therefore, the pyriform-thalamus-neocortex circuit may not be necessary for primary sensory function, although it may play a role in higher-order olfactory information processing.

In the monkey, the MDn is composed of three easily distinguishable cytoarchitectonic regions, pars medialis (magnocellular), pars lateralis (parvicellular), and pars multiformis, which borders the intralaminar nuclei. They project to the orbitofrontal, dorsolateral and the arcuate prefrontal cortical areas, respectively (Tanabe, et al., 1975). The olfactory projections to the MDn and to the orbital

and insular cortex have not been as well defined in the monkey as in the rat, but the same elements appear to be present (Price, 1985). An olfactory-specific region is found within the medial magnocellular part of the MDn in the monkey. In addition to the olfactory input, the pars medialis also receives inputs from limbic and ventral pallidal structures. Therefore, the medial magnocellular region in the monkey correspond to the medial and central segments together in the rat, in which the medial part receives predominantly limbic input, whereas the central segment of the MDn receives olfactory input. In the monkey the olfactory-related areas form only a small part of the orbital cortex. The lateral, parvicellular region of the MD in the monkey is more strongly developed than the lateral segment of the MDn in the rat (Groenewegen, 1988; Leonard, 1972).

Another part of primary olfactory cortex that may be implicated in memory is the lateral entorhinal cortex. It receives projections from both the olfactory bulb and the pyriform cortex, and then projects to the dentate gyrus of limbic system, fields CA1 and CA3 of the hippocampus. The lateral entorhinal cortex is the primary source of sensory afferents to the hippocampus in the rat (Ruth, Collier & Routtenberg, 1982; Staubli, Fraser, Kessler & Lynch, 1986). In rats the olfactory input to hippocampus is relatively prominent, but in primates other sensory inputs may be dominant. The lateral entorhinal cortex is a final cortical

link in the conduction routes from the sensory systems of the neocortex to the hippocampus and the dentate gyrus of the limbic system in both rats and monkeys (Staubli, Fraser, Kessler & Lynch, 1986; Tanabe et al., 1975). Damage to the hippocampus or its major afferent and efferent fiber systems has long been associated with memory impairments (Squire & Zola-Morgan, 1983; O'Keefe & Nadel, 1978).

Although the olfactory projections have not been as well defined in the monkey as in the rat, and there exist some differences between the two species in olfactory system, the same olfactory elements appear to be present in both rats and monkeys. There are enough similarities to justify a comparison of olfactory behaviors between the rat and the primate.

As noted above, the hippocampus and MDn of thalamus have direct connections with primary olfactory cortex. These two structures have long been implicated in human memory processes. Thus, from a anatomical point of view, a major part of the anatomical substrate of olfaction in rats overlays with brain areas that have been implicated as relevant to human memory. In the current study, the effects of lesions in the pyriform cortex, the lateral entorhinal cortex and the MDn on odor memory and learning are investigated.

In the following section, the putative functional characteristics of these three subdivisions of olfactory system are reviewed.

Olfactory Studies of the Rat

Rats have exceptional olfactory learning abilities. The performance of the rat is much better on olfactory tasks than tasks that utilize visual or auditory cues (Nigrosh et al., 1975; Slotnick, 1984). They show errorless acquisition of a two-odor discrimination, rapid acquisition of an olfactory reversal learning set, and positive transfer on the first reversal of a reversal set (Nigrosh et al., 1975; Slotnick, 1984; Slotnick, Kufera and Silberberg, 1991). In fact, the rate at which rats learn olfactory simple discriminations is similar to the rate at which the primate learn visual discrimination. This special facility is not surprising, considering the importance of the olfactory function in rodents' social and cognitive behaviors. The "primate-like" olfactory learning ability, together with the fact that the rat olfactory system has intimate connections with structures known to be relevant to memory processing in primate (see anatomy of rodent olfactory system section for detail), led Otto and Eichenbaum (1992a) to conclude that: "the rat olfactory system has both the functional and anatomical properties that characterize a model system for studying the neurobiological bases of learning and memory".

The Role of the Pyriform Cortex in Odor-guided Behavior

The pyriform cortex is the major primary olfactory cortex, receiving direct projections from the olfactory bulb through monosynaptic connections. It is the major source of olfactory

information for the MDn of thalamus, neocortex, and other areas of primary olfactory cortex, such as the lateral entorhinal cortex. It is conceivable to expect that the pyriform cortex plays an essential role in olfactory functions. Surprisingly, there are little behavioral data available on the role of pyriform cortex in olfaction.

Animal studies and human clinical data suggest that destruction of the olfactory bulb or lateral olfactory tract (LOT) at the level of the anterior olfactory nucleus result in an absence of odor detection (Pribram & Kruger 1954; Sapolsky & Eichenbaum, 1980). However, transection of LOT at the level of the anterior pyriform cortex and the olfactory tubercle (Slotnick, 1985; Slotnick & Berman, 1979) did not result in anosmia. The lesioned rats showed normal retention of an odor detection task and were able to solve intensity discrimination problems. Staubli, Schottler & Nejat-Bina (1986) demonstrated that in the rat lesioning the pyriform cortex severely impaired their ability to acquire an olfactory discrimination task involving a two-odor olfactory maze. The severity of the deficit was correlated with the extent of bilateral damage, specifically of the LOT. Training before the lesion dramatically reduced the extent of the deficits. With enough preoperative training, rats with the pyriform cortex damage were able to meet the learning criterion, although they were consistently slower in solving complex problems than control animals. The discrepancy in the severity of olfactory

deficits following the pyriform lesions among the studies may be accounted for by the difference in the locus and extent of the lesions and by the difference in behavioral tasks used.

The Involvement of Entorhinal Cortex in Odor-guided Behaviors

The lateral entorhinal cortex receives afferents from both the olfactory bulb and pyriform cortex, and projects to the hippocampus and the dentate gyrus. Hippocampus has long been associated with memory. As the lateral entorhinal cortex is the primary source of olfactory sensory afferent to the hippocampus, damage to the lateral entorhinal cortex might affect olfactory learning and memory. However, there is considerable disagreement about the effect of entorhinal lesions that denervate hippocampus. Staubli, Fraser, Kessler & Lynch (1986) tested the effect of the hippocampal denervation by interrupting the lateral olfactory tract projections at the level of the entorhinal cortex. They found that rats with bilateral entorhinal lesions could perform a preoperatively learned two-odor discrimination task in a six-arm maze almost as well as the controls, even when the presurgical training was within less than 1 hour before the surgery. On the other hand, lesioned animals showed no retention of newly learned discrimination task three hours after acquisition. The results are consistent with their own earlier study (Staubli, Ivy & Lynch, 1984), in which they found that entorhinal lesions caused anterograde amnesia due to rapid forgetting of newly acquired information. In both of

the above studies, the performance of entorhinal lesioned rats was evaluated in a simultaneous two-odor discrimination paradigm.

When a different version of the odor discrimination task was used, the entorhinal cortex lesion showed surprising effects. Otto, Schottler and colleagues (1991) reported that rats following the entorhinal cortex lesions showed facilitated, instead of impaired, ability to acquire a single-port go/no-go odor discrimination task, and their performance showed no decline over delays as long as 65 days. The authors attributed the facilitation effect of entorhinal lesions to the nature of the task employed in the study, specifically, the successive-cued odor discrimination instead of the simultaneous-cued discrimination used in some of the studies (Staubli, Fraser, Kessler, & Lynch, 1986; Staubli, Ivy, & Lynch, 1984). They further suggested that the memory processing demands in the simultaneous-cue discrimination favored a hippocampal-dependent memory processing mechanism, while the successive-cue paradigm favored a memory process independent of hippocampus. The facilitation of successive odor discrimination was also reported by Eichenbaum et al., (1988) in rats after fornix lesions.

In a study of particular relevance to the current experiment, Otto and Eichenbaum (1992b) successfully developed an olfactory delayed non-matching to sample task that is conceptually analogous in memory demands to those visual

delayed non-matching to sample task (DNMTS), namely, the olfactory continuous delayed non-matching-to-sample (CDNMTS) task (for details see procedure section). Rats with the entorhinal cortex and most of the perirhinal cortex aspirated showed normal acquisition of the olfactory CDNMTS task, but performance progressively declined as the delay was extended. This pattern of behavioral deficit, normal acquisition and rapid forgetting, is consistent with monkey studies. Monkeys with lesions of the medial temporal or parahippocampal areas have been reported to show a selective delay-dependent deficit, with normal acquisition of DNMTS for trial unique objects at short delay and progressive declination of performance as the delay was increased (Alvarez-Royo, Zola-Morgan, & Squire, 1991; Overman, Ormsby, & Mishkin, 1990).

The Involvement of MDn in Odor-guided Behavior

The MDn of thalamus is a prominent nucleus of medial thalamus, the central segment of which receives olfactory inputs from the pyriform cortex. As described in the anatomy section, there is a triangular connection among the MDn, neocortex in the dorsal region of the rhinal sulcus, and pyriform cortex. Lesion studies have provided supporting evidence that thalamocortical projections play an important role in olfactory discrimination. Eichenbaum, Shedlack & Eckmann (1980) reported that rats with the MDn and rhinal sulcal lesions showed impaired acquisition of odor discrimination, requiring more trials to reach the criterion

than did controls in learning the go/no-go odor discrimination task. The severity of the impairment appeared to depend on the difficulty and novelty of a given olfactory discrimination. However, neither the MDn nor the rhinal sulcal lesions were found to affect odor detection. Several other studies (Lu & Slotnick, 1990; Slotnick & Risser, 1990; Staubli, Schottler & Nejat-Bina, 1987; Otto & Eichenbaum, 1992b) also demonstrated that the MDn and rhinal sulcal lesions in rats impair the acquisition of olfactory discrimination without causing anosmia.

Memory for preoperatively learned odor discrimination has been reported to be unimpaired by the MDn lesions in several studies (Lu & Slotnick, 1990; Slotnick & Risser, 1990). The good retention of preoperatively learned odor discrimination, however, was not found in an automated olfactory maze study when three odors rather than two were employed (Staubli, Schottler & Nejat-Bina, 1987). The MDn lesions severely impaired both preoperatively trained and naive animals in acquiring the three-odor olfactory maze task. However, when two-odor olfactory maze was used, the MDn lesioned rats could solve the third and all subsequent discriminations, although they failed the first two problems. Task difficulty may account for the disagreement. Discrimination of three simultaneously released odors is a much more difficult task than the two-odor discrimination.

The MDn lesions are also reported to disrupt serial

reversal learning of olfactory discriminations (Slotnick & Kaneko, 1981). Lesioned rats learned the initial two-odor discriminations as well as did the controls, but when the contingencies between the odor stimuli and reinforcement were reversed they made many more errors than controls. The deficit in reversal learning following the MDn lesions was confirmed by later studies (Slotnick & Risser, 1990; Lu & Slotnick, 1990; Mair, Knoth, et al., 1991).

In hamsters, the MDn lesions also produce olfactory behavioral deficits. Sapolsky & Eichenbaum (1980) found that MDn lesions impair odor discrimination and odor preference in hamsters, resulting in inappropriate and inefficient copulatory behavior. However, the ability of the lesioned hamsters to detect weak odorants was not affected by the MDn lesions.

In summary, the MDn lesions have been shown by several investigators to impair two-odor discrimination. The lesioned rats required more trials to learn odor discrimination (Eichenbaum, Shedlack & Eckman, 1980; Lu & Slotnick, 1990), performed poorly on some of the two-odor discrimination problems but not the others (Staubli, Schottler & Nejat-Bina, 1987; Lu & Slotnick, 1990; Slotnick & Risser, 1990), and they made many more errors than controls when the contingencies between the odor stimuli and reinforcement were reversed in serial reversal learning of olfactory discrimination (Slotnick & Kaneko, 1981; Lu & Slotnick, 1990). But in all the studies,

the lesioned rats were able to perform the odor discrimination task, eventually. This observation indicates that the MDn lesioned rats can detect odors and tell the difference between odors. Therefore, the olfactory deficits observed in rats with MDn lesions can not be explained by basic olfactory sensory dysfunction. The deficits may result from disruption of rats' ability to associate a certain stimulus with a reinforcement, or impairment in cognitive processes related to memory, attention, or other cognitive functions.

Although the role of MDn has been emphasized in the studies reviewed above, it is difficult to assign the olfactory deficits specifically to the damage of the MDn. In all the MDn lesioning studies mentioned above, other surrounding structures were also damaged, occasionally the lesions extending beyond the thalamus. The thalamic nuclei that were often simultaneously damaged include the ventromedial, laterodorsal thalamic nuclei and the intralaminar nuclei. At this point, it remains unclear how odor-guided behavior would be affected following damage limited to the MDn, in the absence of other pathology.

Review of Human Korsakoff's Syndrome

Korsakoff's disease is the chronic phase of Wernicke-Korsakoff syndrome. The acute phase referred to as Wernicke encephalopathy, is characterized by nystagmus, abducens and conjugate gaze palsies, ataxia and transient confusion-

apathetic state (Victor et al., 1989). The most striking feature of Korsakoff's psychosis is its severe and enduring memory impairments, both retrograde and anterograde, and relative preserved intelligence. Although Korsakoff patients perform poorly on many memory tasks, their IQ scores are generally within normal range. Dr. Korsakoff, after whom the syndrome was named, described his patients as "appearing to be in complete possession of their faculties", and "only after a long conversation with a patient would one begin to realize that the individual had forgotten everything that had happened during the illness and just prior to the onset of the illness" (translated by Victor & Yakovlev, 1955 Neurology 5, 394-406).

Behavioral Deficits of Korsakoff's Syndrome

Korsakoff patients have been found to be impaired on many memory tasks. They performed poorly on the Tower of London task (Joyce and Robbins 1991), and showed severe impairment on the Wechsler Memory Scale subtests, including paired associates, story recall and visual reproduction (McEntee, Mair, & Langlais, 1984; Victor et al., 1989). Korsakoff patients also showed impairment on measures of DNMTS and delayed matching-to-sample (DMTS) tasks designed for monkey studies (Aggleton et al., 1988; Squire et al., 1988; Oscar-Berman and Bonner, 1985).

However, Korsakoff patients have been reported to be able to acquire very simple motor tasks such as the mirror trace drawing task (Squire, 1987). When tested on serial reversal

learning tasks similar to those used in animal studies, Korsakoff patients were found to perform to criterion once the initial discrimination was learned (Oscar-Berman and Zola-Morgan, 1980).

In addition to memory impairments, Korsakoff's disease is consistently associated with olfactory deficits. Gregson, Free and Abbott (1981) compared the performance of alcoholic Korsakoff, non-Korsakoff alcoholic and control subjects (12 in each group) on seven measures of visual and odor memory. The Korsakoff patients performed substantially worse than either of the other two groups on all three olfactory tasks, including measures of odor naming, labeling, and Campbell-Gregson olfactory short-term memory. The impaired olfactory performance of Korsakoff patients sufficiently differentiate them from alcoholics and normals. Thus, the authors suggested that olfactory tests could be used as diagnostic discriminator of Korsakoff's disease for routine clinical use.

Jones, Moskowitz and Butters (1975) measured odor recognition memory in 14 Korsakoff patients using an odor quality discrimination task, in which 20 pairs of odor stimuli were presented to the subjects at two delay interval, 0 and 30 seconds, and the subject had to decide whether the second stimulus was the same as or different from the first. They found that Korsakoff patients performed significantly worse than both the alcoholic and non-alcoholic controls, at a level no greater than chance. When asked to detect and then identify

five common kitchen odorants, these Korsakoff patients found common kitchen substances difficult to identify.

In another study by Jones, Butters, Moskowitz, and Montgomery (1978), the psychophysical methods of magnitude estimation were used to assess the olfactory, gustatory, visual and auditory capacities of Korsakoff's patients, long-term alcoholics and right-hemisphere lesion patients. The odor intensity ratings of Korsakoff's patients as a group were less accurate than those of the other groups, indicating impairments in their olfactory scaling capacities. The Korsakoff's patients showed an elevated threshold for the detection of butanol odor (8% saturation as opposed to a range of 0.2-.5% for the other groups). The impaired ability of odor intensity estimation was also observed in Korsakoff's patients in an earlier study by Jones, Moskowitz, Butters, and Glosser (1975). The raised threshold for the detection of butanol and the observation that Korsakoff patients had higher thresholds in odor estimation than did controls led the authors to conclude that Korsakoff patients have impaired olfactory sensitivity. They further suggested that the olfactory sensory impairment may in part explain the difficulty that Korsakoff patients have in odor recognition test and olfactory intensity scaling.

Mair, Capra, et al., (1980) measured the olfactory sensitivity of Korsakoff patients using signal-detection method, a more accurate measure of olfactory sensitivity than

the magnitude estimation method used in previous experiments. Comparing the performance of 10 Korsakoff's and 8 controls, they found that, on the average, the Korsakoff subjects adopted more stringent criteria than did the controls, making fewer hits and fewer false alarms. The mean d' for Korsakoff patients, however, was not significantly different from that of the controls', indicating that the detection performance of the two groups was virtually identical. This result contradicts the sensitivity hypothesis raised by Jones et al., (1975, 1978). In the same study, Mair and colleagues also tested odor recognition memory of these Korsakoff patients under two stimulus conditions: one with pairs of dissimilar odorants (easy to discriminate), and the other with pairs of similar odorants (hard to discriminate). Subjects had to make same or different judgement of each pair of these odorants, which were presented one at a time with retention intervals ranging from 5 to 30 seconds. The Korsakoff patients did not perform above chance during the session with similar distractors. They demonstrated impaired, but above chance level, performance during the session using dissimilar odorants. Another important finding from this study is the lack of decay in performance of recognition memory for odors over the retention intervals tested. The same Korsakoff patients showed temporal decay on short-term recognition of pictures of human faces and recall of consonant trigrams.

Mair, Doty, et al., (1986) tested a group of 21

Korsakoff's patients on the University of Pennsylvania Smell Identification Test (UPSIT), a standardized multiple-choice test of odor identification developed by R.L. Doty and his colleagues. The UPSIT consists of 40 microencapsulated odorants and four verbal labels for each odorant, one of the four labels matches the odorant. Korsakoff patients showed consistent impairment on UPSIT, averaged 41 percent correct compared to above 90 percent correct for normals. As all the patients included in this study were able to detect consistently the presence or absence of odorants released from scratched Microfragrance strips, the poor performance of Korsakoff patients on UPSIT can not be explained by anosmia.

The literature reviewed above suggests that Korsakoff's disease impairs several measures of odor perception, including identifying common odorants, naming or labelling odorants, scaling of odor intensity, and discriminating between odor qualities as in odor recognition memory tests. Although there is little doubt that olfactory deficits are consistent signs of Korsakoff's disease, there is still disagreement regarding to the nature of these olfactory deficits. Jones et al. (1975, 1978) have suggested that the olfactory impairments observed in Korsakoff patients reflect decreased sensitivity to odorants. But there are several lines of evidence arguing against this sensitivity theory. Mair, Capra, et al. (1980) demonstrated that although Korsakoff patients adopted more stringent criteria than the normal controls, their ability to

detect weak odorants was not impaired. The patients could discriminate between odor qualities when odorants were easy to discriminate. Those Korsakoff patients who showed impairment on UPSIT were clinically screened for anosmia, they were able to detect consistently the presence or absence of odorants released from scratched Microfragrance strips without error (Mair et al., 1986). It seems that Korsakoff's disease impairs the capacity to discriminate differences between odorants, but spares absolute sensitivity to odorants.

Odor-discrimination tasks, such as those used in the studies by Jones et al., (1975) and Mair et al., (1980), require the comparison of successively presented stimuli, with a delay imposed between the presentation of two stimuli. It is possible that the olfactory discrimination deficits of Korsakoff psychosis might result from or be adversely affected by the profound memory impairment that characterizes Korsakoff disease. It is also possible that the olfactory and memory disorders associated with Korsakoff's disease are all associated with a single global cognitive deficits, such as attention. Currently, there is not enough data to reach a definitive conclusion.

Neuropathology of Korsakoff's Psychosis

The neuropathology in Korsakoff's psychosis varies from patient to patient. Brain lesions are most commonly seen in areas along the walls and floor of the third ventricle, in periacqeductal regions of the midbrain, as well as the

mammillary bodies and medial thalamus (Victor et al, 1971, 1989; Mair, Warrington et al., 1979, Mayes, Meudell et al., 1988). The variability and multiplicity of lesions seen in Korsakoff patients make it hard to determine the minimal critical lesion associated with Korsakoff amnesia. Currently, there are three major competing views concerning the critical lesions in Korsakoff's syndrome. The amnesic symptoms of Korsakoff's disease have been attributed to the degeneration of the mammillary bodies, the MDn of thalamus, and to the simultaneous damage of both of the two systems.

Mammillary bodies are frequently damaged in Korsakoff's disease, although they are usually not the sole locus of damage. In all the 53 cases of Wernicke-Korsakoff's disease examined by Victor et al., (1971), the two patients examined by Mair et al., (1979) and the two cases studied by Mayes et al., (1988) the mammillary bodies were markedly damaged. Victor, Adams and Collins (1971, 1989) argued, nevertheless, that it is not the mammillary bodies, but the MDn of the thalamus the critical minimal lesion underlying the amnesic syndrome. They reported that five patients who had mammillary body but not medial thalamic lesions, showed no amnesia.

Some researchers strongly argued in favor of a thalamic role in diencephalic amnesia (Victor et al., 1971,1989; Markowitsch, 1982). Victor et al., advocate the view that the damage of the MDn, commonly described in postmortem studies of Korsakoff patients, is responsible for the memory impairment

of Korsakoff patients. They reported (1987) that in all cases where medial thalamic lesions were found amnesia was observed, and lesions in the MDn were the only pathological sign that consistently predicts the occurrence of amnesia. However, the boundaries of MDn are ill-defined, the medial thalamic lesions in different studies were not always in the same loci. A critical thalamic lesion for Korsakoff's psychosis is argued to affect the parvicellular portion of the MDn by Markowitsch (1982), the magnocellular portion of MDn by Victor, Adams and Collins (1971;1989). The two patients studies by Mair, Warrington and Weiskrantz (1979) had normal large cells in the MDn bilaterally, and the whole nucleus appeared normal. Lesions were found in the vicinity of the paratenial nucleus lying medial to the MDn. One of their patients had well established retrograde and anterograde amnesia, but the lesions were limited to the mammillary complex and the paratenial nuclei of the thalamus. In the two patients examined by Mayes et al., (1989) there were very small lesions in proportion to the volume of the MDn, smaller in the patient with the more severe anterograde amnesia. It seems that severe amnesia can occur in Korsakoff patients without appreciable damage to the MDn of the thalamus. But considering these studies together, there is strong evidence against the mammillary bodies and in favor of the thalamus as the critical site of pathology in Korsakoff's amnesia. But there is not enough evidence to conclude that the MDn of thalamus is the

minimal critical lesion, and it remains controversial as which part of the thalamus is responsible for the memory deficit.

As in most cases, mammillary body and medial thalamic lesions were often both present, this could mean either of the two is critical for amnesia or that the combination of the two is necessary. In the 43 cases of alcoholic Wernicke-Korsakoff disease examined by Victor and colleagues (1989), although the 5 cases that were not amnesic showed lesions in mammillary bodies but not medial thalamus, in all the 38 cases with amnesia lesions involved both mammillary bodies and the MDn. There is supporting evidence from animal studies. Mishkin (1978, 1982) argued that permanent, severe amnesia occurs only if there is damage to both of the two limbic-diencephalic pathways. One of the pathways involves mammillary bodies, and the other involves medial thalamus.

The Neuropathology of Olfactory Deficits in Korsakoff's Disease

The MDn is the only structure consistently affected by Korsakoff disease that is also known to receive direct inputs from primary olfactory cortex, and to connect reciprocally to neocortical areas. Thus, it might be argued that lesions affecting the MDn may be responsible for the olfactory deficits associated with Korsakoff's disease. This hypothesis has also been supported by studies of patients with lesions of olfactory-related prefrontal cortical areas. Potter and Butters (1980) demonstrated that prefrontal patients exhibited

impairments in odor discrimination comparable to those of Korsakoff patients, and showed normal detection of weak odorants also as Korsakoff's patients. Jones-Gotman and Zatorre (1988) measured butanol sensitivity and UPSIT performance among 120 patients with focal surgical lesions of cerebral cortex. Those in whom the lesions included orbital cortex (n=16) were significantly impaired on the UPSIT, and those with orbital sparing (n=13) were not. None of the patients exhibited impairments in absolute sensitivity. Results from these two studies suggest that lesions affecting MDn target areas in orbitofrontal cortex can disrupt the ability to discriminate and identify odors without impairing absolute olfactory sensitivity. Animal studies have provided further support for the argument that MDn lesions account for the olfactory deficits associated with Korsakoff's disease. The experimental lesions of the thalamus affecting the MDn can disrupt performance of odor-guided behaviors (discussed in later section).

However, there are reasons to question the importance of the MDn in human olfactory perception. First, the MDn receives olfactory inputs in a restricted zone, and there is no definitive evidence that the thalamic olfactory pathway is affected in Korsakoff's disease. Second, anatomically the projection from primary olfactory cortex to the MDn and then to orbital frontal cortex may not be an important pathway for olfactory information processing. This is because there are

much more direct and robust projections to the same neocortical areas from pyriform cortex than from the olfactory zone of the MDn. The MDn is a relay nucleus, receiving robust inputs from multimodal sensory areas. It is likely that the MDn participates in complex, integrative cognitive processes rather than plays an essential role in olfaction. Lastly, data from animal studies of experimental lesions affecting the MDn are inconclusive (animal studies are discussed later).

In summary, Korsakoff's disease results in severe anterograde and retrograde amnesia, and impairments on several measures of olfactory perception as well. Several structures are consistently involved in Korsakoff disease, and are suggested to be the critical lesions responsible for the amnesic symptoms. These structures include the mammillary bodies, the MDn of medial thalamus, and the thalamocortical connections. There is also substantial evidence in favor of the role of the MDn in Korsakoff's olfactory deficits. However, the minimal critical lesion(s) for either the amnesic or the olfactory symptoms are still uncertain.

A Rodent Model of Korsakoff's Syndrome

It is widely accepted that Wernicke-Korsakoff syndrome is directly or indirectly caused by acute thiamine deficiency. Mair and colleagues have developed a rodent model of subacute thiamine deficiency, using a method combining a thiamine-deficient diet and daily injections of pyrithiamine. The

pyrithiamine induced thiamine deficiency (PTD) treatment produces in rats certain patterns of pathological changes and behavioral impairments, which are comparable with those observed in human Wernicke-Korsakoff syndrome. The similarities between the PTD treatment and Korsakoff's disease in etiology, neuropathology, and behavioral impairment have led to the conclusion that the PTD model of thiamine deficiency can serve as a neurologically valid rat model of the Wernicke-Korsakoff syndrome (see Langlais, 1992; Mair, Robinson and Koger, 1992 for reviews).

Following PTD treatment rats develop consistent lesions in two regions, the medial thalamus and the mammillary bodies. In the medial thalamus, lesions are centered on the internal medullary lamina (IML), in a bilaterally symmetric fashion, involving thalamic intralaminar nuclei, portion of the MDn, the posterior nuclear group and parafascicular nucleus of thalamus (Knoth & Mair, 1991; Mair, Anderson, et al., 1988; Mair, Knoth et al., 1991; Mair, Otto, et al, 1991). As discussed above, these two sites are also consistently damaged in Korsakoff's disease.

The PTD rats have been shown to be impaired in their ability to learn several tasks, including spatial delayed alternation (Mair, et al., 1985), spatial DNMTS for positive reinforcement (water) (Mair, Anderson, et al., 1988; Knoth & Mair, 1991) and for aversive reinforcement (shock escape) (Mair, Otto, et al., 1991), and spatial DMTS (Mair, Knoth,

Rabchenuk, et al 1991). The impairment of PTD animals on spatial DNMTS persisted with extensive training before and after treatment (Knoth & Mair, 1991).

On the other hand, the PTD rats have been shown to retain capacity to acquire discrimination tasks based on spatial or visual (light-dark) cues (Mair, Anderson, et al, 1988; Mair, Otto, et al., 1991), although they require more trials than controls to learn some discrimination tasks. For spatial serial reversal learning, PTD rats showed positive transfer comparable to that of controls across serial reversal problem sets, although they made significantly more errors in mastering each problem (Mair, Knoth et al., 1991).

The issue of working memory and reference memory

Several memory distinctions have been used to describe the pattern of memory deficits of Korsakoff syndrome and its animal model. Squire (1986) used the terms of procedural memory (memory for skills and operations) and declarative memory (memory for facts and episodes). He suggested that procedural memory is spared while declarative memory is impaired in Korsakoff's patients and other cases of amnesia resulting from damage to diencephalic structures. Other memory distinctions, such as representational memory versus dispositional memory, and working memory versus reference memory, are also often used. But the working memory and reference memory distinctions are most preferred in describing the memory deficits observed in the animal models of

Korsakoff's psychosis.

As decried by Honing (1978) and Olton and colleagues (1979), in tests of working memory stimulus information is useful for only one trial, but not across subsequent trials. Delayed NMTS and MTS procedures are examples of tasks that require working memory. In both procedures, in order to make a correct response the sample stimulus must be remembered throughout the delay interval, and then be compared with the choice stimuli. However, the particular sample stimulus to be remembered changes from trial to trial. Thus, working memory is "erasable" memory that is replaced on a regular basis. The persistent deficits on DNMTS and DMTS observed in Korsakoff patients and PTD rats can be taken as evidence of impaired working memory.

In tests of reference memory, the strategy of responding is the same on every trial. For example, in discrimination tasks, one stimulus is always associated with reinforcement and the other never is. Correct responses can be made based on the present stimulus only and the stimulus-response contingency is the same throughout an experiment. The spared performance on discrimination tasks in the PTD rat, and the normal positive transfer on serial reversal task in Korsakoff's patients indicate that their reference memory remains intact. Therefore, the pattern of behavioral deficits exhibited by the PTD rats is qualitatively similar to that of observed in Korsakoff's patients, which can be best summarized

as "an impaired capacity for working memory with sparing of reference memory".

The behavioral impairment observed in the PTD rats is consistently associated with lesions of the IML sites. Recovered PTD rats with sparing of tissue in the region of the IML of the thalamus learned to perform DNMTS tasks as well as controls (Mair, Anderson, et al, 1988; Mair, Otto, et al., 1991). When given extensive pretreatment training, rats recovered from PTD treatment without complete IML lesions improved in posttreatment training to a level comparable to controls, although they showed deficits comparable to the IML-lesion group in initial training (Knoth & Mair, 1991). The IML is a system of myelinated axons enclosing the anterior nucleus and surrounding the lateral and ventral borders of the MDn. Interspersed within the IML are small cell groups, intralaminar nuclei, referred to collectively as nonspecific nuclei. PTD treatment tends to damage several thalamic nuclei, including the MDn and the nonspecific nuclei. To determine more precisely which specific nucleus or neural pathway is responsible for the behavioral impairment observed in PTD rats, more studies are needed.

Lesion Studies of the Rodent Model

Animal lesion studies are particularly useful in linking structure with function. With the PTD model as a guide for the placement of lesions, a series of lesioning experiments have been conducted in our laboratory in an attempt to identify the

critical neurological system(s) that might be responsible for the behavioral impairments produced by PTD treatment.

In several studies rats were pretrained on a spatial DNMTS task, and assigned by a matching procedure to treatment groups. Radiofrequency (RF) lesions were placed in the following sites that are known to be involved in PTD model: lateral portion of the internal medullary lamina (the L-IML), midline thalamus (MT), the mammillary bodies (MB), the combination of MT and MB, and fornix (Mair & Lacourse, 1992). Rats in different treatment groups were then compared for performance on spatial DNMTS task. Spatial DNMTS performance was impaired following either L-IML or fornix lesions, but only lesions of the L-IML site produced behavioral deficits comparable to PTD treated rats on this same task.

L-IML lesions have been shown to impair other measures of working memory, including spatial delayed MTS task (Stevens & Mair, 1996), 8 arm radial maze with imposed delays (Harrison & Mair, 1993) and olfactory continuous delayed-non-matching-to-sample (CDNMTS) (Koger & Mair, 1994). The olfactory CDNMTS study (Koger & Mair, 1994) is particularly relevant to the present investigation. The olfactory CDNMTS task is conceptually analogous to other delayed conditional discriminations used to measure working memory. This task is a single port go/no-go procedure in which responses are reinforced only if the odor on the current trial is different from the odor delivered on the preceding trial (i.e., a non-

match, or S+ trial). In order to make a correct go or no-go choice, the rat must remember an odor stimulus across the delay, and the stimulus information must be updated from trial to trial, thus, working memory is required. Rats with the L-IML lesions showed persistent impairment on olfactory CDNMTS, but they performed as well as controls on a two-odor discrimination task. The two-odor discrimination task has the same procedural demands as CDNMTS except that one odor is always associated with reinforcement while the other never is. Thus, it can be regarded as a test of reference memory (for more details on the two olfactory tasks see Procedure in Method session). Koger and Mair (1994) interpreted the impairment on olfactory CDNMTS and normal performance on the discrimination task as evidence of "an impaired capacity for working memory with sparing of reference memory", a behavioral impairment pattern similar to that observed with spatial tasks (described above).

To further pinpoint the critical neural substrates of the behavioral impairments produced by PTD treatment and RF L-IML lesion, the effects of lesions limited to either the anterior or posterior half of L-IML on spatial DNMTS were examined (Mair, Robinson, Koger, Fox, & Zhang, 1992; Zhang, 1992). It was found that animals with lesions destroying either the anterior half or posterior half of the L-IML site performed at a level comparable to that of controls, and significantly better than animals with complete L-IML lesion. So, it appears

that complete L-IML lesion is necessary to disrupt spatial DNMTS performance.

Histological analysis using Fink-Heimer silver technique for tracing degenerating fibers has shown that both PTD treatment and RF L-IML lesions produce signs of degenerating axons throughout cortex in layers (I and VI) associated with nonspecific thalamocortical projections, which are the termination fields of the intralaminar nuclei and the paralaminar nuclei. Degenerating axons are also found in the specific projection areas of the MDn in frontal cortex along the medial wall (MW) and dorsal bank of rhinal sulcus (RS) in layer III or IV. (Mair, Ferguson, Knoth & Langlais, 1989; Zhang & Mair, 1992). These findings verify that both PTD treatment and L-IML lesions disrupt the thalamocortical projections of both the MDn and non-specific nuclei. The role of cortical projections in the behavioral deficits associated with the L-IML lesion has been investigated by lesioning the cortical projections of the MDn in the medial wall (MW) and rhinal sulcus (RS) areas of the rat frontal cortex. Lesions of the MW produced persistent deficits comparable to L-IML lesions for spatial DNMTS (Harrison & Mair, 1996) and DMTS task (Stevens & Mair, 1993), transient impairment on olfactory CDNMTS (Koger & Mair, 1994), but did not affect the performance for radial arm maze (Harrison & Mair, 1996), serial reversal learning (Harrison & Mair, 1996). While lesions of rhinal sulcus showed transient deficits on all of

the above tasks, which recovered with sufficient postsurgical training (Koger & Mair, 1994; Harrison & Mair, 1996). Other investigators suggest that damage of the projection target of both pyriform and the MDn in prefrontal cortex, the orbital prefrontal cortex, impairs odor-guided learning in the monkey (Tanabe, Iino, & Takagi, 1975) and the rat (Eichenbaum, Clegg, & Fealey, 1983). Eichenbaum, Clegg and Fealey (1983) demonstrated that destruction of the orbital prefrontal cortex results in deficits in odor discrimination, but not in spatial delayed alternation; while ablation of medial prefrontal cortex results in deficits in spatial delayed alternation, but not in odor discrimination. The impairment in odor discrimination following orbital prefrontal cortex lesions is reported to be greater than that of following lesions of the MDn (Eichenbaum, et al., 1980).

The L-IML lesions involve many nuclei, most consistently, including the MDn and intralaminar nuclei. Intralaminar nuclei, referred to collectively as nonspecific nuclei, are a group of nuclei embedded in the IML, including the central medial nucleus, the paracentral nucleus, and the parafascicular nuclei (Macchi & Bentivoglio, 1986). The effects of the MDn lesions and putative effects of nonspecific lesions on memory are discussed in the next section.

Medial Thalamic Damage and Amnesia

Clinical studies have demonstrated that medial

diencephalic damage can cause severe amnesia in cases of Korsakoff's syndrome (Victor, et al., 1989) and vascular lesions of thalamus (Von Cramon, et al., 1985). Among the structures most frequently implicated in diencephalic amnesia is the MDn. Victor and colleagues (1989) suggested that lesions of the MDn were critical for memory deficits. Von Cramon, Hebel and Schuri (1985) challenged this idea. They examined 6 of their own patients and 5 patients reported in the literature with vascular lesions in thalamus and concluded that a major part of the MDn was not generally involved in these cases. Moreover, the two patients without amnesia showed comparatively large parts of the MDn were involved. As damage to other structures was also present in all of the clinical reports, it remains unclear how much memory impairment would occur following damage restricted to the MDn or to other structures alone.

In the monkey, circumscribed bilateral lesion of the posterior portion of the MDn was reported to cause substantial impairment on a trial unique delayed NMTS task (Zola-Morgan & Squire 1985). The same monkeys learned pattern discrimination problems at the same rate as the controls. This pattern of behavioral impairment is consistent with human amnesic patients who preserve capacity for skill learning. Aggleton and Mishkin (1983a) assessed the thalamic contributions to memory in monkeys by lesioning the medial portion of both the anterior thalamic nucleus and the MDn (1983a). Lesioned

monkeys showed severe impairment on visual object recognition test and normal performance on visual pattern discrimination learning. In another study, Aggleton and Mishkin (1983b) placed lesions in the medial portions of either the anterior thalamus or posterior thalamus, and demonstrated that both lesions produced a moderate impairment on visual object recognition. Viewing the two studies together, Aggleton and Mishkin (1983b) suggested that damage in either anterior or posterior thalamus can induce a memory loss but that combined damage to both regions is required to produce a full-blown amnesia. Markowitsch (1982) reached similar conclusion in an extensive review of human and animal research involving medial thalamic pathology. He concluded that " although transient amnesic deficits followed restricted MDn lesions, impairments usually only persisted with more extensive medial thalamic pathology involving structures adjacent to the MDn", and he also pointed out that there apparently exists no report of amnesia associated with a lesion confined exclusively to the MDn. Until such a case is found the critical role of the MDn in memory processes cannot be proved.

Results from rats studies of the thalamic role in memory have been very inconsistent. Rats with the MDn lesions were found by some to be unimpaired on delayed alternation (Greene & Naranjo, 1986), the Morris water maze and radial arm maze task (Kolb, Pittman, et al., 1982). Kessler, Markowitsch and Otto (1982) found subtle effects of the MDn lesion on radial

maze tasks. Kivlahan and Mair (1992) reported only limited effects of the MDn lesions on spatial DNMTS performance. The fact that in rats recovered from PTD treatment the MDn was often spared or partially damaged (Mair, Anderson, et al. 1988) also casts doubt on the importance of the MDn.

On the other hand, there are a number of studies demonstrating that rats with lesions in the MDn were impaired on radial maze tasks (Stokes & Best, 1988; 1990a; 1990b; M'Harzi, Jarrard, et al., 1991) and non-spatial DNMTS tasks (Hunt & Aggleton, 1991; Mumby, Pinel & Dastur, 1993). M'Harzi et al., (1991) found that the extent of the delayed NMTS impairment was correlated with the extent of cellular damage in the MDn. Stokes and Best (1990b) claimed that it is necessary that at least 80% of the MDn be included in the lesion for behavioral impairments to occur. In reviewing 10 radial maze studies of rats with MDn lesions, Hunt & Aggleton (1991) found 4 of them reported normal levels of performance, while 6 studies found deficits. In all the 6 studies that showed deficits lesions involved other thalamic nuclei and/or structures outside of the thalamus.

As in all the studies reviewed above lesions routinely involve other structures besides the MDn, it is hard to rule out the possibility that behavioral deficits obtained reflect, to some extent, the effect of damage to those "other structures". The nonspecific nuclei and intralaminar white matter are the most likely candidates. Lesioning of the MDn

with traditional lesioning technique also destroys fiber systems which surround or pass through the MDn. It is possible that the destruction of passing fibers, rather than the nuclear lesion itself, may be responsible for the behavioral deficits as suggested by Von Cramon et al. (1985) and Markowitsch (1988). Nonspecific nuclei are embedded in the internal medullary lamina, they project to widespread neocortical areas in layer VI, which are referred to as the nonspecific thalamocortical projections. As noted above, in the MDn lesion studies, PTD treatment and RF L-IML lesions both the MDn and nonspecific nuclei are involved. In a recent review paper, Mair (1994) suggested that damage to the internal medullary lamina and its associated nonspecific nuclei might be responsible for the working memory deficits associated with large thalamic lesions. Unfortunately, no data on the effect of nonspecific nuclei on memory are available. The current study tried to examine how olfactory learning would be affected following damage limited to the MDn, the nonspecific nuclei, as well as to the L-IML.

The CURRENT INVESTIGATION

General Plan

Lesion Technique and Lesion Sites

In animal lesion studies, the interpretation of results depend to a large extent on the exact locus and extent of the lesions produced. The traditional lesion techniques, electrolytic or radiofrequency lesion, produce undifferentiated lesions of neurons, fibers of passage, and glial cells. The functional deficits exhibited by brain-damaged animals might in part or even mostly be due to the destruction of passing fibers rather than that of the cell bodies of target site(s).

Excitotoxins, such as kainic acid, and N-methy-D-asparate (NMDA), are able to destroy neurons while sparing fibers of passage. They are thought to bind to excitatory amino acid receptors on neuronal dendrites and to overstimulate them fatally. In the current investigation, NMDA is used as a tool for producing brain lesions. NMDA is the excitotoxin of choice not only because it is one of the most commonly used excitotoxins, but also because there is basis to hypothesize that excitotoxicity mediated by NMDA receptors may be the pathophysiological mechanism responsible for the selective lesions within the diencephalon following PTD treatment (Langlais, Mair et al. 1988; Langlais & Mair, 1990). Treatment

with MK-801, a blocker of the NMDA subtype of glutamate receptor, at the end of PTD treatment reduces damage to the diencephalon (Langlais & Mair, 1990) and intervention with MK-801 earlier in PTD treatment can prevent the behavioral impairments and lesions caused by PTD treatment in rats (Robinson & Mair, 1992).

RF lesions of the L-IML have been shown to impair performance of rats on a variety of tasks, including olfactory CDNMTS (Koger & Mair, 1994). The MDn and the non-specific nuclei are the major neural structures affected by the RF lesions of the L-IML sites. As noted above, the effects of restricted MDn lesions on memory is still unproven, and little is known about the role of non-specific nuclei in memory. The current study is designed to test whether excitotoxic lesions of the L-IML would have the same effect on olfactory CDNMTS and to assess the separate contributions of the MDn and the non-specific nuclei lesions. The primary olfactory cortical areas, the pyriform and lateral entorhinal cortex, have been demonstrated to be involved in odor-guided behavior. However, the rodent literature presents divergent evidence regarding the degree and nature of the olfactory deficits observed in rats with primary olfactory cortical lesions. The effects of the pyriform and lateral entorhinal cortex lesions on olfactory CDNMTS task are examined in this study.

Task and Task Manipulations

In search of literature, it appears that human Korsakoff

patients and rats following PTD treatment and RF L-IML lesions show similar pattern of memory deficits when visual or spatial tasks are used. The common pattern can be summarized as "an impaired capacity for working memory with sparing of reference memory". One question this study attempts to answer is would this pattern emerge in the olfactory modality for rats with thalamic and primary olfactory cortical lesions? Olfactory working memory was tested in the current study using a single port olfactory continuous delayed NMTS task (CDNMTS), developed by Otto and Eichenbaum (1992b). Delayed NMTS tasks are most often used to study working memory in animals. Continuous NMTS is a variant of the NMTS procedure. The continuous NMTS differs from traditional NMTS task in that each stimulus serves both as a comparison stimulus (with respect to the preceding trial) and as a sample stimulus (with respect to the following trial). In the olfactory CDNMTS task, a repeated odorant (match trial) signals the non-availability of reinforcement, while a change in odorant (non-matching trial) signals the availability of reinforcement. Thus, it is the change in odorant, not particular odorants, that serves as the cue for reinforcement. As the stimulus information changes from trial to trial, the olfactory CDNMTS task can be regarded as a test of working memory. Eight different odors served as stimuli in the present study.

Another task used in this study is a two-odor discrimination task. The two-odor discrimination task uses the

same go/no-go procedures as the CDNMTS task, except that instead of eight odors only two odors are used in each session, and one of them is always associated with reinforcement and the other with the unavailability of reinforcement. In other words, for the discrimination task the stimulus-response contingency is fixed for any given session. The two-odor discrimination task is, therefore, a test of reference memory.

Manipulation of delays. Memory is generally studied in procedures that include a delay between presentation of discriminative stimuli and the corresponding responses. The rate at which performance accuracy changes as function of the delay is referred to as forgetting function. White (1985) suggests that the forgetting function has two characteristics, discriminability at zero delay and rate of decrement in discriminability with increasing delay. Unfortunately, in olfactory tasks it is technically difficult to measure performance at zero delay. The delay in the olfactory CDNMTS can not be shorter than 4 seconds, because of the time needed for exhaust and changeover of the odors between trials and the concern over adaptation to the olfactory stimuli occurring at shorter intervals.

To generate a "forgetting" function it is also necessary to manipulate delay intervals over several values. One problem with the delay manipulation in some of the studies is that the animals were trained extensively on short delays both before

and after surgery, and then they were tested for a few trials with much longer delay. For example, in Otto & Eichenbaum's (1992b) study, the performance of the rat on olfactory CDNMTS was measured at the delay of 3, 30, and 60 seconds. The density of reinforcement dropped dramatically as the delay changed from 3, 30, to 60 seconds. Under situation like this, the decline in reinforcement rate consequently changes the response contingencies saliency, which might in part responsible for the poor performance of the lesioned rats at long delays. However, if the delay changes gradually and different delays are intermixed within a session, the reinforcement density would be more stable. In the current investigation, five delays were used, 4, 6, 9, 13.5, and 20.25 seconds. Delays were presented in two ways: random ordered by trials and random ordered by blocks of trials. In a random by trials session, the five delays were chosen randomly with replacement on a trial to trial basis. Therefore, the probability of each delay being chosen at any given trial is equal. The potential problem with this procedure is the high irregularity of delays across session. For instance, a 4 second delay may be followed by a 20.25 second delay and vise versa. The dramatic change in delays from trial to trial may disrupt rats's performance, which is confounded with the delay effects. In addition, the random by trials session does not guarantee an equal number of trials for each delay. However, given the large numbers of trials, it is unlikely to pose any

problem. In the random by blocks of trials session, the order of the delay presentation was chosen randomly without replacement, and a block of 12 trials were conducted at each of the delay before moving to the next delay. This arrangement makes it certain that there are equal number of trials, 12, for each delay. As trials were run in blocks, it is likely that short delay follows short delay, and longer delay follows longer delay, which reduces the irregularity of delays within sessions. But it may introduce a confound between delay and frequency of trials. As with short delays, trials are more frequent in the block. The closer the trials are, the more likely for proactive interference and sensory adaptation to have effects.

The Effects of the number of odors in a session. Proactive inference (PI) is a memory-dependent process. Studies of PI have repeatedly demonstrated that previous conflicting stimuli can reduce the accuracy of responding in short-term memory tasks (Hoing, 1978). The continuous NMTS task is sensitive to the effects of PI and is particularly suited for the study of interference from previous conflicting stimuli (Pontecorvo, 1983). One of the major factors that affects PI in a CDNMTS task is the number of stimuli used in a session. Nonspatial delayed NMTS and MTS tasks generally involve a small set of test stimuli that are presented repeatedly, trial after trial. Studies have shown that rats (Mumby, Pinel, & Wood, 1990) and monkeys (Mishkin & Delacour, 1975) performed better on delayed

NMTS task when different stimuli (nonrecurring or trial-unique item) were used on each trial than when a small number of stimuli were presented repeatedly from trial to trial. In the olfactory CDNMTS task, varying the number of odors used within a session was reported to affect the performance accuracy of both normal rats and rats with lesions in the L-IML sites, rhinal sulcus and medial wall (Otto & Eichenbaum, 1992b; Koger & Mair, 1994). This performance decrement is likely due to interitem interference. In the olfactory CDNMTS task, each stimulus acts both as a sample and as a test stimulus. When the odor set is large, the individual odors are repeated only occasionally within a session. As the odor set size decreases, individual odors are presented more often and the level of interitem interference should increase. It is possible that brain lesions affect the rats' susceptibility to the interitem interference. To test this possibility, rats were trained with three different sizes of the odor sets: 8,4, and 2.

Interference effects may also accumulate over the course of a session as the number of trials increases. The interference within a session was assessed by comparing the performance in blocks of 10 trials, and the session was therefore divided into sevenths.

In summary, the current study was designed to investigate the effect of excitotoxic lesions of medial thalamus (L-IML, MDn and non-specific) and primary olfactory cortex (pyriform and lateral entorhinal cortex) on olfactory CDNMTS and

discrimination tasks, which require working memory and reference memory, respectively. The measurement of the performances of the above lesioned groups, in comparison with the controls, on the two olfactory tasks with different manipulations of task variables would provide information to better understand the following questions: (1) Would excitotoxic lesions in the areas mentioned above impair olfactory memory and learning? Would the pattern "an impaired capacity for working memory with sparing of reference memory" observed in other sensory modalities following medial thalamic lesions remain true for olfactory modality? (2) To what extent can any impairments observed be related to deficits in sensory, procedural, memory or other cognitive functions? 3) Can the impairment on olfactory memory following lesions be accounted for by fast forgetting, or increased susceptibility to proactive interference? With the results of Koger and Mair's study (1994), the present findings will provide a complete analysis of the effects of lesioning central olfactory pathways from primary olfactory cortex to projection areas in thalamus and frontal cortex.

Method

Subjects

Forty two male Long-Evans rats, which were two to six months old at the beginning of presurgical training, served as subjects. Throughout the study, rats were housed in individual

stainless cages in an temperature- and humidity-controlled room on a 12:12 hour light-dark cycle. They received ad libitum access to food and were maintained on a 23.5 hour water deprivation schedule, receiving water during training sessions and for 30 minutes each day following behavioral testing. Training took place during light phase.

Apparatus

Behavioral training took place in a sheet-metal operant chamber (44 cm x 41 cm x 41 cm) with a wire mesh floor and black painted aluminum walls. The chamber was housed in a sound isolating wooden enclosure. At the center of one end was a conical nalgene odor port (4.5 cm in diameter and 1 cm above the floor), a drinking spout (12.0 cm above the floor, 4.0 cm recessed from the front plane of the odor port), and an acrylic shelf between the odor port and the drinking spout (8.0 cm above the floor and extending 4.5 cm deep from the front plane of the odor port into the alcove). The rat could rest its paws on the shelf while responding to the drinking spout. Nose pokes into the odor port and responses to the drinking spout were monitored by infrared photocells mounted on either side of the odor port and the drinking spout. Water (0.1 ml) was delivered to the drinking spout by a brief (0.1 s) activation of a miniature solenoid, licking on the spout was recorded by a contact relay circuit. A 5 W lightbulb was mounted above the water port and a houselight (6 watts) was mounted on the ceiling.

Odor stimuli were generated by an air dilution olfactometer. Air supplied by a compressor was filtered through drierite (CaSO4) and then through activated charcoal before reaching the gas washing bottles containing the odorants. The odorant used on each trial was selected by activation of one of the 8 two-way solenoids, and the odorized airstream was then added to the clean air stream to produce an overall flow rate of 3200 cc/min with a vapor saturation of 10%. The final odorized airstream entered the behavioral chamber into the sniff port immediately (approximately 0.1 s) after a nose poke was made into the odor port by activating the 3-way solenoid that was mounted just outside of the behavioral chamber. Airflows in the olfactometers were constantly monitored and regulated by flowmeters. The lingering odors around the odor port was removed by an exhaust fan via a host (12 cm in diameter) mounted to the top of the alcove containing odor and water ports, and the air in the operant chamber was removed by another exhaust fan through a host mounted on the ceiling of the chamber to outside the laboratory building.

The odorants used in the olfactory CDNMTS task were acetophenone, amyl acetate, anethole, butanol, carvone, eugenol, limonene, phenethyl alcohol. The odorants used in the olfactory discrimination task were eugenol (S+) and amyl acetate (S-).

A PC computer and interfaces were used to control all the

procedural events and recorded all the behavioral responses.

Presurgical Training

Dipper Training. Water-deprived rats were trained to lick at the water spout. Licking of water spout was rewarded by 0.1 ml water, delivered on a FI 5 second schedule. Two sessions of total 120 trials were given during which the house light stayed on. On the first day of the training, it was noticed that the rat would spend much of the time exploring the operant chamber. To facilitate early stage of training, a 3-sided, wooden enclosure (23 cm x 18cm x 20.5 cm) was used to restrict the rat to the immediate area of the odor and water ports during the rest of dipper training.

Shaping. Subjects were then trained to insert their nose into the odor port prior to responding to the drinking spout. For each trial, the houselight was turned on, and a nose poke in the odor port resulted in the delivery of one of the eight odorants. If the odor port photocell beam was continuously broken for 0.2 s, a following response to the drinking spout within 4 s was reinforced with 0.1 ml water. The trial was terminated at the end of the 4 s after the odor port response, regardless of whether the rat responded to the water port, and the house light was turned off. During the following 5 s intertrial interval the house light remained off. The starting of next trial was signaled by turning on the houselight. During the shaping session a different odorant was used on each trial. After two 60-trial sessions, the rat were trained

for another two sessions in which odor port response requirement was increased from 0.2 s to a continuous 0.5 s.

Olfactory continuous delayed non-match to sample (CDNMTS). The first trial was conducted in the same way as the shaping trials: the house light was turned on, an 0.5 s odor port response followed by a response to the drinking spout within 4 s produced 0.1 ml water. The trial terminated at the end of the 4 s response window singled by extinguishing the house light regardless of whether a response to water port was made. A 5 s ITI was followed during which the house light remained off. The house light was turned on indicating the start of the next trial. For the rest of the trials, on half of them the odorant was the same as the odorant in preceding trial (matching or S- trials), on the other half of the trials the odorant presented was different from the odorant on the preceding trial (non-matching or S+ trials). On non-matching trials, a response to the drinking spout within the 4 s response window was reinforced and the response was recorded as a "hit", failing to response to the drinking spout within the response window was recorded as a "miss", the termination of the trial was following by the 5 s ITI. On the match trials, a lick at the drinking spout within 4 s after the odor port response was counted as a "false alarm", and resulted in the immediate offset of the house light for the remaider of the 4 s response window and throughout a 5 s "time out" period, followed by the 5 s ITI with the lights remaining off.

If a drinking response did not occur within 4 s a "correct rejection" was recorded, the trial was terminated, and the 5 s ITI was initiated.

Throughout the experiment, false alarm responses were followed by correction procedures. Correction trials consisted of a repetition of the S- trial on which the false alarm occurred. If the rat responded again (a second false alarm), a second correction trial was followed. The irregular S+/S- trial order was reinstated following the second correction trial, regardless of how the rat responded. Correction trials were not counted in the number of trials per session and performance on correction trials were not included in the performance analysis.

One 70-trial session was run daily. The order of S+ and S- trials was decided randomly on an irregular but balanced schedule. The actual order of odorants was held constant within sessions but varied between sessions.

Initial training of about 600 trials showed that false alarms constituted the majority of errors and misses rarely occurred, which was consistent with Koger & Mair's finding (1994). Compared to this earlier study, the response window was then changed from 4 s to 2 s and the ITI was changed from 5 s to 4 s. So, the minimum retention interval was 6 seconds (2 s response window plus 4 s ITI). The changes remained throughout the rest of presurgical training and postsurgical training.

Following completion of a minimum of 4,500 trials, subjects were rank ordered based on their performance in the most recent six sessions, and they were then matched by performance and randomly assigned to one of the six treatment conditions: sham control, excitotoxic lesions in pyriform cortex, the lateral entorhinal cortex, the L-IML, the MDn, and the nonspecific nuclei of thalamus.

Surgery

Rats were anesthetized by i.m injection of a combined dose of ketamine (90 mg/kg) and Rompun (10 mg/kg). Surgery was performed under sterile conditions using a Kopf stereotaxic instrument with the incisor bar set at 3.3 mm below the interaural line (IA). The skull was opened with sterile surgical procedures. Lesions were produced by injection of 100 mM N-methyl-D-asparate (NMDA) using a Hamilton 10 ul 701 series syringe, which was driven by a Kopf microinjection unit at a speed of 0.2ul per minute, and the needle was left in place for another minute before removal. Lesions were placed in following areas: pyriform cortex (n=6), lateral entorhinal cortex (n=7), L-IML (n=8), MDn (n=7) and nonspecific nuclei (n=7) of thalamus.

For pyriform, the lateral entorhinal cortex, and the L-IML lesions, there were 6 injection sites in each hemisphere, .8ul of 100 mM NMDA per injection site. For the MDn and nonspecific lesions, 3 injections were given in each hemisphere, .4ul of 100 mM NMDA per injection site. Sham-

operated controls were treated like lesioned rats, except that no injection was made. The following table shows coordinates used for all lesions.

Stereotaxic Coordinates for excitotoxic injections (in Millimeters)

AP	DV	ML
	Piriform cortex	
+12.2	+3.2	+3/-3
+10.7	+2.4	+4/-4
+ 9.2	+1.8	+4.6/-4.7
+ 7.7	+1.0	+5.3/-5.3
+ 6.2	+0.6	+5.8/-5.9
+ 4.7	+0.8	+6.5/-6.5
	Entorhinal cortex	
+4.2	+1.5	+6.5/-6.5
+3.2	+1.5	+6.2/-6.2
+2.2	+2.2	+4.4/-4.4
+2.2	+2.2	+5.4/-5.4
+1.2	+3.2	+4.8/-4.8
+0.2	+5.0	+4.5/-4.5
	Lateral internal medullary lamina	
+5.2	+3.6	+1.0/-1.0
+5.2	+4.8	+1.0/-1.0
+6.2	+3.6	+1.0/-1.0
+6.2	+5.0	+1.0/-1.0
+7.2	+3.6	+1.0/-1.0
+7.2	+5.0	+1.0/-1.0
	Nonspecific nuclei of thalamus	
+5.2	+3.6	+1.6/-1.6
+6.2	+3.6	+1.4/-1.4
+7.2	+4.0	+1.4/-1.4
	Mediodorsal nucleus of thalamus	
+5.2	+3.8	+0.6/-0.6
+6.2	+4.6	+0.6/-0.6
+7.2	+4.8	+0.6/-0.6

Anterior-posterior (AP) coordinates were measured from the interaural line (IA), medial-lateral (ML) coordinates were measured from the center of the cerebral sinus and

dorsoventral (DV) coordinates were measured relative to the surface of cortex.

The introduction of an excitotoxin into the mammalian CNS typically produces intense gliosis and loss of parvicellular neurons. The neurotoxic process of NMDA occurs over a relatively short time, less than 24 hours.

Postsurgical Training

Reacquisition. After recovery from surgery, water deprivation was reinstated and subjects were retrained on olfactory CDNMTS the same way as during presurgical training for 15 days, a 70-trail session per day (1050 trials total).

Manipulation of retention interval. In the olfactory CDNMTS procedure the ITI is functionally equivalent to the retention interval. The effects of increasing the ITI were first examined by mixing five different lengths of ITIs, ranging from 4 seconds to 20.25 seconds, within a 60 trial session. A block of 12 trials was run on each delay before moving to the next delay. As the order of delay presentation was randomly chosen without replacement for each session, and trials were grouped in blocks, this manipulation is referred to as random ordered by blocks procedure. A total of 420 trials were conducted on this procedure.

Rats were then trained on another procedure designed to test the effect of increasing ITIs, which is referred to as random ordered by trials procedure. The same five delays were used, except that the delay was randomly chosen for each individual trial, instead of blocks of 12 trials for each

delay. As the delay for each trial was chosen by a random with replacement program, there might be unequal number of trials for each delay within a session. Seven 60-trial sessions of random by trials were conducted.

Stimulus set manipulation. In order to examine the interference effect, the size of the set of odors utilized was reduced from 8 to 4 and then to 2. The number of odorants were held constant in individual sessions. A block of five sessions (70 trials per session) were conducted at each odor set size. For sessions with fewer than 8 odorants, different subsets of stimuli were utilized during each of the sessions. In order to measure the cumulative proactive interference effects within a session, the performance in each session was recorded as blocks of 10 trials, the first 10 trials, the second 10 trials, etc. Each session was thereby subdivided into sevenths.

Task verification. The solenoids and relays that controlled the delivery of odorants generated many auditory stimuli during olfactory CDNMTS training. In order to verify that the olfactory stimuli, not these sounds, served as discriminative stimuli, one verification session was conducted. The tubing from the odor delivery flowmeter was disconnected during the verification session. Nose poke in the odor port resulted in delivery of clean air stream instead of an odor stimulus.

Discrimination training. The procedure for this go-no-go

discrimination task was the same as the olfactory CDNMTS, except that only eugenol and amyl acetate were used in each session, with eugenol served as S+ stimulus and amyl acetate as S- stimulus. A minimum of 12 sessions (840 trials) of discrimination task were conducted for each subject.

Quantitative Analyses

Only rats with complete or near complete lesions were included in final data analyses. Subject #206 in L-IML group was excluded for incomplete lesion. Performances of the six treatment groups, measured in proportion of correct, were analyzed using ANOVA with repeated measures. If the overall F value was not significant, the analysis was terminated without comparing the performances among individual groups. If the overall F value was significant, Post Hoc comparisons were conducted using the Newman-Keuls procedure. This procedure maintains the type I error rate at alpha for each comparison, rather than for the complete set of comparisons as in the Tukey Honestly Significant Difference (HSD) procedure (Pagano, 1990). Therefore, it is more powerful than the Tukey HSD procedure.

Performances of the treatment groups were also compared using planned comparisons. In planned comparisons, each lesioned group was compared with the sham control group individually. Planned comparisons are more powerful than Post Hoc procedures in detecting differences among groups. As the literature review and anatomical analyses have suggested that

lesions of the five sites included in this study are likely to affect olfactory learning and memory (see introduction section for details), there are theoretical ground to do the planned comparisons of each lesioned group with the controls.

Histological Analyses

Upon completion of all behavioral training, animals were sacrificed under deep anesthesia by transcardiac perfusion of physiological saline followed by 10% neutral buffered formalin. The brains were extracted and stored in the formalin solution until they were sectioned in the coronal plane at 30 um. Every fifth section was mounted onto gelatinized slides and stained with cresyl violet. The placement and extent of lesions were then verified by two independent observers who were unaware of the surgical treatment and behavioral performance of the individual animals being examined.

Results

Presurgical Performance

The performance of the six groups during the six sessions (420 trials) immediately preceding surgical treatment was assessed using a one-variable, between subject analysis of variance (ANOVA). There was no significant difference between the groups, $F(5,35) = .351$, $p = 0.88$, indicating the treatment groups were well matched presurgically (see table 1).

Initial Postsurgical Training

The average performances of each group during the 15 sessions (1015 trials) of initial postsurgical training are shown in Table 2. All the five lesion groups exhibited some degree of initial impairment and subsequent improvement in performance with continued training (see Fig.1). A two-variable ANOVA (session x treatment) revealed a significant effect of treatment, $F(5, 35) = 8.30$, $P = 0.0001$; and a significant difference across sessions, $F(14, 490) = 20.86$, $P < 0.0001$. The interaction between the treatment and training sessions did not reach statistical significance, $F(70, 490) = 1.22$; $P = 0.122$. Planned comparisons (Table 3) with controls showed significant differences for the L-IML and pyriform groups. Post hoc analyses (Student-Newman-Keuls $\alpha = 0.05$) revealed that pyriform group performed significantly worse than did any other treatment group, while the L-IML group was significantly different from the control and nonspecific lesioned groups. For individual performances see Figure 13.

Manipulation of Retention Interval

Random ordered by trials. In this manipulation, the order of delay presentation was decided by a random with replacement procedure on a trial by trial basis. This delay manipulation procedure did not produce a clear trend of temporal decay (see Fig. 2). In general, performance accuracy seemed to be at the best with 9 seconds delay and fell off with shorter and longer delays. The entorhinal, non-specific and control groups did not seem to differ from each other, pyriform group performed

worst across all the delays, with the L-IML and MDn groups moderately impaired. A two-variable (treatment x delay) ANOVA revealed a significant treatment effect, $F(5, 35) = 6.94$, $P = 0.0001$ and a significant delay effect, $F(4, 140) = 3.71$, $P = 0.007$. The interaction between treatment and delay did not reach statistical significance, $F(20, 140) = 0.61$, $P = 0.9$. Planned comparisons (Table 3) showed that the pyriform, L-IML and MDn groups were significantly different from the controls. Post hoc analysis (Student-Newman-Keuls, $\alpha = 0.05$) showed that the pyriform and MDn groups were impaired comparing to control, nonspecific and entorhinal groups, but they did not differ significantly from each other or from L-IML. The average performances of each group with the random by trials procedure appear in Table 4.

Random ordered by blocks of trials. The same five delays, ranging from 4 to 20.25 seconds, were used in this manipulation. A block of 12 trials was run on each delay, the order of delay presentation was decided randomly without replacement for each session. The random by blocks manipulation produced a slightly different pattern in performance (see Fig. 3). For sham control and the MDn lesioned groups, performance accuracy decreased as the retention interval increased from 4 to 20.25 seconds. For the L-IML and the non-specific lesion groups, performance was at the best level with retention interval of 13.5 seconds and less accurate at longer or shorter delays. A similar trend was

reported in rats with RF L-IML lesions by Koger and Mair (1994). No clear trend was detected in performance of pyriform lesion group, most likely due to a floor effect. A two-variable (treatment x delay) ANOVA revealed a significant group difference, $F(5, 35) = 3.14$, $P = 0.019$, and a significant delay effect, $F(4, 140) = 4.03$, $P = 0.004$. The differential effects of delays was not supported by the analysis, since the interaction between treatment and delays did not reach statistical significance, $F(20, 140) = 1.55$, $P = 0.0739$. Planned comparisons (Table 3) showed that only pyriform lesion group was significantly worse than controls. Post hoc analysis (Student-Newman-Keuls, $\alpha = 0.05$) showed that rats with pyriform lesions performed significantly worse than did any other treatment group. The average performances of each group are summarized in Table 5.

Manipulation of Stimulus Set Size

The effects of the stimulus set size was assessed by reducing the number of stimuli used in a session from 8 to 4 and to 2; and the accumulation of proactive interference within the course of a session was measured by dividing the session into seven 10-trial blocks. As showed in Fig. 4, for all the groups, performance accuracy decreased as the number of stimuli reduced from 8 to 2; and in general, proportion correct decreased along the course of a session. These trends were verified by a three-variable (treatment x number of odors x block) ANOVA. The analysis showed a significant effect of

treatment, $F(5, 35) = 3.2$, $P = 0.0157$; odor set size, $F(2, 70) = 233.1$, $P = 0.0001$; and block, $F(6, 210) = 3.66$, $P = 0.0018$. A significant interaction between block and number of odors was also observed, $F(12, 60) = 2.25$; $P = 0.009$, indicating that the proactive interference accumulated within sessions at different rates when different number of stimuli were used (see Fig. 4). But the interaction between group and block, group and odor set size, or the three way interaction did not reach statistical significance. Planned comparisons (Table 3) showed that the pyriform group performed significantly worse than did controls, while the difference between the L-IML group and the controls was nearly statistically significant ($P = .051$). Post hoc analysis (Student-Newman-Keuls, $\alpha = 0.05$) showed that the pyriform group was impaired comparing to other groups. The average performance of each group with different number of odor stimuli is summarized in Table 6.

Verify Session

When the odor delivery tube was disconnected, the performances of both controls and lesions fell to chance level (table 7). A one factor ANOVA showed no group effect, $F(5, 35) = 1.14$, $p = 0.36$. The poor performance was characterized by increased false alarm rate, which indicates that the natural bias in the olfactory CDNMTS task is to respond on all trials when the stimulus information is ambiguous.

Discrimination Training

All the groups, even the pyriform group, which showed the

most severe impairment on CDNMTS under all the manipulation conditions, learned the discrimination task (Fig. 5). This was confirmed by a two-way ANOVA (group x session), which showed no difference between the groups ($p = .36$). But there was a significant effect of session, $F(11, 385) = 78.2$, $p = 0.0001$, and significant interaction between group and session, $F(55, 385) = 1.46$, $p = 0.024$, indicating that although the performance of each group improved at different rate across the 12 sessions, they all learned the task and eventually performed at a level no different from the controls. The average performances of all the treatment groups are summarized in Table 8. For individual performances see Figure 13.

Lesion Analyses

The brain sections were examined under a light microscope, and lesions were traced using a drawing tube onto templates. Three drawings were made for each of the lesioned subjects in the L-IML, MDn and non-specific groups, at levels of 7.2, 6.2 and 5.2 mm relative to interaural line (IA). The maximum and minimum lesions of each group are shown in figure 6, 7, and 8, respectively. The gray areas represent the maximum lesions and black areas represent the minimum lesions of the group.

For the entorhinal group, the lesions were described at three levels, 3.7, 2.2 and 0.7 mm relative to IA. The maximum entorhinal cortical lesion is shown in figure 9, and the minimum entorhinal cortical lesion is shown in figure 10. Five

drawings were made for each rat in pyriform-lesioned group, at levels of 12.7, 10.7, 8.7, 6.7, and 4.7 mm relative to IA, reflecting the anterior and posterior dimensions of the lesion. Figure 11 and 12 show the maximum and minimum lesions of pyriform cortex.

All subjects except rat #206 in L-IML group were judged to have complete lesions, and were included in the quantitative and histological analyses.

Discussion

The Reacquisition of Olfactory CDNMTS Task

As expected, performance dropped for all the treatment groups on olfactory CDNMTS on the first day of training after surgery. As can be seen from Fig. 1, there was improvement in performance for all groups over subsequent training. The non-significant interaction between group and session indicates that groups improved at a similar rate over the course of the fifteen recovery sessions. However, the level of performance accuracy was not the same for each group. The pyriform group performed more poorly than did any other five groups. The rats with L-IML lesions were impaired compared to the controls and rats with nonspecific lesions.

The impairment observed in rats with L-IML lesions is consistent with a previous study by Koger and Mair (1994), in which they found that RF lesions of L-IML region disrupted performance of the olfactory CDNMTS task in rats. However, the

impairment of the L-IML-lesioned rats in the current study was less severe comparing to that of in Koger and Mair's study (1994), 58.6% of performance accuracy in their study compared to that of 75.6% in the current study. There are several possible explanations. One of which is that the excitotoxic lesioning technique used in this study spared the fibers of passage while damaged the nuclei of target, while RF lesioning technique used in Koger and Mair's study produced nondifferential lesions of both fibers and nuclei of the target areas. The sparing of fibers and the relatively less extensive lesions may account for the difference in the severity of the behavior deficits observed in the two studies. Another possible explanation is that rats in the current study were trained more extensively and reached a higher accuracy level, 86.7%, before surgery comparing to the rats in their study, whose average presurgical performance accuracy level was only 74.5%.

Rats with pyriform lesions were most severely impaired on olfactory CDNMTS task under all the task manipulation conditions. This may be explained by the anatomical significance of the pyriform cortex in the olfactory central pathway. After all, it is the major source of olfactory information to thalamus, neocortex, and many other brain areas.

Neuroanatomical evidence has shown that entorhinal cortex is the major source of projections and the only source of

olfactory information to the hippocampus and dentate gyrus. Hippocampus has been implicated as a critical structure in a number of studies of temporal lobe amnesia (Squire & Zola-Morgan, 1991; Horel, 1978). Therefore, there is a basis to speculate that damage to the lateral entorhinal cortex might affect olfactory memory. However, the current study did not provide evidence to support this speculation. Rats with entorhinal lesions showed no impairment on the olfactory CDNMTS task. This result is consistent with the findings that entorhinal cortical lesions did not impair odor discrimination learning (Otto, Schottler, et al., 1991) or initial acquisition of the olfactory CDNMTS task (Otto & Eichenbaum, 1992b). However, Otto and Eichenbaum (1992b) demonstrated that rats with entorhinal cortex aspirated showed more rapid forgetting on the olfactory CDNMTS task when delays increased from 3 to 60 seconds, which was not confirmed by the present study.

Although the role of MDn in memory in general remains controversial, the connections of the MDn with the olfactory cortex, the neocortex, and other areas suggest that the MDn may involve in olfactory memory processing. However, results from this study indicated that an intact MDn was not necessary for the performance of olfactory CDNMTS task. This result is consistent with the finding in Koger and Mair's (1994) study, in which they demonstrated that lesions of rhinal sulcus and medial wall areas, which are innervated by the MDn, do not

result in long lasting olfactory CDNMTS impairment.

Based on a series of experiments on an animal model of Korsakoff's syndrome, Mair (1994) has proposed that nonspecific nuclei may play a critical role in diencephalic amnesia. Non-specific nuclei lesions in this study did not show impairment on the olfactory CDNMTS task. Unfortunately, there is no existing study of non-specific nuclei for a comparison. Histological analysis suggested that the non-specific nuclei lesions in the current study were not extensive enough to include all the non-specific nuclei. To test the possibility that more extensive non-specific nuclei would show significant deficits, another group of rats with excitotoxic lesions including all nonspecific nuclei are in training now. The training procedures are kept the same. The primary data showed that rats with more extensive non-specific lesions were impaired on the reacquisition of the olfactory CDNMTS task.

Manipulation of Retention Interval

The purpose of this manipulation was to employ multiple delays to test whether impairments are exacerbated by temporal decay or an abnormally rapid rate of forgetting. One hypothesis in this study was that increasing retention interval would affect lesioned groups differently from the controls. Data collected from both random by trials and random by blocks of trials procedures showed that the interaction effect of group and delay did not reach statistical

significance, indicating that increasing retention interval did not affect the lesioned groups differently from the controls under both conditions. In other words, the reason that rats with L-IML and pyriform lesions were deficient on olfactory CDNMTS task was not due to fast forgetting.

There are several possible reasons for the lack of temporary decay among lesioned groups in this study. First, it may reflect the characteristic of odor memory itself. For normal human subjects, unlike visual and auditory memory, odor memory remains intact as time passes. As Engen (1991) stated that "the most prominent feature of odor memory is its imperviousness to time", and " even the memory of poorly learned odors remains unchanged". The same is true for human Korsakoff patients. Korsakoff patients showed no temporal decay when tested on an olfactory short-term recognition memory over three delay intervals, 5, 15 and 30 seconds (Mair, Capra, McEntee, & Engen, 1980). But when the same K orsakoff subjects were tested on short-term recognition of pictures of human faces and recall of consonant triagrams task, their performances dropped as the retention interval increased, at a rate faster than that of the controls.

The other possible reasons may lie in the nature of the olfactory CDNMTS task. In general, interference of previous trials with subsequent trials diminishes and performance accuracy improves as ITI increases (Dunnett & Martel, 1990; Pontercorve, 1983). Thus, within certain range, ITI and

retention interval have opposite effect on performance accuracy. In the olfactory CDNMTS task, ITI and retention interval were functionally equivalent. Any potential decline in response accuracy with increasing the retention interval, therefore, may be obscured by the decreased proactive interference associated with increasing ITIs.

Comparing the results from the two types of delay manipulations, it is found that the L-IML and MDn groups performed more poorly in the random by trials procedure (significantly different from the controls) than in the random by blocks of trials procedure (not significant different from controls). One possible explanation is that when delays are chosen on a trial by trial basis, animals must adapt to sudden shifts of delays, because under this procedure, the delays on consecutive trials can differ dramatically. For example, a 4 second delay can be followed by a 20.25 second delay or vise verse. The irregularity and sudden drastic change in delays from trial to trial may have adversely affected rats' performance.

Manipulation of Odor Set Size

Previously learned information can result in the rapid forgetting of more recently learned information, a phenomenon called proactive interference. Proactive interference is the major cause of forgetting in everyday life. In laboratory experiments the degree of proactive interference was prominent in comparison with the degree of retroactive interference

(Wixed & Rohrer, 1993). The major factors that affect proactive interference in the olfactory CDNMTS task are the number of stimuli used and the position of the trial within a session. When a large number of odorants are used, the individual odors are repeated only occasionally within a session, whereas when a small odor set is utilized, individual odors are presented more often. As in the olfactory CDNMTS task, each stimulus acts both as a sample and as a test stimulus, the more frequent a stimulus is repeated within a session, the more interitem interference it creates. The interference effects may also accumulate across a session, as the number of trials increases. Reducing the number of odors used within a session has been demonstrated to decrease the performance accuracy of normal rats and rats with lesions in rhinal sulcus, medial wall or L-IML regions on olfactory DNMTS task (Koger & Mair, 1994; Otto and Eichenbam 1992b). Koger and Mair (1994) also found that when sessions were divided into the initial, middle, and final blocks, the performance in the final third of a session was significantly worse than that of in the first third of a session, indicating a trend of performance decay over the course of a session. This trend was most evident when only two or four stimuli were used within a session.

Results from the current study confirmed the effects of odor set size observed by Koger and Mair (1994) and Otto and Eichenbam (1992b). For all the treatment groups, the

performance accuracy decreased as the number of odors used within a session reduced from 8 to 2. There was also significant accumulation of proactive interference within a session assessed by comparing the performance in seven blocks of 10 trials. However, there was no significant interaction between group and block, or group and number of odors, indicating that the lesioned animals were no more susceptible to interference than controls. Thus, the hypothesis that the impairment on olfactory CDNMTS following medial thalamic or olfactory cortical lesions may be attributable to their increased susceptibility to proactive interference has not been substantiated.

Verification of the Task

When the odor tube was disconnected, performance of rats on olfactory CDNMTD task in all the six groups dropped to a non-differential and chance level. This result demonstrated convincingly that olfactory stimuli, not auditory or other stimuli, worked as discriminative stimuli that guide this task. As the errors were constituted by dramatically increased false alarm rate, it suggests that rats have a natural bias to increase frequency of responding when under uncertain situation.

Discrimination

Rats in all the groups, learned the discrimination task. The most dramatic and interesting finding came from the pyriform group. The rats following pyriform lesions were so

severely impaired on olfactory CDNMTS task, however, they learned the discrimination task as well as and at a rate comparable to the controls. In fact, the performance of two rats with the complete pyriform lesions in this study reached an accuracy level of over 90%. The result indicated that pyriform cortex, the largest primary olfactory cortex, was apparently not critical for simple odor discrimination, although it is essential for olfactory CDNMTS task. In other words, pathways other than the central olfactory pathways were sufficient to mediate basic sensory function.

General Discussion

The Nature of the Behavioral Deficits

How to interpret the impairment observed in rats following lesions in the L-IML sites and pyriform cortex? There seem to be several possible ways that the olfactory CDNMTS task can be impaired. First, the deficits may result from sensory dysfunction, in other words, rats with the L-IML and pyriform lesions could not discriminate the difference between odors. Second, the deficits may reflect motor dysfunction, such as hyperactivity or inability to inhibit responses. Third, the lesioned rats may have difficulty to learn the procedural aspects of the task, which may account for the olfactory CDNMTS deficits. The procedural aspects of the task include first breaking the photo cells in the odor port, keeping nose in the odor port for at least 0.5 second, responding to water

port within the 2 second response window on S+ trials, and withholding response to water port on S- trials. Fourth, the impairment on olfactory CDNMTS may due to increased vulnerability to proactive interference of the lesioned rats. Finally, the lesioned rats might have been unable to remember the previous odorant across delay, or could not establish the correct association among the discriminative stimuli and responses. In other words, the olfactory CDNMTS deficits may reflect dysfunction in memory, or other cognition processes, such as association or attention. However, the normal performance of two-odor discrimination task by rats in all the treatment groups rules out the first three possibilities. Because in order to make the correct responses in the go/no-go simple discrimination task, the subject has to be able to differentiate one odor from the other; to be able to suppress responses to S- stimuli; and to be able to master all the procedural requirements of the discrimination task, which are similar to olfactory CDNMTS task. The fourth possibility, increased susceptibility to proactive interference for the lesioned rats, can not be established, either, because the proactive interference measured by the effects of odor set size used in a session had equivalent effects on all the treatment groups. It seems very likely that the olfactory CDNMTS impairments observed following the L-IML and pyriform lesions reflect working memory deficits. Two lines of evidence support the memory deficits argument. First, L-IML lesions

have been shown to impair performance on other working memory tasks that require rats to remember information about auditory and spatial cues (see Introduction for details). Second, the olfactory CDNMTS task fits the definition of working memory, and is conceptually analogous in memory demands to those visual and spatial DNMTS tasks.

Stevens (1995) argued against the interpretation of the effects of medial thalamic lesions as working memory deficits. He suggested that for a working memory deficit to be established, it would require that conditional discrimination performance be intact when no delay is present. If behavior is impaired at zero delay, the deficit would reflect an impairment that was not specifically related to memory function. If, however, a brief delay is necessary to disrupt performance, then the deficit can be attributed to processes that are specific to the initial stages of remembering. In the current study, The L-IML and pyriform groups showed impairment when tested at the shortest delay, suggesting that such a deficit may be present without a delay. But for olfactory CDNMTS task it impossible to have delays less than 4 seconds due to the minimum time needed for exhausting and changing of the odors between trials. Moreover, some investigators argued that performance with zero delay is not critical, because change in discriminability from a given delay is independent of the levels of discriminablility at earlier delays (White 1985), and variations in the degree of learning generally have

no effect on forgetting rate (Slamecka 1985).

It appears that the olfactory CNMTS deficits following L-IML and pyriform lesions result from an impairment in the ability to remember information across delays and to update information across trials, that is a working memory deficit. But there may be other possible explanations. For instance, the lesioned rats maybe unable to efficiently form the association among the odorants and responses, and to modify the associations flexibly across trials, which are necessary for successful performance of the olfactory CNMTS. In the olfactory CNMTS task, each odorant serves as both a choice stimulus, with respect to the preceding trial, and as a sample stimulus, with respect to the following trial. The availability of reinforcement depends on the whether the current odorant is the same or different from the odorant on previous trial. The presentation of any particular odorant may signal the availability of reinforcement on some trials, and signal the unavailability of reinforcement on other trials, because it is the change in odorant, not particular odorants, serves as the cue for reinforcement. Therefore, in order to make the correct responses, the subjects have to not only remember the previous odorant across the retention interval, but also continuously modify the association between a particular odorant with response. The complexity in response contingencies and constant change in association are not present in simple discriminations, in which the association

are held constant, one stimulus is always associated with reinforcement while the other never is. Thus, it is possible that the impairments on olfactory CNMTS reflect that fact that the lesioned rats were unable to establish the flexible associations among the discriminative stimuli and responses that are necessary to perform the task. The same rats were able to perform the simple discrimination task, in which such association requirements are absent. Sufficient presurgical training can largely reduce postsurgical deficits that are caused by impaired acquisition of the non-mnemonic skills, such as the procedural steps and associative function, that are required to perform the task. In the present study, all the subjects received extensive presurgical training. All the lesioned rats correctly performed all the steps required to perform the olfactory CDNMTS task even on the first day of postsurgical training, although their performance accuracy dropped compared with their presurgical performance. Thus, the deficits observed after surgery were unlikely due to rats' inability to meet the procedural or other nonmnemonic demands of the task.

Implication in Diencephalic Amnesia

In general, different behavioral tasks are used to test brain-damage-induced amnesia for different species. Some tasks used to test the effects of medial thalamic lesions in humans, monkeys and rats share some common properties. For example, the odor recognition task for humans, the nonrecurring-items

objective recognition task for the monkey, the spatial delayed NMTS task for the rat, and the olfactory CDNMTS task in the present study are all analogous in term of the memory demands. In all the above tasks, a sample stimulus is present, following a delay, either the sample stimulus or a novel stimulus (as in human odor recognition and olfactory CDNMTS tasks in rats), or both of the sample and novel stimuli (as in objective recognition task in monkeys and the NMTS in rats), are presented. To perform correctly on any of these tasks, the subject must remember the sample stimulus throughout the delay interval, and this particular sample stimulus changes from trial to trial. Tasks with this kind of memory demands are referred to as working memory tasks, or short term recognition memory. Another group of tasks, the odor detection task in human, visual pattern discrimination task in the monkey, the spatial serial reversal task in the rat, and the two-odor discrimination task in the present study, are analogous in the memory demands that can be described as reference memory procedures. Because in all of these tasks, the stimulus-response contingencies are fixed and the strategy of responding is the same on every trial.

The similarities in the behavioral tasks for different species provide a broader comparative basis for making inferences about the nature of the behavior deficits and their anatomical bases. Ultimately, the comparative analyses of the pattern of behavioral deficits following damage in

diencephalic brain areas in human and animals contribute to a better understanding of "diencephalic amnesia" or Korsakoff's syndrome in human.

As reviewed in the introduction section, human Korsakoff patients appear to be impaired on olfactory recognition task, but not on odor detection task (Mair, Capra, et al., 1980). It has been reported that monkeys with bilateral lesions in thalamus show a marked deficit on the trial unique delayed NMTS or object recognition task, and normal performance on learning pattern discrimination problems (Aggleton & Mishkin, 1983a; Zola-Morgan & Squire, 1985). In the rat, PTD treatment and L-IML lesions are found to impair spatial NMTS task, but spared spatial serial reversal task (Knoth & Mair, 1991; Mair & Lacourse, 1992; Harrison & Mair, 1996). For humans, monkeys and rats lesions of medial thalamus have been related to a consistent pattern of deficits, selective impairment of many tasks that require working memory, and sparing of many tasks that require reference memory.

The current study demonstrated that excitotoxic L-IML lesions in rats produce impairments of an olfactory task (CDNMTS) that shares the memory elements with the odor recognition memory for human, a task that Korsakoff patients perform poorly on. However, the same rats showed normal performance on the two-odor discrimination task, which is analogous to the human odor detection task, a task that Korsakoff patients have no difficulty with. The same pattern

was also reported by Koger & Mair (1994) in rats following RF L-IML lesions.

The Neural Mechanisms of Olfactory Memory

An important finding in this study is that rats with pyriform lesions were able to perform an odor discrimination task, although they showed very severe impairment on the olfactory memory task. The normal performance on odor discrimination indicated that the pyriform lesions do not impair the ability of rats to differentiate odors, which is consistent with the observations that transection of lateral olfactory tract at the level of the anterior pyriform cortex and the olfactory tubercle in rats did not result in anosmia (Slotnick, 1985; Slotnick & Berman, 1979; Staubli, Schottler & Nejat-Bina, 1986). However, Staubli, Schottler and Nejat-Bina (1986) showed that rats with ablations of the pyriform cortex were severely impaired on acquisition of odor discriminations; even with substantial presurgical training, they required more trials to meet criteria than controls on simple discrimination and had great difficulty learning complex problems. This observation had led the authors to conclude that "an intact pyriform cortex is needed to acquire the procedures involved to perform an olfactory discrimination task".

In the present study, the pyriform lesioned rats could perform odor discrimination as well as the controls, and learned the task at an equivalent rate as the controls. The

normal performance of odor discrimination, in addition to the fact that rats with pyriform lesions were able to correctly perform all the steps required in olfactory CDNMTS task in initial postsurgical training, indicate that they did not have difficulty in performing the procedures involved in olfactory CNMTS or simple discrimination. In contrary to Staubli, Schottler and Nejat-Bina's conclusion, the present study showed that an intact pyriform cortex is apparently not necessary for learning to perform a simple olfactory discrimination, although it is critical for olfactory memory and other higher order olfactory information processing.

The pyriform cortex is the gateway by which olfactory information reaches neocortex, the MDn of thalamus, and hippocampus via the lateral entorhinal cortex. The connectivity between the pyriform cortex and MDn, along with the similarities in deficits on olfactory tasks following pyriform and L-IML lesions, suggest that the olfactory impairments observed in the above two lesion groups may be a consequence of disconnection of the pathways between MDn and pyriform cortex. However, there are several reasons to argue against such a hypothesis. First, the present study demonstrated that the MDn lesions that damage the olfactory-related central segment of MDn do not produce any significant impairment on olfactory CNMTS. Thus, the disruption of connections between pyriform and MDn can not account for the deficits on olfactory CNMTS common to both pyriform and L-IML

lesions. Second, L-IML lesions were previously reported to impair spatial NMTS (Mair & Lacourse, 1992; Mair, Robinson, et al., 1992), spatial MTS (Stevens & Mair, 1993), radial arm maze tasks (Harrison, 1996), and serial reversal learning (Harrison, 1992). Thus, the effects of L-IML lesions on olfactory CNMTS are more likely to be the manifestation of its global effects on learning and memory, rather than the effects specific to the olfactory modality.

Lesioning the lateral entorhinal cortex or the MDn did not disrupt the olfactory CDNMTS, indicating that other olfactory pathways may be critically involved. Koger and Mair (1994) demonstrated that neither medial wall nor rhinal sulcus lesions produce persistent impairment on olfactory CDNMTS. Taken together, it seems that destruction of any of the pathways from pyriform cortex individually, pyriform-MDn, pyriform-lateral entorhinal cortex, or pyriform-prefrontal cortex, does not produce severe or lasting effects on performance of olfactory CDNMTS. It is conceivable that when one pathway is damaged, the remaining pathways are sufficient to mediate the olfactory CDNMTS. To test whether there exist parallel pathways mediating odor memory, it would be necessary to lesion pathways in combination of two or all of them. It is also possible that pyriform cortex alone is critical for olfactory CDNMTS, in other words, olfactory memory requires an intact pyriform cortex.

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APPENDIX

Table 1. The average presurgical olfactory CNMTS performance - Mean Proportion Correct (6 sessions preceding surgery).

Treatment Group	Mean	Standard Deviation
Sham Control	.873	.042
Entorhinal	.863	.064
L-IML	.856	.041
MDn	.857	.068
Non-specific	.869	.047
Pyriform	.847	.065

Table 2. The average CNMTS performance for the initial 15 postsurgical sessions - Mean Proportion Correct.

Sessions #1 - 7

Treatment Group	S1	S2	S3	S4	S5	S6	S7
Sham Control	.822	.853	.818	.804	.867	.855	.920
Entorhinal	.693	.730	.752	.774	.756	.798	.842
L-IML	.634	.712	.672	.671	.746	.743	.763
MDn	.699	.780	.822	.771	.792	.849	.851
Non-specific	.735	.839	.806	.812	.829	.873	.843
Pyriform	.646	.645	.602	.617	.640	.671	.657

Sessions #8 - 15

Treatment	S8	S9	S10	S11	S12	S13	S14	S15
Control	.912	.888	.894	.867	.871	.900	.878	.859
Entor.	.808	.808	.841	.855	.863	.869	.865	.851
L-IML	.757	.734	.812	.833	.837	.807	.806	.813
MDn	.835	.818	.848	.878	.873	.882	.867	.812
Non-spe.	.853	.827	.865	.865	.888	.869	.888	.884
Pyriform	.667	.705	.723	.730	.713	.715	.712	.738

Table 3. Planned Comparisons - Probabilities (two-tailed) for planned comparisons with Controls.

Behavioral Measure	MDn	Non-spe.	L-IML	Pyri.	Entor.
Olfactory CNMTS					
postsurgical	.201	.495	.002*	.001*	.071
delay by blocks	.544	.891	.235	.002*	.423
delay by trials	.004*	.722	.023*	.003*	.826
stimulus set size	.346	.856	.051	.003*	.445
Odor Discrimination	.603	.633	.104	.520	.938

Table 4. The effects of increasing retention intervals, random ordered by trials - Mean proportion correct.

	Retention Intervals (seconds)				
Treatment Group	4	6	9	13.5	20.25
Sham Control	.851	.866	.913	.885	.847
Entorhinal	.856	.859	.893	.887	.831
L-IML	.798	.786	.814	.784	.782
MDn	.765	.755	.794	.778	.743
Non-specific	.881	.843	.874	.883	.821
Pyriform	.727	.680	.715	.708	.732

Table 5. The effects of increasing retention intervals, random ordered by blocks of trials - Mean proportion correct.

	Retention Intervals (seconds)				
Treatment Group	4	6	9	13.5	20.25
Sham Control	.896	.867	.852	.846	.803
Entorhinal	.825	.833	.829	.809	.815
L-IML	.767	.803	.838	.841	.786
MDn	.844	.854	.825	.824	.801
Non-specific	.861	.848	.861	.885	.835
Pyriform	.731	.734	.700	.733	.703

Table 6. The effects of the number of odor stimuli within a session - Mean Proportion Correct.

	Number of odorants utilized		
Treatment Group	8	4	2
Sham Control	.848	.771	.630
Entorhinal	.808	.761	.612
L-IML	.796	.687	.589
MDn	.833	.751	.580
Non-specific	.853	.761	.650
Pyriform	.718	.657	.579

Table 7. The performance of olfactory CNMTS on verify session - Mean proportion correct.

Treatment Group	Mean	Standard Deviation
Sham Control	.517	.032
Entorhinal	.490	.027
L-IML	.496	.047
MDn	.481	.025
Non-specific	.514	.047
Pyriform	.497	.020

Table 8. The average performance of two-odor discrimination (12 sessions) - Mean proportion correct.

Treatment Group	Mean	Standard Deviation
Sham Control	.815	.103
Entorhinal	.819	.119
L-IML	.747	.117
MDn	.794	.119
Non-specific	.835	.130
Pyriform	.788	.104

Figure 1. Initial Postsurgical Training (15 sessions).

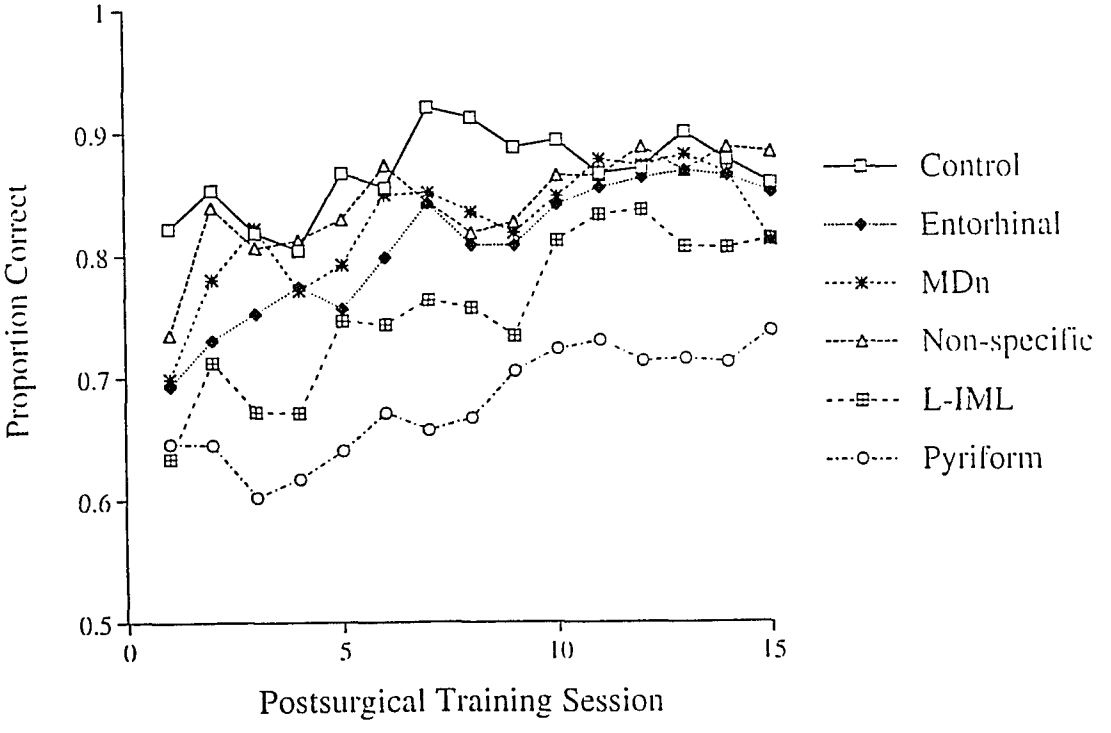

Figure 2. The Effect of Retention Interval - Random by Trials.

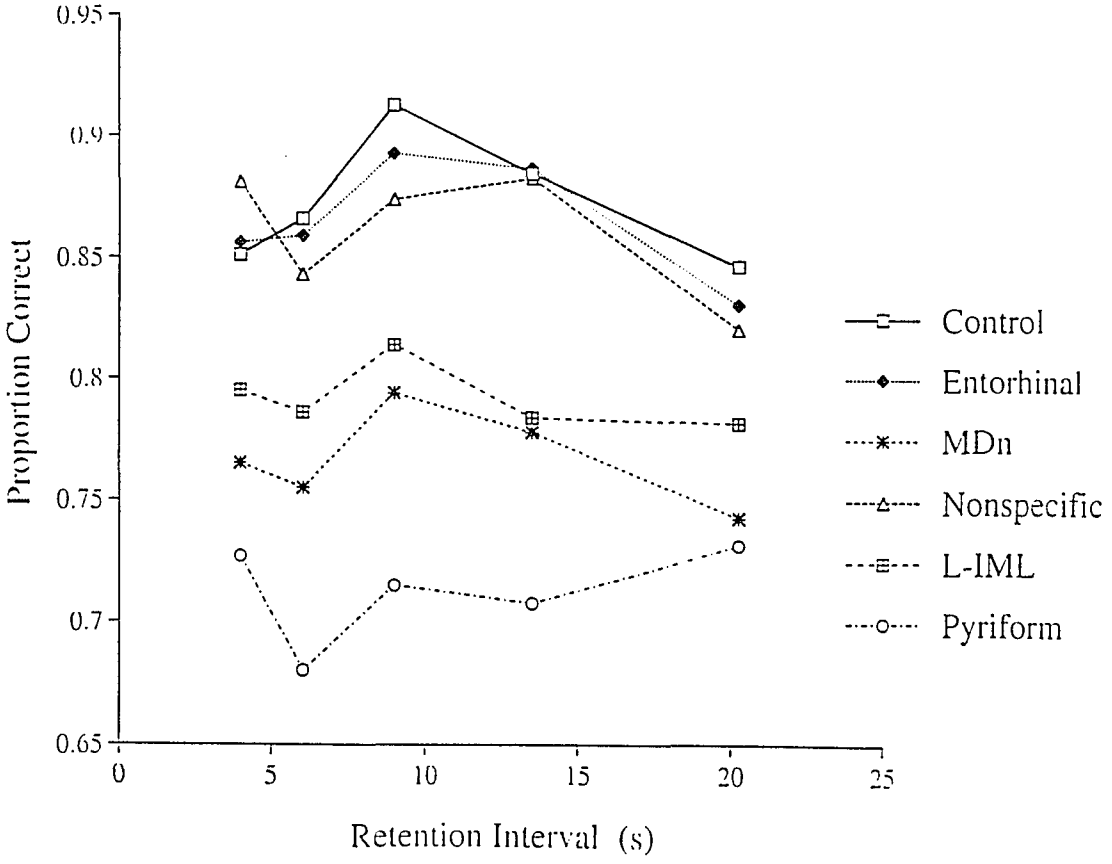

Figure 3. The Effect of Retention Interval - Random by Blocks of Trials.

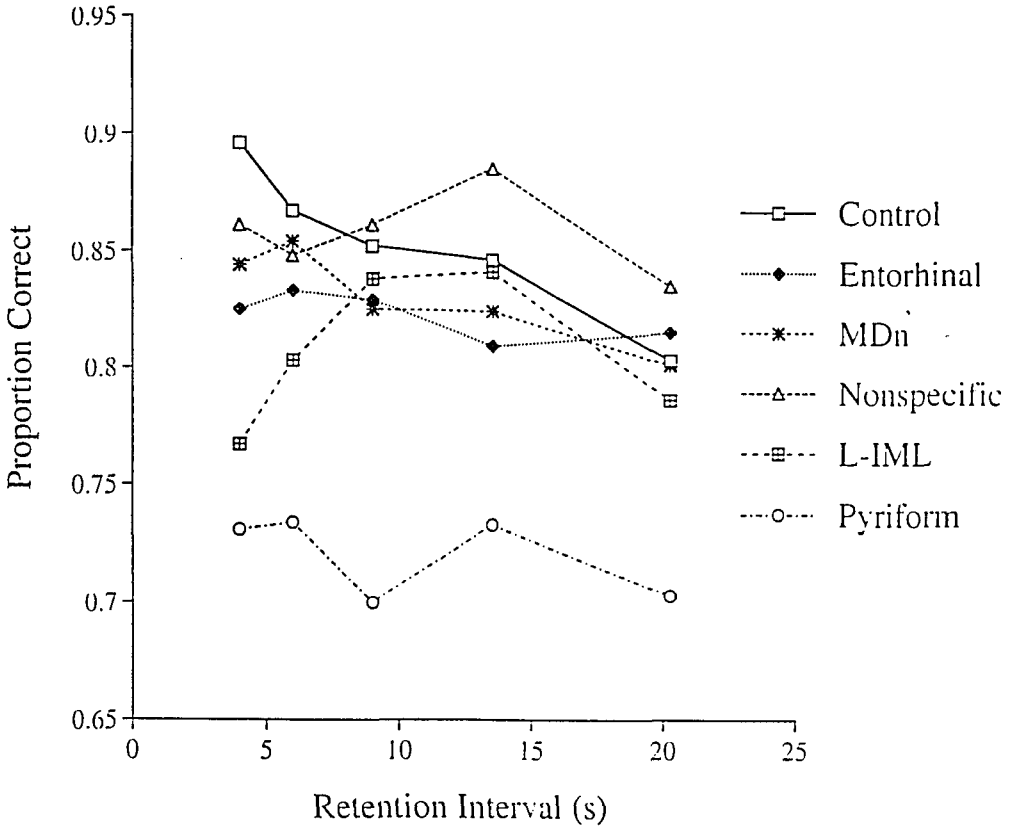

Figure 4. The Effects of the Odor Set Size.

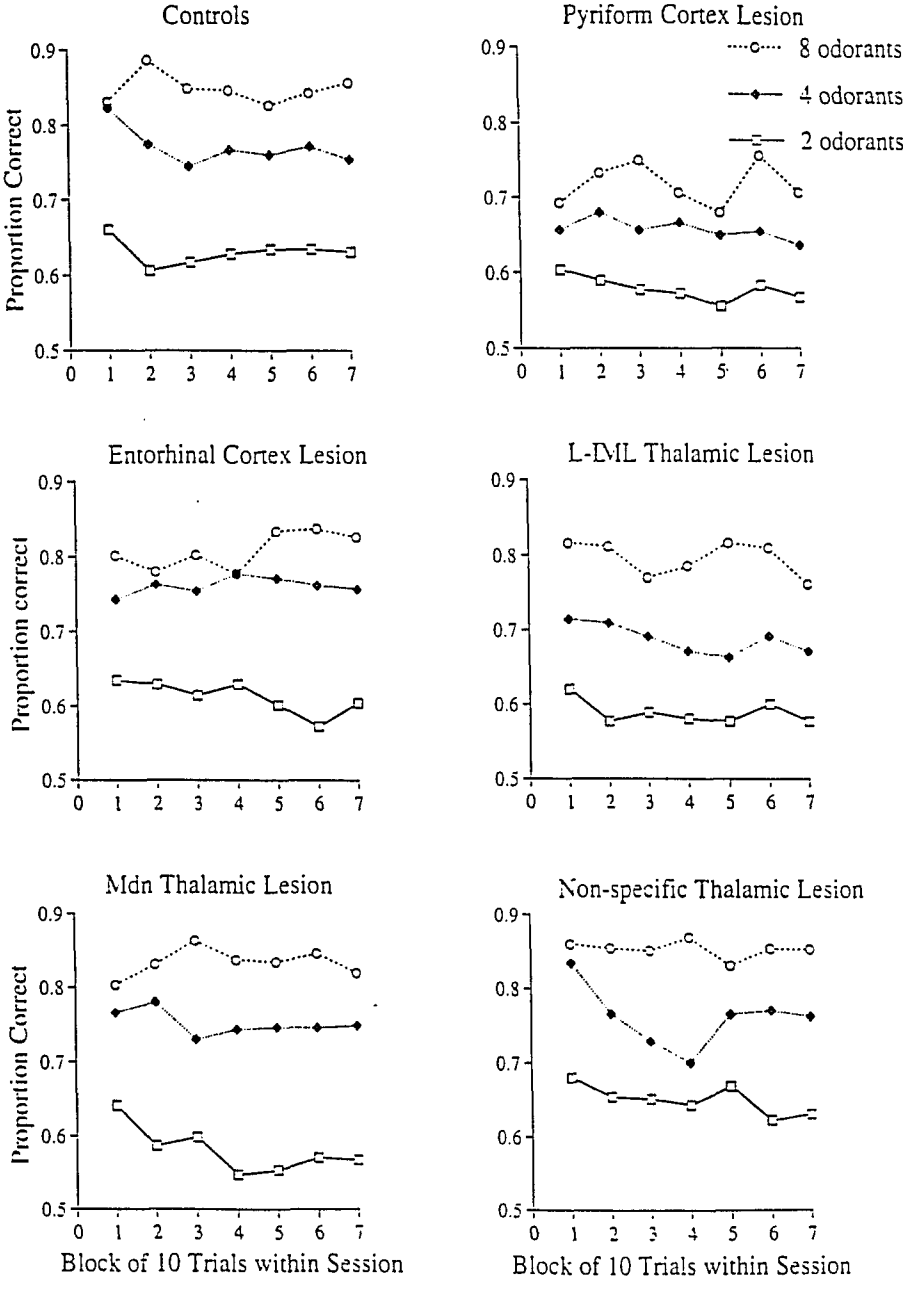

Figure 5. Performance on Two-odor Discrimination.

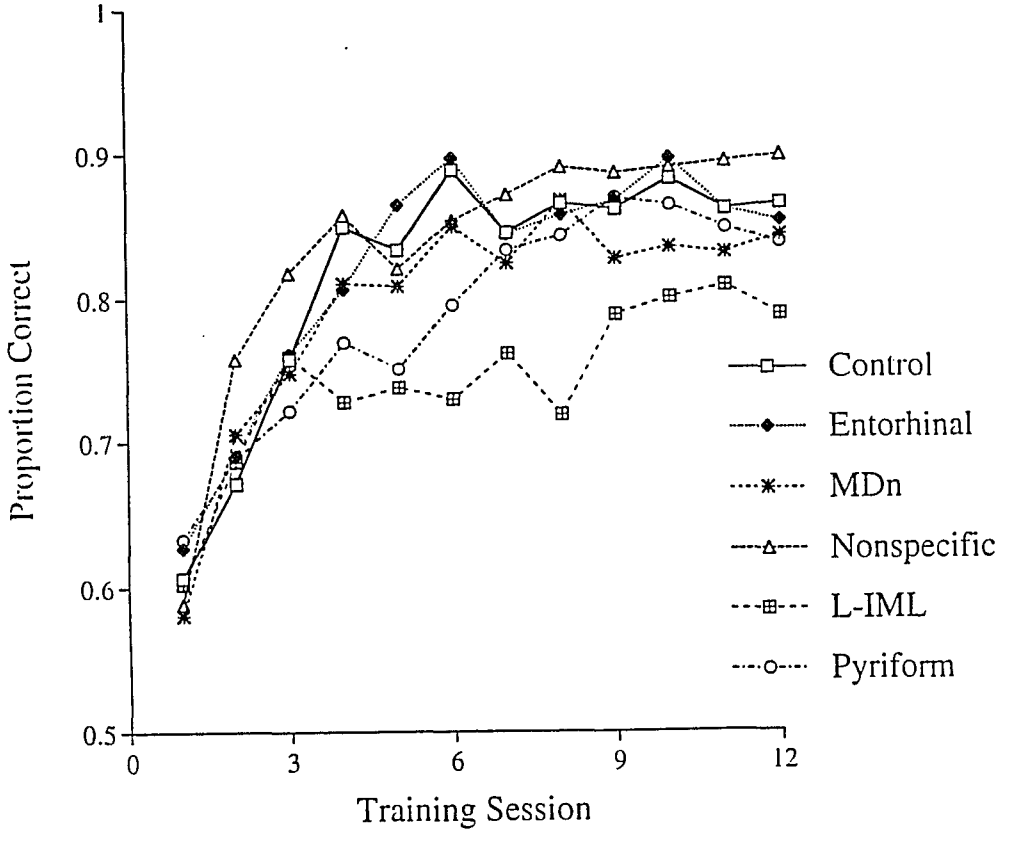

Figure 6. The individual performances of postsurgical olfactory CDNMTS and discrimination.

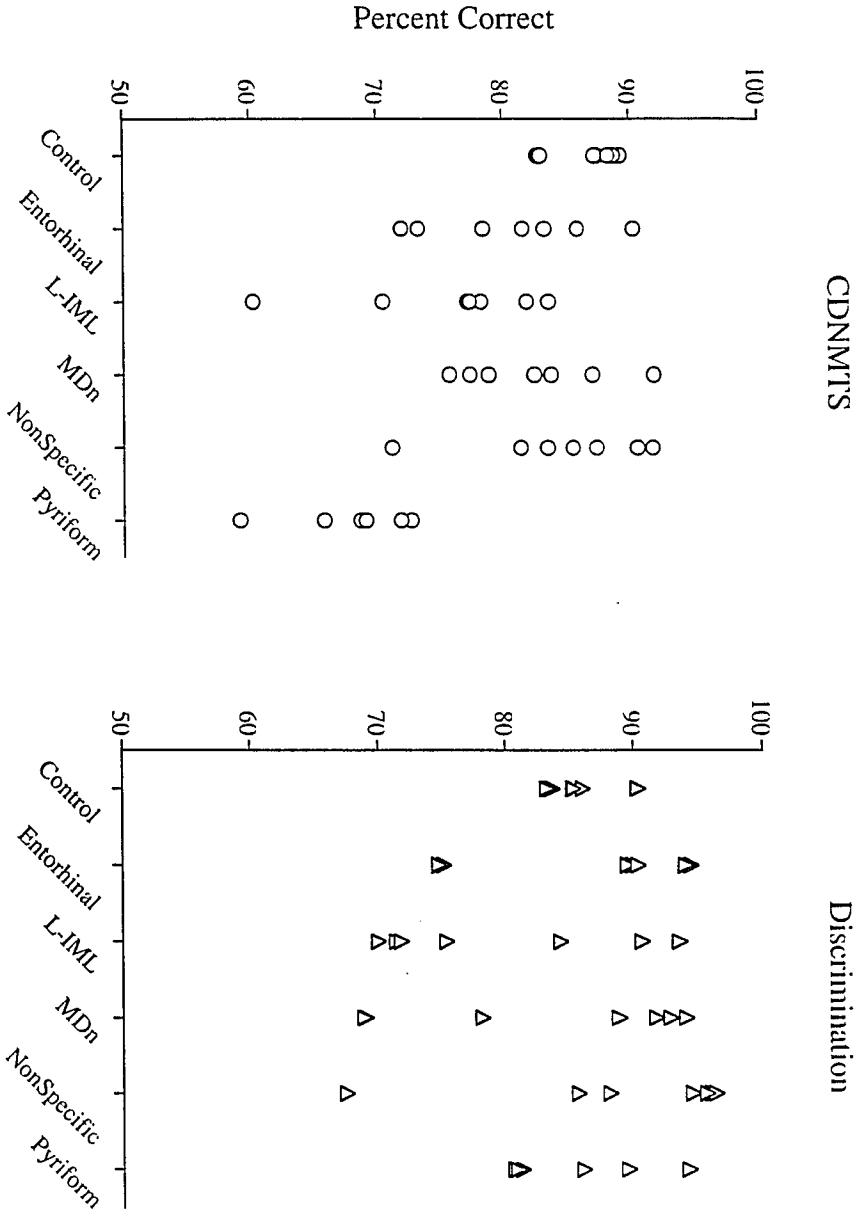

Figure 7. The Minimum and Maximum Lesions of the L-IML Group (at levels 5.2, 6.2 and 7.2 mm relative to IA).

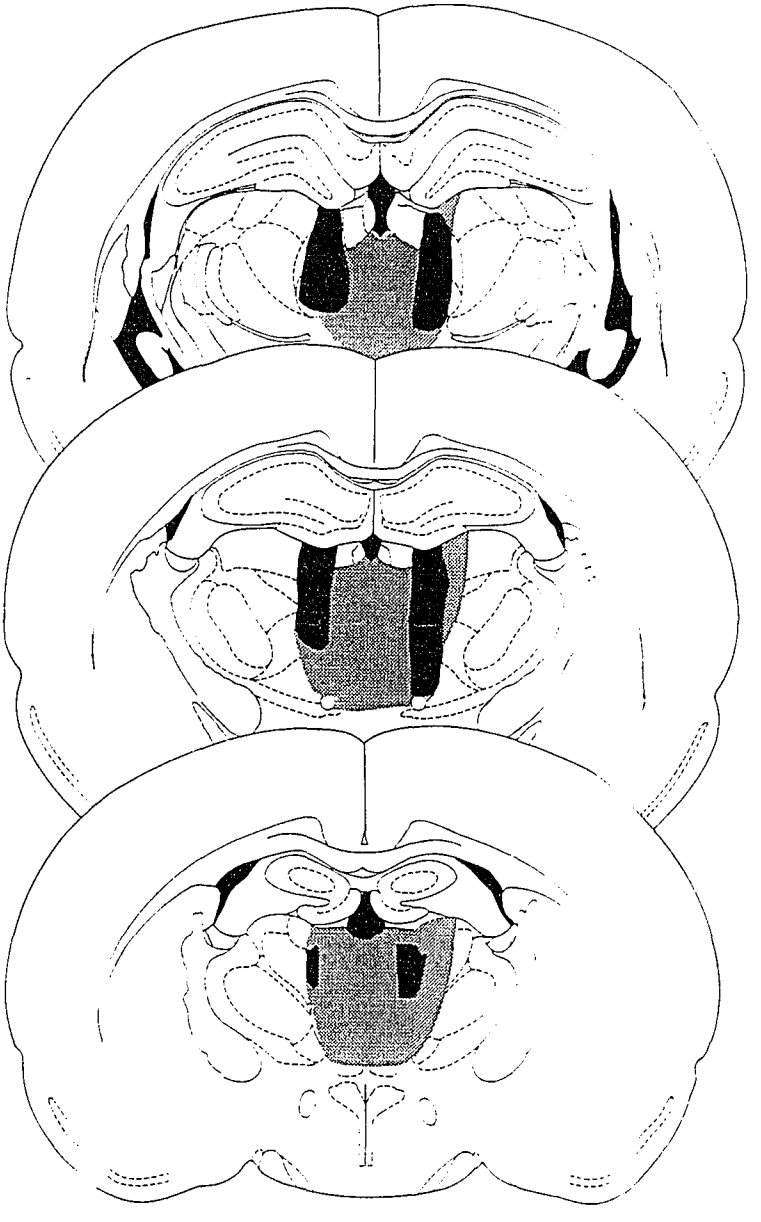

Figure 8. The Minimum and Maximum Lesions of the MDn Group (at levels 5.2, 6.2 and 7.2 mm relative to IA).

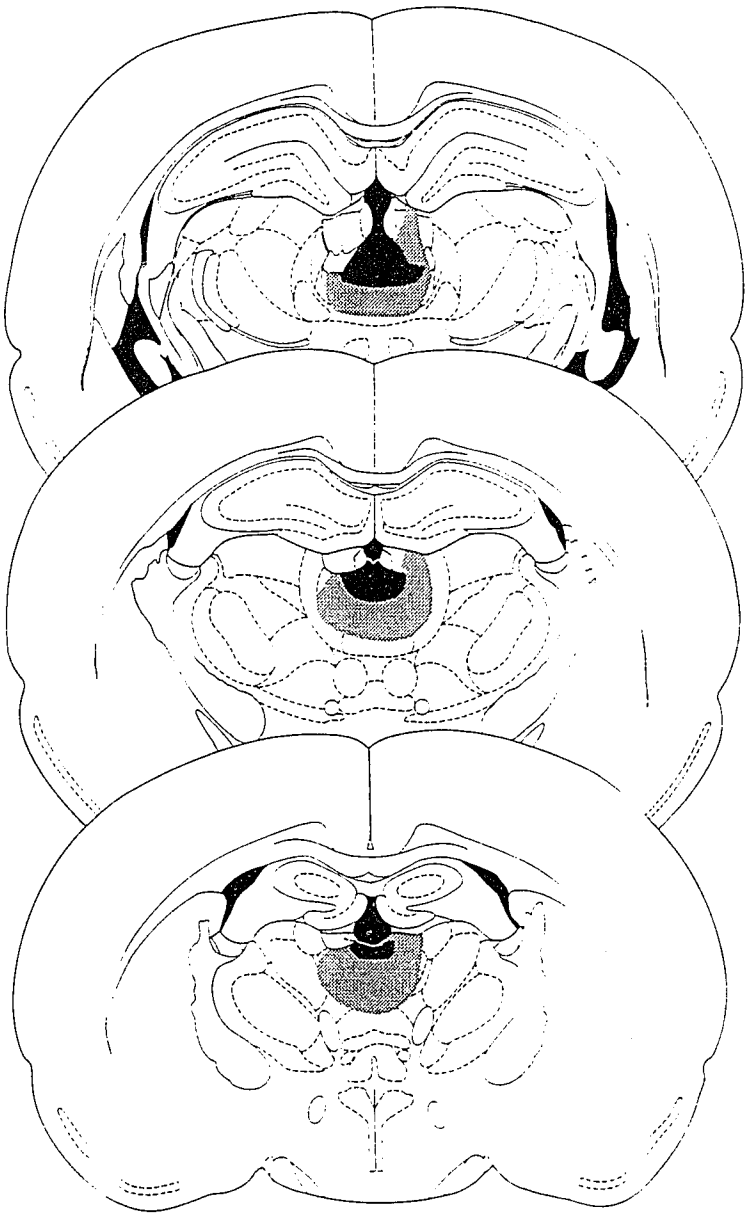

Figure 9. The Minimum and Maximum Lesions of the Non-specific Group (5.2, 6.2 and 7.2 mm relative to IA).

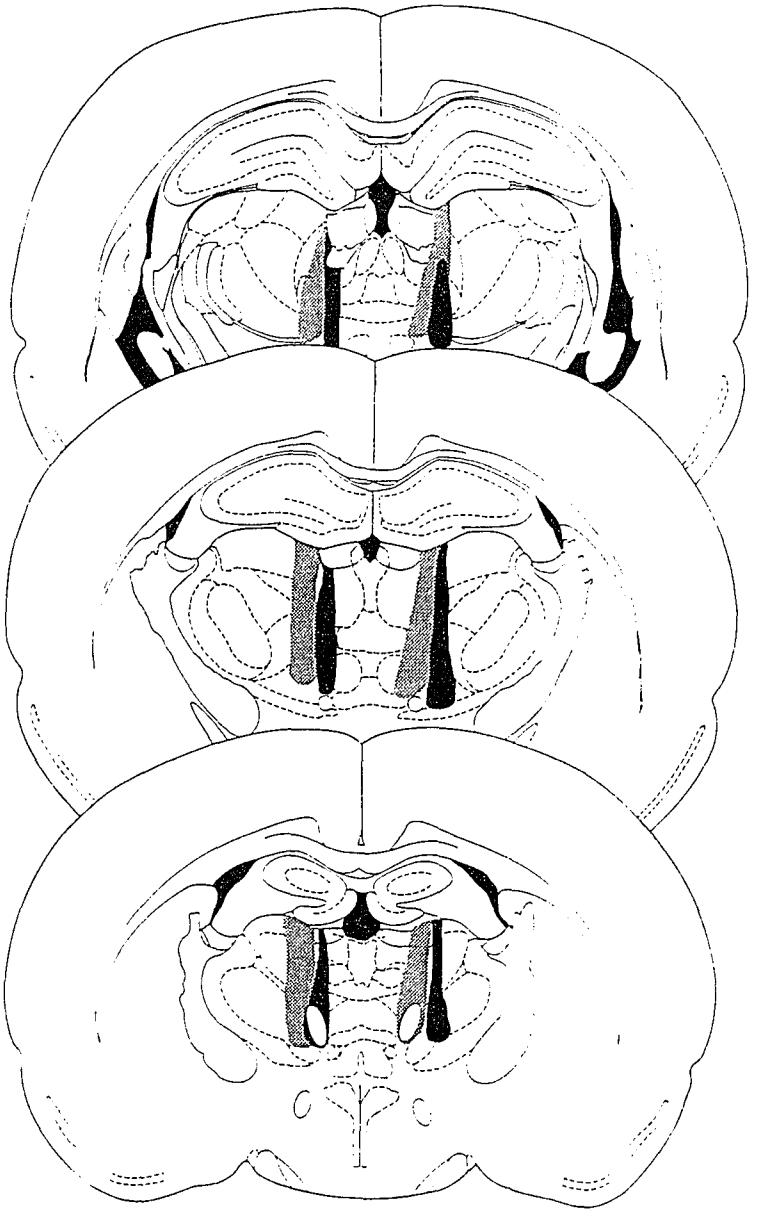

Figure 10. The Maximum Lesion of the Entorhinal Group (at 0.7, 2.2 and 3.7 mm relative to IA).

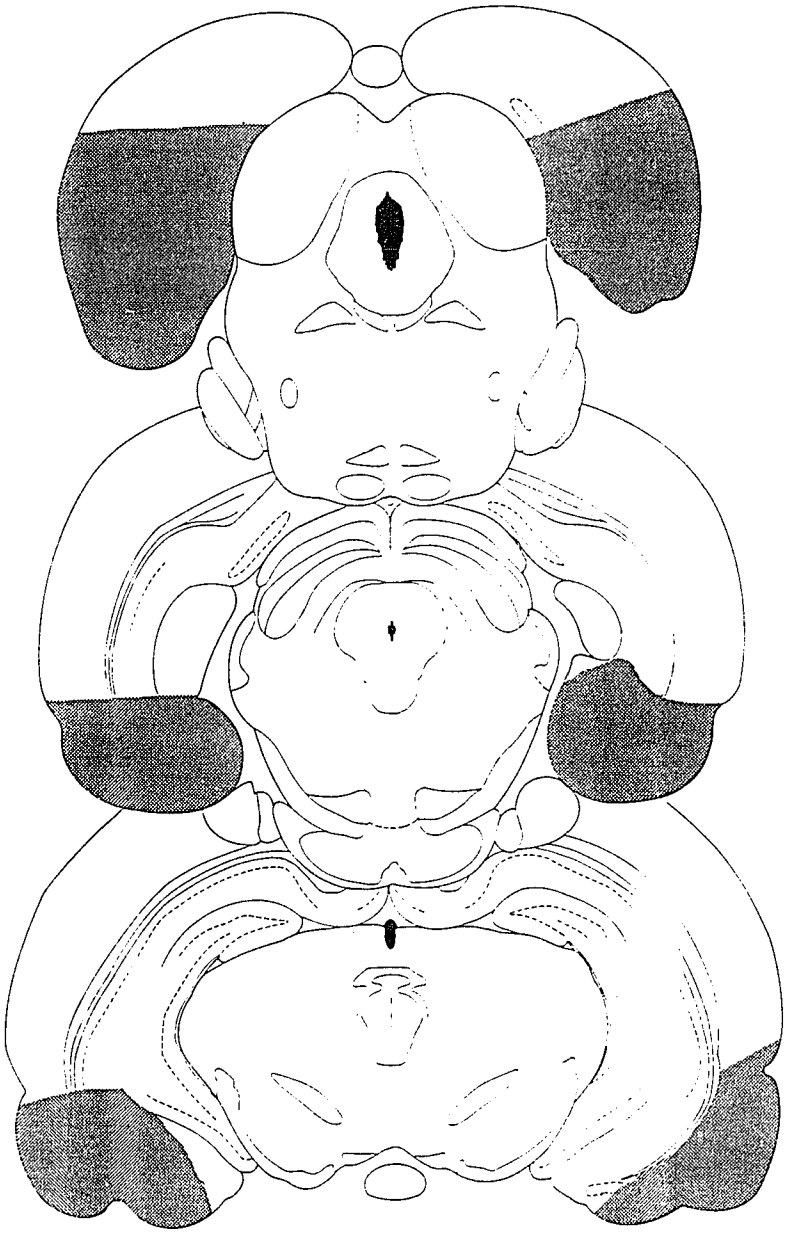

Figure 11. The Minimum Lesion of the Entorhinal Group (at 0.7, 2.2 and 3.7 mm relative to IA).

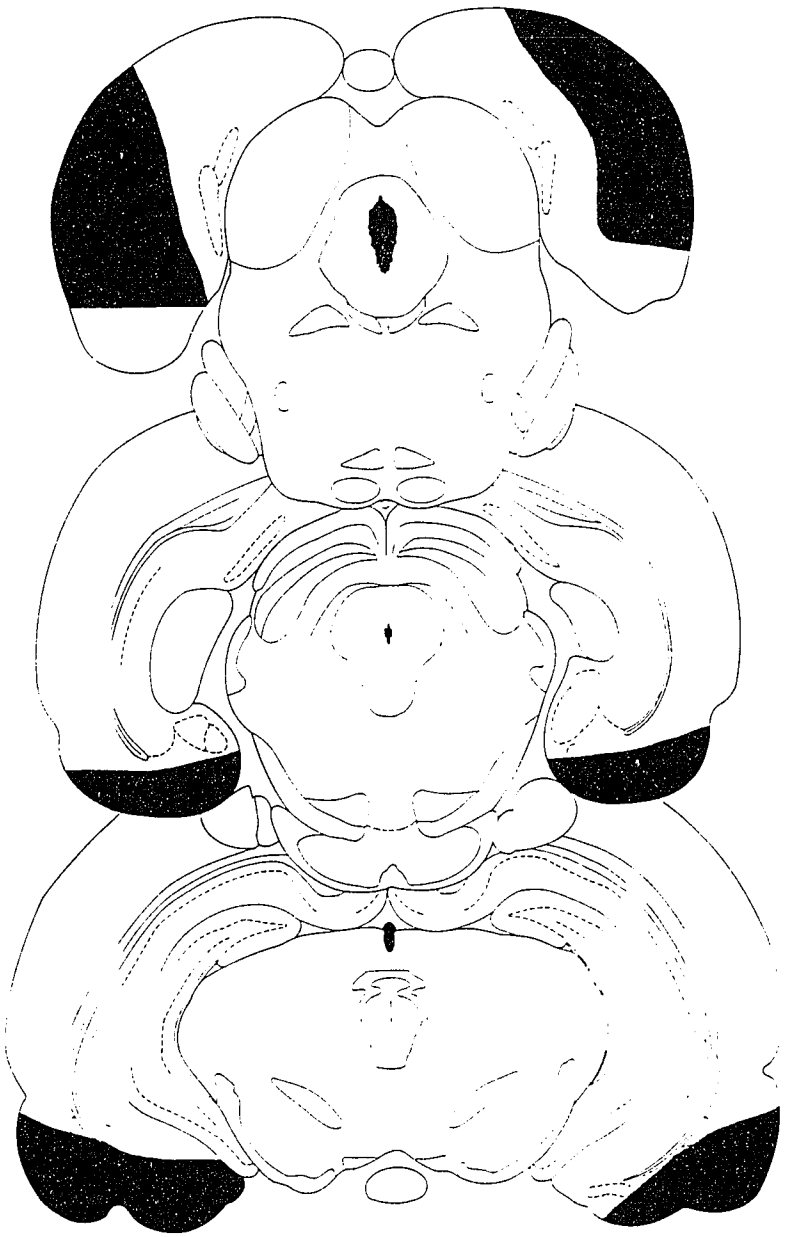

Figure 12. Maximum lesion of the pyriform group (at 4.7, 6.7, 8.7, 10.2 and 12.7 mm relative to IA)

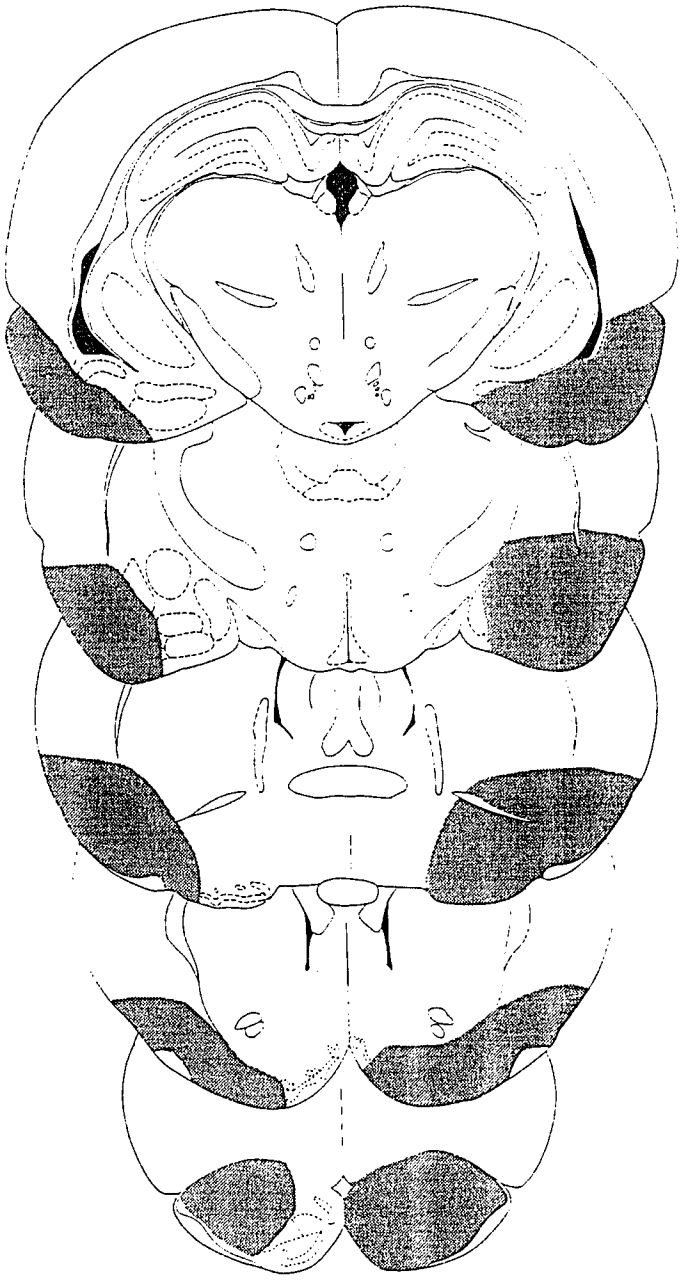

Figure 13. Minimum lesion of the pyriform group (at 4.7, 6.7, 8.7, 10.2 and 12.7 mm relative to IA)