Thalamocortical contributions to olfactory non-matching to sample and discrimination in the rat

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Thalamo-cortical contributions to olfactory non-matching to sample and discrimination in the rat

Koger, Susan Margaret, Ph.D.
University of New Hampshire, 1993
THALAMO-CORTICAL CONTRIBUTIONS TO
OLFACTORY NON-MATCHING TO SAMPLE AND DISCRIMINATION
IN THE RAT

BY

SUSAN MARGARET KOGER

B.A. Kean College, 1988
M.A. University of New Hampshire, 1991

DISSERTATION

Submitted to the University of New Hampshire
in Partial Fulfillment of
the Requirements for the Degree of

Doctor of Philosophy

in

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May, 1993
This dissertation has been examined and approved.

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Date

4/26/93
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ABSTRACT

THALAMO-CORTICAL CONTRIBUTIONS TO OLFACTORY NON-MATCHING TO SAMPLE AND DISCRIMINATION IN THE RAT

by

Susan Margaret Koger
University of New Hampshire, May, 1993

Twenty-eight male rats were pretrained on a go/no-go, continuous olfactory non-matching to sample (CONMTS) task, and randomly assigned to one of four treatment groups: radiofrequency lesions of either the medial wall or rhinal sulcal cortical projection sites of the mediodorsal thalamic nucleus (MDn); lesions of the lateral internal medullary lamina site (L-IML) of thalamus; or sham surgical control.

All three lesioned groups exhibited a significant impairment on initial retraining of CONMTS. However, the two cortical groups rapidly improved, and did not differ from the control animals for the remainder of CONMTS training. Alternatively, the L-IML deficit persisted throughout retraining. The cortical and control subjects exhibited susceptibility to proactive interference effects created by reducing the number of odor stimuli, and a moderate decay in
performance was observed with increased intertrial intervals. No differential effect of these manipulations was observed in the L-IML group, apparently due to a floor effect.

Subsequent training on go/no-go odor discrimination tasks demonstrated that the CONMTS deficit, characterized by an increase in "false alarms", was not attributable to an inability to suppress responding to nonreinforced odors. All subjects, including the L-IML lesioned rats, learned the discrimination tasks at equivalent rates.

The present findings demonstrate that singular destruction of specific MDn projection sites in prefrontal cortex does not disrupt performance of an olfactory working memory task. The L-IML lesions produced deficits on working, but not reference, memory components of the paradigm. This effect of L-IML lesions is consistent with previous studies utilizing spatial stimuli, demonstrating that the amnestic effects seen following thalamic destruction are multimodal.
INTRODUCTION

Mammalian olfaction is anatomically distinct from the other sensory modalities since paleocortical regions receive direct projections from the olfactory bulb. In turn, paleocortex innervates neocortex both directly, and by indirect afferents that first pass through the thalamus (e.g., Powell, Cowan, & Raisman, 1965; Price, 1985). The other sensory systems relay information indirectly to cortex via transthalamic pathways. In addition to its thalamic and neocortical afferents, paleocortex also projects directly to the hypothalamus, amygdala, and hippocampus (Powell, et al., 1965; Price, 1985). This unique structural organization may have corresponding functional significance, creating a special role for olfaction in mammalian behavior. In fact, many mammals depend critically on olfactory capabilities for food detection, reproduction, species recognition, maintenance of spatial and social organization, transmission of danger signals, and defensive reactions (e.g., Stoddart, 1980).

There is evidence that two regions which receive direct afferents from primary olfactory cortex, the mediodorsal thalamic nucleus (MDn) and prefrontal cortex (PFC) dorsal to the rhinal sulcus, are involved in odor-guided behavior in rodents (Eichenbaum, Shedlack, & Eckmann, 1980; Sapolsky & Eichenbaum, 1980). Similarly, olfactory impairments were documented in human and nonhuman primates following focal
destruction of orbital cortex, the region of primate PFC which receives direct olfactory innervation (Jones-Gotman & Zatorre, 1988; Potter & Butters, 1980; Tanabe, Yarita, Iino, Ooshima, & Takagi, 1975). Furthermore, humans with thalamic pathology in the region of the MDn, such as that associated with Korsakoff's syndrome, exhibit consistent olfactory deficits (e.g., Talland, 1965; Jones, Moskowitz, & Butters, 1975a; Mair, Capra, McEntee, & Engen, 1980).

Other research has demonstrated a relationship between thalamic pathology and the profound amnestic effects identified with Korsakoff's syndrome (Victor, Adams, & Collins, 1989) and a corresponding rodent model (Mair, Anderson, Langlais, & McEntee, 1988; Knoth & Mair, 1991; Robinson & Mair, 1992). Due to the widespread innervation of PFC by thalamic structures implicated in amnestic syndromes, Goldman-Rakic (1987) proposed that amnesia is the result of subcortical-prefrontal disconnection.

Since disruption of pathways between the MDn and PFC has thus been implicated in both olfactory and memory impairments, it is conceivable that the two effects are related, or result from similar processes. In that regard, prior research has not established whether the observed effects of thalamic or PFC destruction on odor-guided behavior reflect a specific impairment in central olfactory processing, or if the effects are related to the profound amnestic effects of diencephalic pathology.
The present dissertation was therefore conducted for two reasons: First, to further delineate the role of specific thalamo-cortical pathways in olfactory guided behavior in rats; and second, to investigate whether the previously observed amnestic effects of thalamic pathology in rats include olfactory "working memory". Because of the implications of this investigation in terms of further understanding human amnesia, it is first necessary to address the validity of a rodent model in research on thalamo-cortical contributions to behavior.

**Rodent Models**

Although it may be true that "Rats are not men . . . Men are bigger and better than rats" (Herrick, 1926, p. 365, as cited in Kolb, 1990a), Kolb argued that there are enough similarities between rodent and primate brain organization and function to justify a rodent model in neuropsychological research (Kolb, 1984, 1990a, c; Kolb & Tees, 1990). In that regard, there is considerable evidence that rats have frontal cortex analogous to PFC of primates by virtue of its afferents from the MDn of thalamus (Leonard, 1969; Krettek & Price, 1977; Groenewegen, 1988), and the density of reciprocal thalamic connections (Uylings & van Eden, 1990). This observation has stimulated considerable research aimed at defining the structural and functional properties of thalamic and cortical regions of the rat brain, with the ultimate goal
of utilizing rodent models to advance the understanding of behavioral dysfunction following brain damage in humans.

The following review will examine the characteristics that constitute the criteria for interspecies anatomical comparisons. These include cytoarchitectonic attributes of the PFC, the configuration and relative density of subcortico-cortical and cortico-cortical pathways, and the putative functional characteristics of these pathways. Finally, the mammalian olfactory system will be described, with a focus on MDn-PFC pathways in odor-guided behavior.

**Cytoarchitecture.**

The PFC of the rat comprises several anatomically distinct regions: medial precentral or frontal (Fr2) cortex; anterior cingulate (Cg) cortex including both dorsal (Cgl) and ventral (Cg3) aspects; prelimbic (PL) and infralimbic\(^1\) (IL) cortices; dorsal and ventral agranular insular (AI) cortex; and orbital cortices, including medial (MO), lateral (LO), ventral (VO), and ventrolateral (VLO) subdivisions (Krettek & Price, 1977; Zilles, 1985)\(^2\). The pattern of lamination,

---

\(^1\) It should be noted that Krettek and Price (1977) and Groenewegen (1988) included infralimbic (IL) cortex in defining prefrontal cortex. Zilles (1990) argued, however, that IL cannot be designated prefrontal cortex due to the differences in its architecture and connectivity relative to cingulate regions, and is more appropriately designated a section of periallocortex.

\(^2\) A list of abbreviations may be found in Table 1.
established by autoradiography, varies between the areas; however, all of these regions of rodent PFC lack an internal granular layer analogous to the granular layer 4 of PFC in primates (Krettek & Price, 1977; Zilles & Wree, 1985).

Subcortico-Cortical Connectivity.

Due to the agranular nature of the PFC in rats, projections from the MDn of thalamus have historically constituted the definitive criterion for prefrontal identification. Leonard (1969) identified two major MDn projection zones within rat PFC: the dorsal lip of the rhinal sulcus (i.e., sulcal cortex); and the medial wall and shoulder of frontal cortex, located anterior and dorsal to the genu of the corpus callosum.

Krettek and Price (1977) and Groenewegen (1988) extended Leonard's (1969) findings, demonstrating that although the rat MDn cannot be clearly subdivided based on cytoarchitecture, it can be parcelled on the basis of its afferents to distinct prefrontal sites. The dorsal regions along the medial wall of PFC, including Fr2 and CgL cortices, receive projections from the lateral segments of MDn. Lateral MDn in rats, like monkeys, primarily receives brainstem innervation. In the primate, the lateral, parvocellular region of MDn projects to the cortex bordering the principal sulcus in the dorsolateral convexity (Fuster, 1989), suggesting an anatomical homology.
between the medial wall and principal sulcal cortex in rats and primates, respectively.

In rodents, more ventral locations along the medial wall and rhinal sulcus are innervated by medial MDn. Medial MDn can be further partitioned into anterior and posterior components: Anterior medial MDn projects to PL and Cg3 cortex along the medial wall, while the posterior medial portion projects to AI cortex, dorsal to the rhinal sulcus. The central segments of the rat MDn innervate AI and LO regions within sulcal cortex. Medial and central MDn in the rat may be analogous to medial, magnocellular MDn in monkeys because these regions receive limbic, olfactory, and ventral pallidal projections (Groenewegen, 1988). However, the two species apparently differ in terms of the specific organization: In rats, the central portion of MDn is largely associated with olfactory input, while medial MDn is influenced by limbic structures. Alternatively, in monkeys there is apparently more overlap of afferents within the terminal fields of MDn (Groenewegen, 1988).

Thus, in a manner similar to other mammalian species including primates, rats possess distinct subregions of MDn. Furthermore, output from these regions is organized topographically to discrete regions of neocortex (Goldman-Rakic & Porrino, 1985; Groenewegen, 1988).

Thalamic nuclei adjacent to MDn, including the intralaminar (nonspecific) nuclei, also send afferents to the
rat PFC (Herkenham, 1980): The thalamic ventromedial complex projects to VLO and AI cortex; the anteromedial nucleus of thalamus innervates Cg and Fr2 regions; and the medioventral thalamic nucleus projects to IL cortex (Krettek & Price, 1977). Comparably, in monkeys, other thalamic nuclei innervate PFC, including the ventralis anterior, rostral intralaminar, and pulvinar nuclei of thalamus (Fuster, 1989).

Nonthalamic structures including the amygdala also project directly to the rat PFC, and terminate in the same cortical regions as the MDn-cortical pathways which receive innervation from these limbic structures. Specifically, the basolateral nuclei of the amygdala projects to dorsal AI cortex and to medial MDn, and medial MDn also projects to dorsal AI cortex (Krettek & Price, 1977). In the monkey, the amygdala projects to medial and orbital areas of the PFC, as well as to medial, magnocellular MDn which in turn also innervates medial and orbital PFC (Fuster, 1989). Thus, in both rats and monkeys, there is a topographical organization of subcortical projections to cortex both directly and indirectly via MDn.

Prefrontal cortical efferents to subcortical structures are extensive and generally reciprocate the afferents, in both rats (Groenewegen, 1988) and monkeys (Fuster, 1989). One notable system of projections in the rat extends from Cg, Fr2, and PL cortices to the pretectum and superior colliculus, a circuit involved in ocular motility, and thought to be
comparable to the primate frontal eye fields (Kolb, 1984, 1990c; Sesack, Deutch, Roth, & Bunney, 1989; Zilles, 1990). The frontal eye fields in the monkey (i.e., Brodmann's area 8) project to the pulvinar, pretectum, superior colliculus, and oculomotor nuclei of the brainstem, and thus apparently constitute a significant component of the mechanism for visual attention (Fuster, 1989). In addition, PFC projects extensively to the caudate nucleus and putamen (the basal ganglia) in monkeys (Fuster, 1989) and to the ventral striatum, basal forebrain, and midbrain locomotor region in the rat (Sesack et al., 1989). Sesack et al. (1989) have thus argued that these projections may play a critical role in other forms of motor control and "goal-directed behaviors" (p. 239).

Thus, the PFC in both rats and monkeys is distinguished by specific patterns of innervation from several subcortical structures, most notably the MDn of thalamus. There is evidence for an anatomical and corresponding functional homology with respect to subcortical-PFC reciprocal connectivity in the two species receiving the majority of empirical attention to date.

Cortico-Cortical Connectivity.

The PFC is heavily interconnected with sensory cortices in rats as well as in other mammalian species, and is thus thought to play an associational or integrational role in
behavior (Kolb, 1984; Fuster, 1989). In rats, primary olfactory (pyriform and periamygdaloid) cortices project to ventral AI, VLO, and LO regions of sulcal cortex in addition to projecting to central MDn, which innervates these same sulcal areas (Price & Slotnick, 1983; Price, 1985; see also The Mammalian Olfactory System: Anatomical Considerations, to follow). Similarly, studies in monkeys has revealed direct innervation of lateral posterior orbital cortex by primary olfactory (pyriform) cortex (Tanabe et al., 1975).

Other prefrontal regions in rats, including orbital and Cg cortices, are heavily interconnected with secondary visual cortex; the Fr2 region receives somatosensory and auditory inputs; and both Fr2 and orbital cortices are reciprocally connected with motor cortical regions (Kolb, 1990b). Studies of cortical projections to PFC in monkeys have demonstrated innervation by secondary, but not primary visual, auditory, or somatic sensory regions. It appears that these projections converge on contiguous regions of PFC (Fuster, 1989).

The agranularity of the rat frontal lobe may be indicative of a role in motor function (Zilles, 1990), and primary motor cortex has been delineated in the rat in areas adjacent to prefrontal cortical regions (lateral precentral, or Fr1 and Fr3) (Donoghue & Wise, 1982, as cited in Zilles, 1990). The polysensory nature of PFC and its supposed involvement in motor control across species has contributed to the theoretical consideration of PFC as a bridging mechanism,
wherein sensory stimuli are integrated and motor responses are
initiated (Fuster, 1989; Goldman-Rakic, 1987).

In addition to its association with sensory and motor
cortices, the PFC is reciprocally connected with perirhinal
cortex and is thereby associated with the hippocampus and
amygdala, resembling the organization in primates (Kolb,
1990b).

The Mammalian Olfactory System

Anatomical Considerations.

Odor information is transmitted from the receptor neurons
in the mammalian olfactory epithelium via axons, which form
the olfactory nerve, to the olfactory bulb. Within the bulb,
the olfactory nerve synapses with mitral and tufted cells, the
axons of which project to the brain primarily via the lateral
olfactory tract (LOT) (e.g., Brodal, 1992; Scott, 1986;
Shepherd, 1988). Direct olfactory projections thereby reach
several cortical regions located on the ventral surface of the
brain, including pyriform cortex, the olfactory tubercle, the
anterior olfactory nucleus, the anterior cortical nucleus of
the amygdala, the periamygdaloid cortex, and the lateral
entorhinal cortex (Powell et al., 1965; Price, 1985). Price
and his colleagues have delineated the connectivity between
these primary olfactory cortical structures and other cortical
as well as subcortical regions in several electrophysiological

Of primary relevance to the current investigation are olfactory projections to the thalamus and PFC in rats. First, the central segment of the MDn of thalamus receives olfactory innervation via the inferior thalamic peduncle and stria medullaris (Heimer, 1972) from the deep layers of primary olfactory cortex (i.e., the polymorphic zone of the olfactory tubercle, the ventral endopiriform nucleus of pyriform cortex, and deep regions within the periamygdaloid cortex) (Price & Slotnick, 1983). Second, regions of PFC lying dorsal to the rhinal sulcus receive projections from pyriform and periamygdaloid cortices; these afferents terminate in LO and ventral AI cortices (Price, 1985). Third, these same regions of sulcal cortex also receive afferents from the central segment of the MDn of thalamus (Price & Slotnick, 1983; Price, 1985; Groenewegen, 1988). Fourth, entorhinal cortex, which receives afferents from both the olfactory bulb and pyriform cortex, projects diffusely to all regions of the cortical mantle (primarily to layers 1, 2, and 6). Entorhinal terminal fields are most apparent in IL and PL cortices of medial PFC, as well as orbital cortex (Swanson & Kohler, 1986).

Thalamo-Cortical Involvement in Olfactory-Guided Behavior.

Bilateral olfactory bulbectomy or transection of the anterior LOT apparently produces anosmia, evidenced by a
failure to acquire odor detection or discrimination tasks in both rats (Eichenbaum et al., 1980) and hamsters (Sapolsky & Eichenbaum, 1980). However, damage to either thalamic (MDn) or rhinal sulcal targets of primary olfactory cortical projections in rats does not affect odor detection (Eichenbaum et al., 1980; Lu & Slotnick, 1990; Slotnick & Kaneko, 1981) or threshold levels for detection or discrimination (Eichenbaum et al., 1980). Eichenbaum and his colleagues have therefore argued that specific MDn-rhinal sulcal cortical projections are not necessary for detection of odor stimuli, as destruction of these regions does not produce a basic sensory impairment. However, they argue that these thalamo-cortical pathways are necessary for "associative, motivational, or cognitive aspects of odor cue utilization"; that is, the appropriate utilization of, and normal (efficient) responses to, olfactory stimuli (Sapolsky & Eichenbaum, 1980, p. 288; see also Eichenbaum et al., 1980). This conclusion was largely based on evidence that damage to either the MDn or sulcal cortical terminal regions of olfactory afferents produces specific deficits in odor discrimination in rodents.

An alteration in maternal aggression was reported following rhinal sulcal lesions, presumably due to a disruption of central olfactory pathways (Ferreira, Dahlof, & Hansen, 1987). The authors interpreted the effect as representing a decrease in the mothers' ability to discriminate between their pups and intruders. When operant
learning paradigms are employed, intact rats readily acquire olfactory discrimination problems, and demonstrate increasing rates of acquisition on successive odor discrimination problems within a series (Jennings & Keefer, 1969; Slotnick & Katz, 1974; Slotnick, Kufera, & Silberberg, 1991). However, lesions of the MDn or sulcal cortex reportedly led to an increase in trials to criterion on a go/no-go operant paradigm, in which one odor was associated with reinforcement while a second odor was not (Eichenbaum et al., 1980; Eichenbaum, Clegg, & Feeley, 1983; Lu & Slotnick, 1990; Slotnick & Risser, 1990). The effects of MDn lesions seemed most profound when the task required discrimination between a pair of odorants that were judged by humans as qualitatively similar and therefore difficult to discriminate (Eichenbaum et al., 1980).

Task difficulty may also account for the finding that MDn lesions did not affect the initial acquisition of an odor discrimination problem in another study, but when the contingencies between the odor stimuli and reinforcement were reversed, MDn lesioned rats made significantly more errors than did controls (Slotnick & Kaneko, 1981). A greater and more persistent impairment (increased trials to criterion) following MDn lesions was also reported when a three-odor, rather than a two-odor, discrimination task was employed (Staubli, Schottler, & Nejat-Bina, 1987). Although the MDn lesioned rats initially required more trials to criterion on
the two-odor task than controls, the lesioned subjects improved across successive problems and ultimately reached control level performance. No such improvement was observed on the three-odor discrimination task following lesions of the MDn (Staubli et al., 1987).

Whishaw, Tomie, and Kolb (1992) demonstrated that lesions of the rhinal sulcal region did not impair acquisition of a discrimination between a scented and a nonscented length of twine; nor was a tactile discrimination between two diameters of twine affected by these lesions. However, when the task complexity was increased by introducing a compound conditional association, combining elements of scent and twine diameter, the rhinal sulcal lesioned rats required more trials to reach criterion, and made more errors than controls (Whishaw et al., 1992).

Rhinal sulcal lesions also affected the acquisition of a go/no-go olfactory non-matching to sample task, in which reinforcement is contingent on a response to an odor stimulus that differs from the stimulus on the previous trial (Otto & Eichenbaum, 1992). Although these rats required more trials to reach criterion than controls, they eventually reached criterion and performed as well as controls.

Taken together, these studies suggest that lesions of the thalamic or neocortical sites receiving input from primary olfactory cortex retard the rate at which olfactory discriminations are learned. However, the impairment cannot be
ascribed to a sensory impairment or inability to discriminate odors, as the lesioned animals eventually do attain criterion performance. Thus, despite the anatomical involvement of the MDn-rhinal sulcal regions in central olfactory pathways, there is no convincing evidence that lesions of these structures produce a permanent impairment in any olfactory function.

Another consideration is that although the studies reviewed above focus on the role of the MDn, they also typically reported damage to surrounding regions including: the paraventricular and parataenial nuclei (Eichenbaum et al., 1980; Slotnick & Risser, 1990; Staubli et al., 1987); the intermediodorsal, interanteromedial, ventromedial, and laterodorsal thalamic nuclei, as well as the dorsal hippocampus (Staubli et al., 1987); and the stria medularis and habenula (Eichenbaum et al., 1980; Staubli et al., 1987). Further, Lu and Slotnick (1990) reported a distinct correspondence between the extent of thalamic destruction and the degree of impairment.

Thalamo-Cortical Involvement - Non-Olfactory Learning and Remembering.

In an extensive review of the effects of MDn lesions, Markowitsch (1982) concluded that minor, transient impairments are produced by discrete MDn lesions, while profound, chronic deficits result from large thalamic lesions which typically involve surrounding nuclei. For example, spatial delayed
alternation was unaffected following discrete MDn lesions (Greene & Naranjo, 1986); whereas a significant impairment was reported following thalamic destruction that included lateral and medial MDn, and damage to the anterior, anterior reticular, and medial regions of the ventromedial nuclei (Vicedomini, Corwin, & Nonneman, 1982).

Hunt and Aggleton (1991) demonstrated that MDn lesions only affected performance of spatial delayed alternation at the longest delays tested (60 sec), or when the trials were massed by reducing the intertrial interval. More significant and consistent deficits were observed on delayed alternation following destruction of more anterior thalamic nuclei. In another experiment, they reported that an acquisition impairment on a visual/tactile non-matching to sample task was correlated with the extent of thalamic destruction (Hunt & Aggleton, 1991). Large lesions in the MDn region that affected adjacent nuclei also impaired performance of visual/object non-matching to sample, regardless of whether the rats had been trained on the task prior to surgery (Mumby, Pinel, & Dastur, 1993).

Lesions of MDn which intrude on anterodorsal, anteroventral, parataenial, paraventricular, rhomboid, or reunien nuclei also impaired performance on a radial arm maze (Kessler, Markowitsch, & Otto, 1982). This impairment reflected an increase in the number of sessions required to
reach criterion, and the number of errors made following a retention interval (Kessler et al., 1982).

Kolb (1977) demonstrated normal performance on a spatial discrimination task, but increased errors to criterion on subsequent reversals (in which the contingencies between discriminative stimuli and reinforcement were reversed) following lesions that included MDn and the paraventricular nuclei. Somewhat larger thalamic lesions were reported to produce an increase in trials to criterion on the initial learning and subsequent reversal of a brightness discrimination (Tigner, 1974). In contrast, Tigner’s (1974) report documented a lack of effect on initial learning or performance of two reversals of a spatial discrimination following large thalamic lesions. An explanation for the conflicting results reported in these two studies of spatial discrimination reversals following thalamic destruction is unclear, but may relate to differences in methodology. Specifically, Tigner (1974) pretrained his subjects on spontaneous alternation prior to surgery. In addition, postsurgical training on brightness discrimination was conducted prior to the spatial discrimination task; thus, learning on one of the tasks may have transferred to the spatial discrimination procedure. Alternatively, functional recovery may account for the lack of effect on spatial discrimination reversal reported by Tigner (1974). These hypotheses are conjectural, and await clarification.
Mair and colleagues have demonstrated that behavioral impairments observed in rats with thalamic pathology following pyrithiamine-induced thiamine deficiency (PTD) treatment (Knoth & Mair, 1991; Robinson & Mair, 1992; Mair, Knoth, Rabchenuk, & Langlais, 1991; Mair et al., 1988) can be accounted for by bilateral lesions of the internal medullary lamina (the L-IML site). These effects include severe and chronic impairments on spatial delayed non-matching to sample (Mair & Lacourse, 1992; Mair, Robinson, Koger, Fox, & Zhang, 1992), increased errors to criterion on spatial discrimination and serial reversal (Harrison, 1992), and impaired performance on radial arm maze tasks (Harrison, 1992; Mair & Kivlahan, 1993). The L-IML lesion encroaches on thalamic nuclei in the region of the IML, including the lateral portions of MDn, the paracentral nucleus, and the central lateral nucleus, as well as the fiber pathways that course through the IML (Mair & Lacourse, 1992). Lesions which do not destroy the entire anterior-posterior extent of the L-IML site are not sufficient to produce the impairments on spatial delayed non-matching to sample that are observed in rats following PTD treatment (Mair, Robinson et al., 1992).

Thalamo-cortical projections, including specific reciprocal pathways between the MDn and its prefrontal terminal regions as well as those between nonspecific thalamic nuclei and diffuse cortical areas, pass through the L-IML region (Krettek & Price, 1977; Brodal, 1992). In addition,
both L-IML and PTD lesioned rats exhibit degeneration in cortical target areas of specific thalamic projections (cortical layers 3 or 4) within the medial wall and rhinal sulcus of PFC, as well as nonspecific projections (cortical layers 1 and 6) to widespread areas of cortex (Mair, Zhang, & Koger, 1993). It is thus conceivable that the above summarized behavioral effects following thalamic lesions do not result from discrete damage of MDn or surrounding nuclei. Rather, they may result from the disruption of: a) specific thalamo-cortical projections (to the medial wall and rhinal sulcus); b) nonspecific pathways to diffuse cortical areas; or c) both specific and nonspecific thalamo-cortical afferents (Mair, Robinson, & Koger, 1992; Mair, Robinson et al., 1992; Mair, Zhang, & Koger, 1993).

Although it is clear that circumscribed prefrontal damage does not actually produce amnesia (Stuss & Benson, 1986), there are certain similarities between the behavioral effects following thalamic or prefrontal destruction. Thus, it may be that the PFC participates in mnemonic processes (Fuster, 1989; Squire, 1987). For example, lesions of the medial wall in rats, including Fr2 and Cg cortices, produce deficits on spatial delayed alternation (Eichenbaum et al., 1983; Larsen & Divac, 1978; Nonneman & Corwin, 1981; van Haaren, de Bruin, Heinsbroek, & van de Poll, 1985; van Haaren, van Zijderveld, van Hest, de Bruin, van Eden, & van de Poll, 1988; Wikmark, Divac, & Weiss, 1973; Winocur, 1991); delayed response (Kolb,
Nonneman, & Singh, 1974); spatial delayed non-matching to sample (Harrison, 1992); a delay task with a 12-arm radial maze (Kesner, 1989); and the Morris water maze (Kolb, Pittman, Sutherland, & Whishaw, 1982). Medial wall lesions also impaired spatial "order memory", in which rats were trained in an 8-arm radial maze with a variable 4-arms procedure, and then tested for order memory by opening either the first and second, second and third, or third and fourth doors. A visit to the location that had occurred earlier in the presentation sequence was reinforced. The effects on order memory were observed whether 2, 4, or 8 arms were used, when the rats self-ordered the sequence of 4 or 8 locations, and when the same spatial locations were presented on every trial. However, a matching to sample task in the same apparatus was unaffected by medial wall lesions (Kesner & Holbrook, 1987).

Initial deficits were exhibited by medial wall lesioned animals (more errors than control subjects exhibited) in acquiring a discrimination between four baited and four unbaited arms in an 8-arm radial maze, although they eventually attained control level performance (Kolb et al., 1982). A similar, transient deficit was revealed following medial wall lesions in performance of an 8-arm radial maze task (Harrison, 1992), and a visuo-spatial conditional discrimination (Winocur, 1991). However, no spatial discrimination learning or reversal deficits were observed in medial wall lesioned rats (Harrison, 1992).
Far less is known regarding the effects of medial wall lesions on rats' performance of tasks utilizing nonspatial stimuli. Increased trials to criterion on object discrimination and reversal were reported following lesions of the medial wall site, although these rats demonstrated positive transfer between reversals and performed at normal levels for the third and subsequent reversals (Becker & Olton, 1980). Performance of a go/no-go, auditory non-matching to sample task that had been trained prior to surgery was also impaired following medial wall lesions, although the effect was greater following discrete MDn lesions (Sakurai & Sugimoto, 1985).

Temporal discrimination, based on procedures originating in Scalar Timing Theory, was altered following lesions largely restricted to the Fr2 region of the medial wall (Olton, 1989). Briefly, the temporal discrimination technique involves the presentation of a visual or auditory discriminative stimulus, each of which is associated with a particular fixed interval (FI) schedule of reinforcement. Rats' ability to discriminate between short and long FIs is assessed via probe trials, consisting of a presentation of the discriminative stimuli but during which no reinforcers are delivered. lesioned rats displayed a shifted response time of 20% (i.e., they responded at a time that, on average, was 20% later than when food was typically available on reinforced FI trials). Other components of timing behavior remained unaffected, including response
rate and the overall form of the response rate function. However, simultaneous temporal discrimination is also affected by frontal lesions, presumably reflecting a deficit in the ability to “divide attention” in these animals (Olton, Wenk, Church, & Meck, 1988).

Implications for Diencephalic Amnesia Research

Korsakoff’s syndrome, the most common form of diencephalic amnesia, is characterized by pathology in the medial segment of the MDn as well as the pulvinar, lateral dorsal, and medial ventral thalamic nuclei and mammillary bodies, and is associated with severe anterograde and retrograde amnesia (Victor et al., 1989). Korsakoff patients exhibited increased trials to criterion on both spatial and visual discrimination learning and on the first reversal in the spatial task, although they did demonstrate improvement across subsequent reversals (Oscar-Berman & Zola-Morgan, 1980). Deficits were also reported on visual (hue) discrimination, in which comparison stimuli were presented simultaneously, as well as an auditory discrimination task, wherein sounds were presented successively (Mair, Doty, Kelly, Wilson, Langlais, McEntee, & Vollmecke, 1986).

A further aspect of Korsakoff’s syndrome is an impairment of olfactory processing. This effect was attributed to disruption of the olfactory pathways to MDn as a result of the characteristic thalamic pathology (Jones et al., 1975a; Jones,
Moskowitz, Butters, & Glosser, 1975b; Mair et al., 1986; Mair & Flint, 1992; Mair et al., 1980). Although odor detection remained intact in Korsakoff patients (Mair et al., 1980), an olfactory deficit is revealed by impaired odor recognition (Jones et al., 1975a; Mair et al., 1980); odor intensity scaling (Jones et al., 1975b; Jones, Butters, Moskowitz, & Montgomery, 1978); and matching of odorants with verbal labels (the UPSIT task) (Mair et al., 1986).

Multimodal discrimination deficits were also reported following PTD treatment, which represents an animal model of Korsakoff’s (e.g., Mair, Robinson, & Koger, 1992). The PTD treated rats exhibited significantly more errors to criterion than control animals on spatial discrimination, although they eventually acquired criterion (Mair et al., 1988). Furthermore, PTD-treated rats exhibited positive transfer (i.e., improvement) across reversals subsequent to the first (Mair et al., 1991), in a pattern reminiscent of that found in Korsakoff patients (Oscar-Berman & Zola-Morgan, 1980). Acquisition measures for olfactory and auditory discrimination and reversals suggested that these tasks were more difficult than the spatial paradigm, as both control and experimental animals made more initial errors. Although all animals eventually reached criterion, the PTD rats were impaired relative to controls on both tasks (Mair et al., 1991).

In sum, Korsakoff patients and PTD rats are delayed in acquiring discrimination procedures. This observation is
similar to several reports (reviewed above) of discrimination deficits following either thalamic or prefrontal lesions. These learning deficits have been interpreted as a difficulty in forming new associations by Korsakoff patients (Oscar-Berman & Zola-Morgan, 1980), or a deficit in the acquisition of rules, associations, or cognitive skills following thalamic or cortical destruction (Otto & Eichenbaum, 1992; Sapolsky & Eichenbaum, 1980; Winocur & Moscovitch, 1990).

However, Mair and colleagues have pointed out that since criterion is ultimately reached, and since the subjects frequently demonstrate positive transfer between problems, that reference memory (Honig, 1978; Olton, Becker, & Handelmann, 1980) is spared in these populations (Mair et al., 1991; Mair, Robinson, & Koger, 1992). Intact reference memory refers to the ability to respond based on a consistent rule or strategy once the rule is acquired. On the other hand, diencephalic pathology severely and persistently disrupts performance on working memory tasks (e.g., Mair, Robinson, & Koger, 1992), that is, those tasks in which environmental information must be continually updated (Honig, 1978; Olton et al., 1980), such as delayed conditional discrimination tasks.

Korsakoff patients were observed to be less accurate on delayed alternation and delayed response tasks (Oscar-Berman, Zola-Morgan, Oberg, & Bonner, 1982); an object delayed non-matching to sample (Squire, Zola-Morgan, & Chen, 1988); and on an object (Aggleton, Nicol, Huston, & Fairbairn, 1988) or
visual matching to sample task (Oscar-Berman & Bonner, 1985). The effects on matching to sample were noted particularly if delays were imposed between the sample and choice phases (Aggleton et al., 1988; Oscar-Berman & Bonner, 1985), if the sample was presented briefly, and if the choice stimuli were unidimensional (i.e., a pattern or a color) following a sample that consisted of a compound stimuli (i.e., a pattern of lines on a colored background) (Oscar-Berman & Bonner, 1985).

Similarly, spatial delayed alternation was impaired following PTD treatment in rats (Mair, Anderson, Langlais, & McEntee, 1985), as was delayed non-matching to sample performance based on place cues (Knoth & Mair, 1991; Robinson & Mair, 1992). As mentioned above, lesions of the L-IML site of thalamus apparently can account for the PTD deficit on spatial delayed non-matching to sample (Mair & Lacourse, 1992; Mair, Robinson et al., 1992).

Harrison (1992) recently demonstrated that medial wall lesions in rats produced impairments on spatial delayed non-matching to sample that were comparable to deficits produced by PTD treatment and lesions of the L-IML thalamic site. In contrast, lesions to the rhinal sulcal target region of MDn projections did not affect spatial non-matching to sample performance. It is thus conceivable that the pathway from thalamus to medial wall of cortex mediates spatial learning and remembering in rats, while the thalamo-rhinal sulcal system underlies olfactory learning and remembering.
(Eichenbaum et al., 1983). This would lead one to predict deficits on an olfactory non-matching to sample task following L-IML or rhinal sulcal, but not medial wall lesions, in parallel with Harrison's (1992) results.

Conversely, it may be that thalamic-medial wall pathways are critical for the control of response sequences that require temporal organization (Kesner and Holbrook, 1987; Kesner, 1989), or the ability to maintain stimulus information "on-line", and bridge temporal gaps between stimuli and subsequent behavioral acts (Fuster, 1989; Goldman-Rakic, 1987). This ability is evident in delay task performance (Fuster, 1989). Rhinal sulcal regions may be functionally related only to behavior dependent on olfaction, including olfactory learning and many species-specific activities. According to this hypothesis, thalamic-medial wall pathways may mediate the mnemonic and temporal demands of non-matching to sample tasks in general, while olfactory-MDn-rhinal sulcal projections underlie olfactory learning capabilities. In that case, lesions of the L-IML, medial wall and rhinal sulcus should all produce an impairment on an olfactory non-matching to sample task.

The Current Investigation

These hypotheses were tested using a task recently developed by Otto and Eichenbaum (1992). The continuous olfactory non-matching to sample (CONMTS) procedure ostensibly
requires the rat to remember an odor stimulus for a period of time in order to execute a correct response. In the present experiment, a series of odors was systematically presented and the subject was required to respond only to an odor that was qualitatively different from the odor presented on the immediately preceding trial (a go/no-go, non-matching to sample task).

The task contains both reference and working memory components as described by Olton et al. (1980), and thus allows a comparison with prior demonstrations of impaired working memory but spared reference memory following thalamic pathology (Mair, Robinson, & Koger, 1992). The CONMTS task satisfies the criterion for a working memory task, since relevant stimulus information must be updated from trial to trial. Further, the "comparison" stimulus (i.e., the stimulus presented on the preceding trial) is not present at the time of the response requirement. Thus, the animal presumably must remember the previous stimulus to determine if the present stimulus is the same or different.

Task Manipulations.

Several investigators have demonstrated that reducing the number of sample stimuli results in decay of performance on non-matching to sample and other delayed discrimination tasks (Jitsumori, Wright, & Cook, 1988; Kesner, 1989; Mishkin & Delacour, 1975; Otto & Eichenbaum, 1992), presumably because
trials become less discriminable as individual stimuli occur more frequently. In that regard, the rats in the present study were subjected to sessions with a reduced number of odor stimuli. Further, data were collected to determine if performance decays during a session, suggesting a within-session proactive interference effect. In addition, delay-dependent forgetting on this task was assessed by increasing the interval between odor stimulus presentations (Otto & Eichenbaum, 1992).

Rhinal sulcal lesions in rats, and orbital frontal and inferior convexity cortical lesions in monkeys appear to produce an impairment in response inhibition (Eichenbaum et al., 1983; Fuster, 1989; Mishkin, 1964). Therefore, if a deficit is observed on the CONMTS task, it may result from an inability to inhibit responding (i.e., "no-go") on trials in which the odor matches that on the previous trial. In order to test this possibility, subjects were tested on two olfactory discriminations using training procedures comparable to CONMTS, but in which one odor was always associated with reinforcement while a second odor never predicted reinforcement. In addition, this manipulation provided a separation of the working and reference memory components of the task, since the discrimination procedure retained the reference memory requirements of CONMTS but eliminated the working memory aspects. In other words, the procedural aspects of CONMTS and discrimination were identical, but while the
CONMTS task required the continual updating of stimulus information, discrimination procedures are based on a fixed association between one odor stimulus and reinforcement. Otto and Eichenbaum (1992) reported an impairment of CONMTS acquisition following rhinal sulcal lesions. However, they observed no lasting deficit or differential susceptibility to increased intertrial interval or interference effects produced by decreasing the olfactory stimulus set size. These results were contrasted with the effects of perirhinal and entorhinal cortical lesions, which did not disrupt initial task acquisition but produced significant deficits when the mnemonic demands were increased. It is possible that the rhinal sulcal lesions in their study may not have totally destroyed the cortical target of the olfactory pathways. To ensure more complete and selective cortical destruction, stereotaxic techniques were utilized in the present investigation, as they allow more precise tissue destruction than that afforded by aspiration. A second possibility is that a lack of training on the CONMTS task prior to surgery in the experiment by Otto and Eichenbaum (1992) may have resulted in a ceiling effect in the control group's performance. Thus, subtle differences between groups may have been obscured by a failure of the control subjects to attain optimal performance levels. Accordingly, the present experiment involved extensive pretraining on the CONMTS task.
METHOD

Subjects

Two cohorts of subjects were used in this series of experiments: Group A consisted of 29 male Long-Evans rats (University of New Hampshire breeding laboratories). These rats ranged in age from eight to twelve weeks old at the time of initial training and were experimentally naive. Group B included 24 male, Long-Evans rats (Charles River, Wilmington, MA) approximately six months old at the start of the present study. These subjects had served in initial pilot training for this project, but had not been subjected to any surgical manipulations.

During behavioral training, all subjects were maintained on a 23.5 hour water deprivation schedule, receiving water for 30 minutes each day following behavioral testing. Purina rat chow was available ad libitum. The rats were housed individually in a temperature- and humidity-controlled vivarium, on a 12 hour light/12 hour dark illumination schedule.

During postoperative training, a number of animals throughout the colony showed symptoms of obstructive pneumonia accompanied by weight loss, and one rat in the present experiment died. At this point, all animals were placed on ad libitum water containing a broad spectrum antibiotic (Terramycin; approximately 0.02% weight/volume) for a minimum of four days, or until weight was regained and stabilized. The rats were then returned to the deprivation schedule, and received water containing antibiotic for 45 minutes each day following behavioral testing.
schedule (the lights were turned on at 7 am and extinguished at 7 pm). Behavioral training was conducted during the light phase.

**Apparatus**

Behavioral training took place in a sheet-metal chamber with a wire mesh floor (44 cm x 41 cm x 41 cm), housed in a sound isolating enclosure. An alcove (12.5 cm wide), centered at one end of the chamber, contained a Plexiglas insert designed to hold a drinking spout and a modified nalgene funnel which served as the odor port (4.5 cm in diameter and 1 cm above the floor; see Figure 1). The rat could insert its snout into the port to sample odor stimuli, and then rest its paws on the platform above the odor port while responding to the drinking spout. Photocells mounted on either side of the odor port detected and measured the duration of nose pokes into the port. Water was delivered to the drinking spout via a gravity-feed system activated by a solenoid. A contact relay circuit and photocells mounted in front of the drinking spout detected responses to the spout.

A Plexiglas partition, mounted 18 cm above the floor and parallel to the front of the Plexiglas insert, served to exhaust odorants from the chamber via a hose (12 cm in diameter) mounted to the top of the alcove. House lights consisted of a light bulb (6 watts) mounted on the partition (38 cm above the floor) and facing the alcove, and a second
bulb mounted on the ceiling of the sound-isolating enclosure, centered above the behavioral chamber and 85 cm above the chamber floor.

A 16-channel, air dilution olfactometer generated the odor stimuli listed in Table 2. Each of the 16 odorants was arbitrarily and permanently assigned to a channel of the olfactometer. Air supplied by a compressor was filtered through Drierite (CaSO₄) and then through activated charcoal. The air stream then passed through a flexible Teflon PTFE tube (6 mm in diameter) which was connected via tubing (1 mm in diameter) to gas washing bottles containing the odorants. The odorant used on each trial was selected by activation of one of 16 2-way solenoids, and blended with the clean air stream at an overall flow rate of 3200 cc/min with 10% saturation. Following odor selection, the odorized air stream flowed through a 3-way solenoid to a suction compressor at a rate of 3800 cc/min. A nose poke in the odor port activated the 3-way solenoid, channelling the odor to the port. The line from the suction compressor was connected to the odorant carrier tube at 8 cm from the odor port. This design provided rapid odor delivery (approximately 0.1 s) following a rat’s nose poke in the odor port. Initial pilot training of this task suggested that rapid odor delivery was critical to the rats’ acquisition of the task (Koger & Mair, unpublished observations). Flowmeters monitored and regulated airflow and suction pressure through each channel of the olfactometer.
Two Omron Sysmac S-6 programmable controllers were utilized to control the task parameters and record the subjects' behavior. The primary Omron controlled the house lights, intertrial interval duration, delivery of odorant to the chamber, and delivery of water reinforcers. In addition, it received inputs from the two sets of photocells and contact relay circuit, thus registering the rats' responses as described below. The primary Omron also provided a signal to change odorants on specified trials. The second Omron received the signal, and directed outputs to the 16 2-way odor selection solenoids.

Behavioral Training

Group A.

Dipper Training. Initially, subjects were trained to lick at the water spout by delivering 0.1 ml water on a FI 5 s schedule for one session (100 trials). The house lights remained on throughout the session.

Shaping. Subjects were then trained to insert their nose into the odor port (registered by a break in the photocell beam across the odor port opening) prior to responding to the spout (recorded by the photocell beam in front of the spout or by activation of the contact relay). During this phase of training, house lights were turned on, and the presence of a rat's nose in the odor port resulted in the presentation of
one of the sixteen odorants. If the odor port photocell beam was continuously broken for 0.1 s, a response to the spout within 4 s of the odor port response resulted in delivery of 0.1 ml water. Regardless of whether the rat responded to the spout within 4 s, the trial was terminated at the end of this response window, the house lights were extinguished for the duration of a 5 s intertrial interval (ITI)\(^4\), and the odor selection mechanism was advanced to the next stimulus\(^5\). After one session (30 trials), the odor port response requirement was increased to 0.3 s duration for one session (30 trials), and finally to 0.5 s duration for one session (60 trials).

To facilitate early stages of training, a 3-sided, wooden enclosure (23 cm x 18 cm x 20.5 cm) covered with a sheet of Plexiglas was placed inside the chamber to restrict the rat to the area immediately adjacent to the alcove. This enclosure remained in place throughout dipper training (i.e., initial FI 5 s training) and the first two sessions (30 trials each) of shaping.

**Group B.**

Initial training was identical to that reported for Group A, with the exception that dipper training was immediately

\(^4\) It should be noted that since this procedure is continuous non-matching to sample, the intertrial interval is functionally equivalent to a retention interval.

\(^5\) The sequential order in which the stimuli were presented was fixed, although the starting point within the sequence varied between subjects and between sessions.
followed by one shaping session (60 trials) with a 0.5 s odor port response requirement, and no confining enclosure was in place during the shaping session. These subjects had previously been trained on a version of this task with an odor port response requirement of 1.2 s. Thus, they readily adapted to the shorter response requirement and required no additional shaping.

*Continuous Olfactory Non-Matching to Sample (CONMTS).* Both groups of rats were then trained on CONMTS. As in the final shaping session, the house lights were turned on and an odor port response produced delivery of an odor stimulus (the sample S). A 0.5 s odor port response followed by a response to the drinking spout within 4 s produced 0.1 ml water. Regardless of whether the rat made a response to the spout, the house lights were extinguished at the end of the 4 s response window, and they remained off throughout a 5 s ITI. The house lights were then turned on to indicate the next trial, and an odor port nose poke resulted in delivery of an odor that was either the same as or different from the S delivered on the previous trial. If the odor was different from the preceding stimulus (i.e., a non-match, or S+ trial), a response to the drinking spout within 4 s produced delivery of 0.1 ml water, followed by house light offset and ITI. If the odor was the same as the preceding stimulus (i.e., a match, or S- trial), a response to the drinking spout within
4 s resulted in the immediate offset of the house lights for the remainder of the 4 s response window and throughout a 7 s "time out" period, followed by the 5 s ITI with the lights remaining off. If a drinking spout response did not occur within 4 s on either trial type (S+ or S-), the trial was terminated and the 5 s ITI was initiated.

A daily session of CONMTS typically consisted of 50 stimulus presentations. The order of S+ and S- trials was varied on an irregular but balanced schedule. Responses to the drinking spout occurring within the 4 s response window were recorded by the main Omron controller, and were classified according to signal detection terminology, as follows: Hit - a spout response on an S+ (changed odorant) trial; False Alarm - a spout response on an S- (unchanged odorant) trial. Not responding within the 4 s response window were similarly classified: Miss - no spout response on an S+ trial; Correct Rejection - no spout response on an S- trial. Thus, hits and correct rejections were "correct" responses, while false alarms and misses were "incorrect", conforming to the non-matching paradigm.

A correction procedure was employed following false alarms throughout CONMTS training. Correction trials consisted of a repetition of the S- trial on which the false

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6 During initial training of Group A, sessions were run at 100 trials each for 4 - 5 sessions. The number of trials was subsequently reduced to 50 to accommodate a larger number of animals in daily sessions.
alarm occurred. If the rat responded again (a second false alarm), a second correction trial ensued. The irregular S+/S- trial order was reinstated following the second correction trial, regardless of the rat’s response. Performance on correction trials was not included in the response measures, nor were the correction trial stimulus presentations counted in the number of trials per session.

Subjects failing to perform during presurgical training were dropped from the study and returned to ad libitum water. In total, 3 rats from Group A were dropped at the dipper training stage for failing to respond to the drinking spout; 1 subject from Group B was dropped following the shaping session for not completing 60 trials in 30 minutes; and 6 rats from Group A and 1 from Group B were dropped during CONMETS presurgical training for failing to finish 50 trials in 45 minutes. The remaining subjects completed a minimum of 1000 trials prior to selection for surgery.

Two days prior to a scheduled surgery, subjects were rank ordered based on performance (percent correct) across the 4 preceding sessions (50 trials per session). The subjects who had achieved the highest levels of performance were then selected in blocks of four and randomly assigned to one of the treatment conditions: lesions of the L-IML region in thalamus; medial wall of cortex; cortex dorsal to the rhinal sulcus; or sham operated control. This procedure balanced the treatment groups for performance level and extent of training, and
allowed continued presurgical training for slower learners. Following assignment to surgical condition, subjects were put on ad libitum water for at least 36 hours prior to surgery. In total, 28 rats (those performing at the highest levels) were ultimately selected for surgery.

**Experimental Treatments**

In each surgical treatment, subjects were anesthetized by i.m. injection of Rompun (xylazine - 100 mg/ml at doses of 8.5 mg/kg of body weight) and Ketaset (ketamine - 100 mg/ml at doses of 88 mg/kg). A small amount of Dexasporin, an ophthalmic ointment, was placed on their eyes to prevent dryness and irritation. The rats were then positioned in a Kopf stereotaxic instrument with the incisor bar 3.3 mm below the interaural line (IA), and the scalp was opened following sterile surgical procedures. Experimental lesions were produced by lowering a radiofrequency (RF) electrode (Radionics TCZ) to stereotaxic coordinates listed below and, using a Radionics RFG-4A lesion generator, heating the tip to either 70 degrees C for 60 s (L-IML lesions) or to 75 degrees C for 60 s (the two cortical lesion sites). After surgery, the scalp was sutured and an antiseptic solution (Povidone Iodine 10%) applied to the wound. Sham operated controls were treated comparably, except that no electrodes were lowered into their brains.
Thalamic Lesions. As in previous studies (Mair, Robinson, Koger, Fox, & Zhang, 1992; Harrison & Mair, 1993), the L-IML lesions were made bilaterally at 6 sites, 1.0 mm off the midline (measured from the center of the cerebral sinus) at the following positions: anterior-posterior (AP) = 5.2, dorsal-ventral (DV) = 3.6 and 4.8; AP = 6.2, DV = 3.6 and 5.0; and AP = 7.2, DV = 3.6 and 5.0, in mm relative to the IA line.

Cortical Lesions. The AP coordinates were measured from bregma for both medial wall and rhinal sulcal lesions. For medial wall lesions, the medial-lateral (ML) coordinates were measured from the center of the cerebral sinus, and DV coordinates were measured from the surface of cortex over each lesion site. For the rhinal sulcal lesions, ML was based on the position of bregma, and DV was measured relative to the surface of cortex at the most medial lesion site in each hemisphere at each AP location. The medial wall cortical lesions were placed bilaterally at the following coordinates, in mm relative to the above described landmarks: a) ML ±0.8 at AP +4.7/DV -1.0, AP +3.7/DV -1.0 and -2.2, AP +2.7/DV -1.0 and -2.2, AP +1.7/DV -1.0 and -2.2, AP +0.7/DV -1.0 and -2.2; b) ML ±2.0 at AP +4.7/DV -1.0, AP +3.7/DV -1.0, AP +2.7/DV -1.0. The rhinal sulcal cortical lesions were placed bilaterally at the following coordinates, in mm relative to the above described landmarks: a) ML ±1.8 and ±3.0 at AP +4.7/DV -2.2;
b) ML ±1.6, ±2.8, and ±4.0 at AP +3.7/DV -4.0; c) ML ±3.0 and ±4.2 at AP +2.7/DV -5.1 (Harrison & Mair, 1993).

Following surgery, the rats were wrapped in small blankets to maintain body temperature until they appeared alert and mobile (typically 8 to 10 hours), and then placed on ad libitum water and chow for a recovery period of 10 to 17 days. Subjects were then returned to a 23.25 hour water deprivation schedule for 48 hours prior to retraining on CONMTS.

**Postsurgical training**

*Retraining.* Subjects were retrained on CONMTS, as conducted during presurgical training, for 20 sessions (1000 trials total).

*Stimulus Set Manipulation.* In order to determine the effect of reduced stimulus set size, and whether the treatment groups were affected differentially, the rats in the present study were subjected to sessions with a reduction in the number of odor stimuli. Four stimulus set sizes were utilized (2, 4, 8, and 16), with the set size held constant in individual sessions (48 trials/session). The order in which the set sizes were presented between sessions was determined randomly for a block of four sessions (one session at each set size). In order to obtain an adequate sampling of performance, three blocks of four sessions were conducted (for a total of
144 trials/set size). By varying the presentation of the sixteen odorants, a different subset of odors was used in conjunction with each of the smaller stimulus set sizes. For example, in the first block, the 2-stimuli set size might have consisted of the first and second odors in the sequence; the second block, the fifth and sixth; and the third block, the ninth and tenth odorants in the series.

Responses were counted and collapsed across the three sessions at each stimulus set size. Additionally, within-session performance was gathered. That is, an individual rat's responses were recorded at three points within a session, following completion of 16 trials each. Sessions were thereby subdivided into thirds.

**Intertrial Interval.** Subsequent to the stimulus set size manipulation, the effects of increasing the ITI were examined. Initially, two sessions (50 trials per session) were run at the ITI used in previous training (5 s). Two sessions (50 trials per session) were then conducted at each of three longer intervals (10, 20, and 40 s).

**Task Verification.** During a session, the solenoids and relays that are incorporated within the olfactometer generate many auditory stimuli. In order to ensure that these sounds were not serving as discriminative stimuli, and to verify that olfactory stimuli were exclusively guiding performance on this
task, one session (50 trials) was run in which no odors were delivered. The apparatus remained fully intact, with the exception that the tubing from the odor delivery flowmeter was disconnected. Thus, all visual and auditory stimuli remained, but a clean air (non-odorized) stream was presented when the rat made a nose poke response in the odor port.

**Discrimination Training.** Following all other behavioral testing, the same subjects were trained on a two-odor discrimination procedure. The apparatus used for CONMTS was modified to deliver one of two odors on each trial. One odor (eugenol) was designated the $S^+$, and a response to the drinking spout within 4 s of sampling the stimulus for a minimum of .5 s produced a water reinforcer, as described above for CONMTS. Following one session (50 trials) during which only the $S^+$ was presented, the $S^-$ (amyl acetate; the odor not associated with reinforcement) was introduced. As in CONMTS, responses were recorded and classified as follows: Hit - a spout response on an $S^+$ trial; False Alarm - a spout response on an $S^-$ trial. Not responding within the 4 s response window were similarly classified: Miss - no spout response on an $S^+$ trial; Correct Rejection - no spout response on an $S^-$ trial.

The correction procedure employed in CONMTS was continued, wherein false alarms were followed by a repeat of the $S^-$ condition, and a second false alarm led to a second $S^-$
repeat. Following the second correction trial, the irregular S+/S- trial order was reinstated. Performance on correction trials was not included in the response measures, nor were the correction trial stimulus presentations counted in the number of trials per session.

Training on the first discrimination continued for 10 sessions (500 trials total). A new odor pair was then introduced, with geraniol serving as the S+ and phenethyl alcohol as the S-. A previous study demonstrated these two odorants were difficult for humans to discriminate (both were categorized as floral), and that rats with MDn lesions required significantly more trials to reach criterion than did controls when these two odorants served as discriminative stimuli (Eichenbaum et al., 1980). Training on the second pair continued for 10 sessions (500 trials total).

Quantitative Analyses

The initial account of the CONMTS paradigm reported behavioral results in terms of percent correct (Otto & Eichenbaum, 1992). This measure does not differentiate between performance deficits due to false alarms as opposed to misses. Interpretation of observed deficits is therefore restricted, since no distinction can be made between sensitivity to changes in the stimulus, which is presumably dependent on remembering the odorant, and general responsivity independent of remembering. Consequently, the current data were considered
in a manner conforming to signal detection theory to distinguish between stimulus discriminability and the subject's bias toward responding (e.g., Green & Swets, 1966; Nevin, 1991).

Measures of the four treatment groups' performance during each stage of postsurgical testing were compared using analysis of variance (ANOVA) with repeated measures (sessions). The within-subject ANOVAs were conducted in accordance with the procedure suggested by Greenhouse and Geisser to control for violations of the assumption of sphericity (homogeneity of variance) in randomized block designs (cf. Kirk, 1982; Myers & Well, 1991). If an obtained F value was non-significant following a comparison with conventional degrees of freedom \([(p-1)\text{ and } (n-1)(p-1)]\), the analysis was terminated without rejecting the null hypothesis. If the obtained F with conventional degrees of freedom was declared significant, a Geisser-Greenhouse conservative F test was performed. This test requires a larger F value by reducing the degrees of freedom, thus compensating for the increased Type 1 error rate associated with nonsphericity. All of the results that are reported as significant were tested against Geisser-Greenhouse critical values. Post hoc comparisons were conducted using the Student-Newman-Keuls procedure. This method is more powerful than the Tukey procedure for testing pairwise comparisons, although it is more susceptible to Type 1 error (Kirk, 1982; Myers & Well, 1991).
Histological Analyses

Following all behavioral training, subjects were sacrificed under deep anesthesia [i.m. injection of Rompun (xylazine - 100 mg/ml, at doses of 10 mg/kg of body weight) and Ketaset (ketamine - 100 mg/ml, at doses of 100 mg/kg body weight)] by perfusion of physiological saline followed by 10% neutral buffered formalin. The brains were removed and fixed by storage in the formalin solution. Tissue was sectioned in the coronal plane at 30 μm, and every fifth section mounted on gelatinized slides and stained with cresyl violet. Slides were examined microscopically by two independent observers, unaware of the subjects’ behavioral performance, to determine the placement and extent of lesions. Cortical lesions were mapped according to the subdivisions identified by Zilles (1985).
RESULTS

Quantitative Analyses

Exploratory analyses revealed that quantitative measures derived from signal detection theory, designed to separate stimulus discriminability from the subject's bias toward responding (e.g., Green & Swets, 1966; Nevin, 1991), were unsuitable with respect to the obtained data. The computational formulas provided by Green and Swets (1966) for sensitivity ($d'$) and bias ($b$) assume an underlying Gaussian distribution and equivalence of variance. These assumptions are not always valid, and the results are undefined when the subject's probability of a hit equals 1.0 or the probability of a false alarm equals 0. To overcome these empirical obstacles, several nonparametric indices were developed (e.g., $A'$, $B''$: Grier 1971; SI, RI: Frey & Colliver, 1973). However, Grier's (1971) bias measure and Frey and Colliver's (1973) sensitivity index are undefined when the probability of a hit and of a false alarm both equal 1.0. Similarly, Nevin's (e.g., 1991) quantification of discrimination (i.e., sensitivity) and bias are undefined when the probability of a miss equals 0.

Preliminary attempts to utilize signal detection models with the current data established that false alarms constituted the majority of errors during the present study, and accounted for the differential performance by the lesioned
subjects. As exhibited in Figure 2 (CONMTS retraining), the probability of responding on S+ trials (i.e., hits) did not vary significantly between groups. Accordingly, all data were subsequently evaluated and group means were compared based on percent correct. However, the graphic illustrations (Figures 2 – 8) depict the probability of responding on S+ (hits) versus S- (false alarms) trials for each treatment group (see Tables 3-7 for specification of the average probability of false alarms for each task manipulation).

Continuous Olfactory Non-matching to Sample. There was no difference between the groups during the eight sessions (400 trials) immediately preceding surgical treatment (p = .8990). However, a repeated measures ANOVA comparing pre- and postsurgical performance (400 trials both before and after surgery) revealed a significant effect of treatment, F (3,24) = 4.626, p = .0109. Post hoc analyses of the first block of four sessions (200 trials) following postsurgical recovery revealed that each of the three treatment groups differed from the control group (alpha = .01).

With continued postsurgical training, all three surgical groups exhibited some attenuation of their responding during S- trials (Figure 2). Nevertheless, a repeated measures ANOVA

7 It was during the final block (block #5) of postoperative training that the aforementioned obstructive pneumonia became apparent. All animals were immediately placed on ad libitum water and antibiotic. One treatment cohort
across the first four blocks of postsurgical training confirmed the effect of treatment, \( F (3,24) = 12.050, p < .0001 \). In addition, there was a significant effect of trial block, \( F (3,72) = 25.609, p < .0001 \), and a significant interaction between treatment and trial block, \( F (9,72) = 4.238, p = .0012 \). When 1 factor ANOVAs were conducted on separate blocks of postsurgical trials, the two cortical groups did not differ significantly from controls during the second, third, or fourth blocks of postsurgical training (alpha > .05). The L-IML lesioned group differed significantly from the control group (alpha = .01) in each of the four blocks of trials. In addition, the L-IML group differed from the rhinal sulcal group in the second (alpha = .01), third (alpha = .01), and fourth (alpha = .05) trial blocks; and from the medial wall group in the second (alpha = .01) and third (alpha = .05) blocks of trials. The difference between the L-IML and medial wall groups failed to reach statistical significance in the fourth trial block (alpha > .05) (the difference between the groups equalled .087; the critical difference was .089).

(n = 8) had not yet completed 20 sessions at this time. Thus, postsurgical statistical analyses are restricted to the first 16 sessions (4 blocks) following surgery, which all subjects completed. The graphic representation in Figure 2, however, includes all animals completing any portion of the fifth block of trials (n = 7 in all groups except L-IML, n = 5). It should be noted that the apparent improvement exhibited by the L-IML group in block # 5 can be attributed to the elimination of two L-IML subjects from behavioral testing during the fifth block.
Stimulus Set Manipulation. When the number of stimuli presented during a session was manipulated, a repeated measures ANOVA revealed a significant effect of surgical treatment, $F(3,23) = 8.229$, $p = .0007$. Subsequent post hoc analyses demonstrated that the L-IML group differed significantly from control, medial wall and rhinal sulcal groups (alpha = .01).

The number of stimuli presented had a significant effect, $F(3,69) = 28.845$, $p < .0001$. A significant interaction between the number of stimuli and treatment, $F(9,69) = 4.995$, $p < .0001$, reflected a tendency by control and cortical lesioned animals to make fewer false alarms as the number of stimuli increased (Figure 3).

A within-session analysis of performance demonstrated a significant effect, $F(2,46) = 16.400$, $p < .0001$, suggesting an overall change in performance across blocks of sixteen trials within a session. A trend towards an interaction between session thirds and treatment failed to reach significance, $p = .0703$ (Figure 4). The number of stimuli interacted with session thirds, $F(6,138) = 2.487$, $p = .0404$, primarily reflecting poorer performance during the two-stimuli condition as the session progressed; that is, the number of false alarms increased within a session, particularly when only two odors were used. There was no interaction of number of stimuli x thirds x treatment ($p = .6014$).
Intertrial Interval. There was a significant effect of treatment on performance of CONMTS with increasing ITIs, $F(3,23) = 11.737, p < .0001$. Post hoc analyses revealed a significant difference between L-IMLs and the other three groups (alpha = .01). The effect of ITI was significant, $F(3,69) = 3.125, p = .0502$, but there was no interaction between ITI and treatment ($p = .8116$). A graphic representation of performance (Figure 5) revealed a trend toward more false alarms by the medial wall group, relative to the control and rhinal sulcal lesioned subjects, as the ITI was increased.

Task Verification. When the odorized stream was disconnected, performance of all groups fell to chance; that is, the probability of responding on trials in which a stimulus advance signal was given (S+) was equivalent to the probability of responding on trials in which no advance signal occurred (S-) (Figure 6). A 1 factor ANOVA confirmed that there were no group differences in the scores comparing these two measures (probability of response on S+ minus probability of response on S-) ($p = .8979$).

Discrimination Training. A repeated measures ANOVA across the 10 sessions of training on the first discrimination indicated no differences between the groups ($p = .4678$). There was a significant effect of session, $F(9,207) = 49.171, p < .0001,$
resulting from a reduction in responding to the S- by all groups with continued training (Figure 7). No interaction existed between session and treatment ($p = .3405$), signifying that the extent of improvement was comparable between groups.

Similar results were obtained during 10 sessions of discrimination training on a second pair of odorants, such that no effect of treatment was revealed by a repeated measures ANOVA ($p = .4043$). A significant effect of session, $F (9,207) = 56.819, p < .0001$, as in the first discrimination, reflected a significant attenuation of responding on S- trials by all groups (Figure 8). Again, there was no interaction between session and treatment ($p = .9646$). Of note is that the pair of odorants used in the second discrimination task (phenethyl alcohol versus geraniol) was selected because these odorants were shown to be difficult to discriminate (Eichenbaum et al., 1980). However, no differences were observed in the acquisition rate for either discrimination in the present study (cf. Figures 7 and 8).

**Histological Analyses**

All subjects were judged to have complete lesions, and therefore all were included in the quantitative analyses. Figures 9 and 10 represent scatterplots of individual subjects' performance during the first (Figure 9) and fourth (Figure 10) block of trials during postsurgical CONMTS
training. For each lesion group, the subject that had performed at the median during postsurgical block #4 was selected for histological drawings. The brain sections were examined with light microscopy, and were traced using a drawing tube at 2X magnification. Three tracings were made for each of the two cortical lesioned subjects; sections were taken at 4.7, 3.7, and 2.7 mm from bregma to reflect anterior-posterior dimensions of the lesions. Two sections were drawn for the median performing L-IML lesioned subject to depict the anterior-posterior magnitude of the lesion; these were taken at 7.2 and 5.2 mm from IA. Following a radiofrequency lesion, surrounding tissue frequently collapses, and the tissue lining the lesion site is damaged. No compensation was made in the drawings for alterations in the shape of the sections due to collapsed tissue. However, regions contiguous with the lesion that sustained damage (i.e., neuronal loss and proliferation of glial cells) are identified by blackened areas.

Cortical lesions included tissue destruction or severe gliosis, calcification, and cell loss in layers 1 through 4. A medial wall lesion included bilateral lesions of Cg1, Cg3,

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Figures 9 and 10 reflect individual performances during postsurgical blocks 1 and 4, originally presented as group means in Figure 2. In contrast with earlier figures which depicted performance as the probability of responding, percent correct was chosen to represent the data in Figures 9 and 10 since it provides a single measure of each subject's performance. Although percent correct does not distinguish between types of errors (misses and false alarms), it facilitates comparisons between individual animals.
and Fr2 extending, on average, from +0.7 to +5.2 mm from bregma (Zilles, 1985) (Figure 11, left panel). Rhinal sulcal lesions consisted of bilateral damage to LO and dorsal AI cortices from +1.2 to +5.2 mm from bregma, on average (Zilles, 1985). Orbital cortices (MO and VO) were typically spared following rhinal sulcal lesions (Figure 11, right panel). Lesions of the L-IML thalamic site were comparable to those described in prior experiments (Harrison & Mair, 1993; Mair & Lacourse, 1992; Mair, Robinson et al., 1992). The average coordinates were: AP 5.2 mm to 7.2 mm relative to IA (Paxinos & Watson, 1986); DV extending from the habenula through the central medial nucleus of thalamus; and ML centered bilaterally from 0.9 mm - 1.1 mm from the midline (Figure 12). One L-IML lesioned subject exhibited sparing of approximately 0.6 mm of the anterior portion of the target IML site. An examination of his behavioral data revealed a lack of impairment during the fourth block of postsurgical training (see Figure 10).
DISCUSSION

Frontal cortical lesions in either of the MDn projection terminal regions (the medial wall or rhinal sulcus) produced a transient deficit on initial reacquisition of CONMTS. Damage to the L-IML site of thalamus produced a comparable initial deficit. However, only the effect of the thalamic lesions persisted throughout subsequent training, including sessions in which the number of sample stimuli and the ITI were varied. In all four treatment groups, the probability of responding to the S+ was uniformly high, and the majority of errors consisted of responding during S- trials (i.e., false alarms).

The performance of one L-IML lesioned subject was not impaired, and did not differ from controls or the two cortical groups by the completion of CONMTS retraining. Histological analyses revealed thalamic sparing in the most anterior portion of the target lesion site in this L-IML subject. This finding is consistent with a recent report that destruction of the full anterior-posterior extent of the L-IML site is necessary for production of deficits on a spatial non-matching to sample task (Mair, Robinson et al., 1992; see also Hunt & Aggleton, 1991).

Task Manipulations

Reducing the number of stimuli selectively influenced the performance of the control and cortical lesion groups, with
these three groups responding more to S-trials (making more false alarms) during the conditions with two or four stimuli than with eight or sixteen stimuli. These findings are generally consistent with prior evidence of proactive interference occurring in the context of non-matching to sample paradigms (Otto & Eichenbaum, 1992; Pontecorvo, 1983). The present data suggest that cortical lesioned rats were not more susceptible to interference effects than were controls, consistent with Otto & Eichenbaum's (1992) observations following rhinal sulcal lesions in rats. Thalamic lesioned rats made more false alarms than the other three groups regardless of the number of stimuli presented during a session, and their performance did not vary systematically as the number of sample stimuli decreased. However, it is likely that this lack of differential effect of set size on the thalamic group reflects a "floor effect", as their false alarm rate fell within the range of approximately 85 - 90% probability across all four set sizes.

A within-session assessment revealed a similar demonstration of proactive interference effects in the control and cortical lesioned groups. These three groups made significantly more correct rejections during the first third of a session than they did throughout the remainder of the session, demonstrating a decrease in accuracy (increase in false alarms) as the session progressed. This effect was particularly evident when only two stimuli were used in a
session. The two cortical groups did not differ from each other or from the control group. As in the overall set size manipulation, the L-IML lesioned group emitted significantly more false alarm responses during all three session portions, and did not exhibit differential performance as the sessions progressed. Again, this can be attributed to a floor effect.

A third manifestation of proactive interference emerged unexpectedly. The control and cortical lesioned groups exhibited a moderate decrease in accuracy as the CONMTS parameters were manipulated following initial postsurgical retraining. Declining accuracy was characterized by an increase in false alarm responses across all three occurrences of proactive interference. This finding seemingly contradicts the expected pattern of proactive interference effects, which is that the accumulating history of exposure to the same 16 odors should produce more responses indicating "sameness" (i.e., correct rejections and misses). The distinct bias toward responding in this task may account for this counter-intuitive finding (see also Interpretive Issues, to follow).

Increasing the ITI tended (nonsignificantly) to increase the accuracy of the L-IML group, although they continued to execute significantly more false alarms than the other three groups at all four ITIs tested. The two cortical groups did not differ significantly from controls or from each other, although the medial wall lesioned rats exhibited a trend toward more false alarms as the ITI increased.
Despite a significant main effect of ITI on performance, the forgetting functions obtained with the CONMTS paradigm were relatively flat, compared to rats' performance on spatial non-matching to sample (e.g., Mair & Kivlahan, 1993; Mair & Lacourse, 1992). This outcome may reflect the strength of odor memory in rats, and is comparable to findings with non-amnesic humans on both odor-recognition memory (e.g., Mair et al., 1980) and visual non-matching to sample (McKee & Squire, 1992). Healthy human subjects' performance of an odor recognition task was not affected by retention intervals of up to 30 seconds (Mair et al., 1980). Further, normal humans attained 91% correct performance at retention intervals of 10 minutes, and only declined to approximately 75% correct at delays of 30-32 hours on visual non-matching to sample (McKee & Squire, 1992). There are other possible interpretations, however.

First, optimal levels of accuracy were not observed in any of the groups at even the shortest ITI utilized (5 s). Investigations of performance on spatial non-matching to sample have demonstrated significant delay dependent forgetting functions primarily when subjects attain 90 to 95 percent correct performance at the shortest delays (typically less than 2 s; Mair & Kivlahan, 1993; Mair & Lacourse, 1992). Although a forgetting function may not be observed as the ITI is increased from 5 s, shorter ITIs are not appropriate for use with the CONMTS procedure, because: a) adequate time must
be provided for exhaust and changeover of the odors between trials; and b) adaptation to the olfactory stimuli might be more likely to occur with odor presentations occurring at shorter intervals (e.g., Engen, 1971).

Alternatively, a failure to observe significant forgetting on CONMTS may reflect procedural factors. The ratio of the ITI to the retention interval was observed to be critical to performance of matching or non-matching to sample in pigeons, such that a constant ratio produces consistent performance (Roberts & Kraemer, 1982). Although this finding has apparently not been replicated in rats (see Dunnett & Martel, 1990), it is conceivable that a similar mechanism could be contributing to the relative lack of performance decay with increased ITIs in the present study. Specifically, in CONMTS, the ratio of the ITI to the retention interval essentially remains constant as the ITI is increased, since they are functionally equivalent. Less proactive interference occurs with increasing ITIs, presumably because the temporal distance and hence the discriminability of the trials is augmented (Roitblat & Harley, 1988). Thus, any potentially detrimental effects of increasing the retention interval are essentially counterbalanced by an attenuation of interference with increasing ITIs.

In an additional task manipulation, stimulus control by odors was verified in the CONMTS task, as disconnection of the tubing from the odor delivery flowmeter produced chance level
performance in all four treatment groups. No differences were observed between the probability of responding to S+ versus S- trials, with the trial type determined as in CONMTS (the generation of a "stimulus advance signal" by the primary controller, although no odors were actually delivered).

Finally, the introduction of a two-odor discrimination task demonstrated that all subjects were able to acquire a go/no-go procedure when the working memory requirements of CONMTS were eliminated. In other words, since the apparatus and general procedures utilized within the CONMTS task were retained for discrimination training, the ability to perform the discrimination tasks indicates that reference memory capacity remained intact in the lesioned animals. The discrimination procedures were exclusively distinguished from CONMTS by the relation between stimuli and reinforcement. In CONMTS, the relation is dynamic, such that a reinforcer is available only if the present odor differs from the stimulus on the preceding trial. Therefore, a correct response must be predicated on remembering the odor from the previous trial. In contrast, discrimination employs a static contingency: if odor A, then a response will be followed by a reinforcer; if odor B, then no reinforcer will be available. Unlike the results obtained with the CONMTS paradigm, no group differences were observed at any time during the training of two separate odor discriminations.
Interpretive Issues

Virtually all errors by controls or by lesioned subjects were false alarms (responding to the S-) on both CONMITS and discrimination tasks. Because group differences were thus characterized exclusively by a divergence in false alarm rates, it could be argued that the effect of a lesion was to increase responsivity. In fact, responsivity, hyperactivity, and impulsivity are frequently noted characteristics of both monkeys and humans following frontal damage, particularly when the orbital cortex is involved (Fuster, 1989; Stuss & Benson, 1986). Furthermore, performance of go/no-go tasks is impaired following orbital lesions in primates, presumably due to an inability to suppress competing response tendencies (Stuss & Benson, 1986). The responsivity issue raises questions concerning the validity of the go/no-go CONMITS task as a measure of remembering.

It is clear that rats have a strong bias toward responding within the context of the CONMITS paradigm, evidenced by an overall response probability of approximately 75% (100% probability of responding on S+ and 50% probability of responding on S-) at their "best", and following extensive training. Further, all subjects displayed an elevated response bias when the odorized stream was disconnected in the task verification described above. A similar trend was observed in discrimination training, wherein all subjects exhibited approximately 100% probability of responding to the S+, and
very high initial responding to the S-. Thus, the effect of a lesion may be to reduce suppression of the inherent tendency to respond in this go/no-go paradigm.

Three lines of evidence argue against the hypothesis that the CONMTS deficits resulted from an inability to suppress responding. First, the task verification condition presumably created a situation in which the trial type (S+ and S-) was indeterminate. The subsequent increase in responsivity, exhibited by intact and lesioned subjects alike, implies a bias of rats to respond when stimulus information was insufficient to determine the correct choice. It could thus be argued that the increase in false alarms by the lesioned rats during CONMTS retraining represents the expected pattern of performance for an animal unable to utilize the stimulus cues.

Second, an increase in false alarm responses was noted as the number of stimuli was reduced, as well as within and between sessions. As discussed previously, this finding stands in contrast with the expected pattern of proactive interference effects, which would predict fewer false alarm responses with increasing interference from prior experiences. The bias toward responding in this task may account for this finding. The accumulating exposure to the same stimuli may create a condition in which the subject has increasing difficulty distinguishing match from non-match trials. As in the task verification condition, the rats' tendency may be to respond when unable to utilize the stimulus cues.
Third, discrimination training results augment the evidence against interpreting lesion effects in terms of an increase in responsivity. When the task was altered to exclude the working memory demands (i.e., eliminating the non-matching to sample requirements) and to impose a specific and static contingency between one odor and reinforcement, no differences were observed between the groups. Initially, all four treatment groups exhibited very high levels of responding, but they learned to suppress responses to the S- at comparable rates. In fact, by the final sessions of training on the first discrimination, all subjects were exhibiting much higher levels of accuracy, dominated by hits and correct rejections, than was observed at any point during CONMTS training. It is therefore clear that both the intact and lesioned subjects could suppress their bias to respond when the task was simplified. Thus, general responsivity cannot account for the differential group performances observed in the CONMTS task.

A second issue concerning task validity relates to indirect effects on CONMTS performance through the use of a correction procedure. An increase in false alarms, and consequently of nonreinforced S- trials, is accompanied by a reduction in the density of reinforcement since the number of S+ trials remains constant. A reduction of reinforcement density could have adversely affected postsurgical performance (Nevin, personal communication). However, there is no evidence in the current results that CONMTS performance is affected by
reinforcement density. Although all three treatment groups exhibited an initial increase in responsivity (and, by extension, experienced a significant reduction in reinforcement density), both cortical lesioned groups rapidly regained control group levels of correct rejection rates. It is thus unlikely that the situation parameter changes associated with increased responsivity produced a lasting effect, since the medial wall and rhinal sulcal lesioned subjects recovered from a deficit that was initially comparable to the impairment in the L-IML group. While a reduction in reinforcement density may have contributed to the initial performance decrement following surgery, it cannot account for the persistent CONMTS impairments observed in the L-IML lesioned group.

Comparisons with Prior Research

Lesions of the Rhinal Sulcus.

Rhinal sulcal lesions were previously shown to affect the rate at which rats learn olfactory discriminations (Eichenbaum et al., 1980; 1983), compound conditional odor discriminations (Whishaw et al., 1992), and CONMTS (Otto & Eichenbaum, 1992). The present experiment demonstrated that these lesions also affect initial postsurgical performance of CONMTS acquired prior to rhinal sulcal ablation. However, by the second block (200 trials) of postsurgical retraining, these subjects
returned to performance levels that did not differ statistically from controls.

The current findings were consistent with the prior report of an initial (acquisition) impairment of CONMTS following rhinal sulcal lesions (Otto & Eichenbaum, 1992). However, the interpretation that the rhinal sulcal cortex mediates the acquisition of procedural information necessary for task performance (Otto & Eichenbaum, 1992) cannot account for the current results since the subjects in this study were pretrained on the CONMTS task prior to surgery. In addition, the rhinal sulcal lesioned animals acquired the odor discrimination tasks in the present investigation at a rate comparable to that exhibited by the other three groups.

The short-lived effects of cortical lesions on go/no-go CONMTS in the present investigation are comparable to initial acquisition or relearning deficits on go/no-go tasks observed in monkeys with orbital frontal lesions. These monkeys emitted significantly more false alarm responses than did controls. However, the frontal lesioned monkeys demonstrated a clear tendency to overcome the inappropriate response patterns with time and continued training (Fuster, 1989).

Lesions of the Medial Wall.

Lesions of the medial wall of PFC affected CONMTS performance in a transient manner, similar to the effects of rhinal sulcal lesions. Further, a minor (nonsignificant)
deficit was observed in the medial wall group at the longest ITI (40 seconds). Although the limited number of subjects may have restricted the power of the analyses and consequently obscured the significance of the effect, the present results stand in contrast with Harrison's (1992) documentation of deficient performance by medial wall lesioned rats on spatial non-matching to sample with a minimal delay (3 seconds) between the sample presentation and the opportunity to respond.

Eichenbaum and colleagues (1983) argued that MDn projections to the medial wall and rhinal sulcus were involved in the mediation of spatial and olfactory learning, respectively. The initial deficit on CONMTS manifested by medial wall and rhinal sulcal lesioned groups in the present investigation suggests that both cortical areas may be involved in olfactory learning. However, animals with lesions of either area were capable of relearning the CONMTS task and demonstrated normal acquisition of odor discrimination. One possible explanation is that olfactory projections to the entorhinal cortex can mediate CONMTS performance. Although entorhinal cortical lesions did not impair odor discrimination learning (Otto, Schottler, Staubli, Eichenbaum, & Lynch, 1991) or initial CONMTS acquisition, more rapid forgetting and increased susceptibility to proactive interference on CONMTS was observed in these animals (Otto & Eichenbaum, 1992). If olfactory-entorhinal pathways are involved in CONMTS
performance, then the transient impairment following medial wall lesions may reflect damage to the entorhinal projections to areas in PFC (i.e., PL and IL cortices) (Swanson & Kohler, 1986).

It is conceivable that pathways from thalamus to either the medial wall or rhinal sulcal region of PFC are capable of mediating performance on the CONMTS task. In that regard, the destruction of one cortical region might create a partial disruption of previously learned response strategies, while the remaining pathways could be sufficient to mediate relearning of the task or the acquisition of other odor guided tasks. In order to test this hypothesis directly, it would be necessary to obliterate both regions of PFC in combination.

In sum, the present investigation confirmed that despite the anatomical relationship between prefrontal and primary olfactory cortex, there is no evidence that olfactory learning or working memory is permanently affected by lesions of the PFC in rats. The current findings seem to contrast with prior research on primates sustaining focal destruction of orbital frontal cortex. Human subjects were impaired on an odor recognition task that resembles the CONMTS task (Potter & Butters, 1980), and on a task which requires that odorants be matched with verbal labels (Jones-Gotman & Zatorre, 1988). In addition, orbital lesioned monkeys exhibit deficient odor quality discrimination (Tanabe et al., 1975). However, a failure to repeatedly test these subjects precludes a direct
comparison with the present study, since improvement over time and subsequent testing might have occurred in the human and monkey subjects.

Lesions of the L-IML Thalamic Site.

A profound and enduring effect was observed in thalamic lesioned rats on go/no-go CONMTS performance, characterized by a consistent elevation of false alarm rates relative to the control and cortical lesioned groups. This deficit persisted throughout retraining of CONMTS, and manipulations of the number of odor stimuli and ITI. An increase in responsivity cannot account for this effect, since these subjects were able to suppress responding to the nonreinforced stimulus in go/no-go odor discrimination procedures. In fact, the L-IML lesioned rats acquired both odor discriminations at a rate equivalent to that exhibited by the other three groups.

As described above, the primary distinction between the two tasks relates to working memory demands (Honig, 1978; Olton et al., 1980). It appears that L-IML lesions produced a selective deficit in the ability to update information regarding stimulus-reinforcement relations across trials. Specifically, CONMTS dictates that an odor that was associated with reinforcement on the previous trial will not be followed by a reinforcer on the present trial. However, when the association was held constant (as in the discrimination task), no impairment was observed in L-IML lesioned rats.
It could be argued that L-IML lesions interfere with olfactory working memory via a disruption of projections from primary olfactory cortex to the central segment of MDn. In fact, damage to the MDn and surrounding regions was previously associated with transient impairments in odor guided behavior and olfactory discrimination learning in rodents (Eichenbaum et al., 1980; Slotnick & Risser, 1990). Further, odor recognition memory is consistently impaired in human Korsakoff patients (Mair et al., 1980; Potter & Butters, 1980), who are characterized by extensive thalamic pathology in the region of the MDn (Victor et al., 1989). The present investigation casts doubt on an interpretation of L-IML effects specifically in terms of an olfactory deficit for two reasons: First, L-IML lesioned rats were not impaired in acquiring an odor discrimination task; and second, lesions of the L-IML site were previously observed to impair spatial non-matching to sample (Mair & Lacourse, 1992; Mair, Robinson et al., 1992), performance on radial arm maze tasks (Harrison, 1992; Mair & Kivlahan, 1993), and acquisition of spatial discrimination and reversal (Harrison, 1992). Thus, the effects of L-IML destruction are not specific to the olfactory modality.

A second interpretation of the L-IML effects relates to a disruption of thalamo-cortical pathways. As discussed above, specific reciprocal pathways between the MDn and its prefrontal terminal regions, as well as those between nonspecific thalamic nuclei and diffuse cortical areas, pass
through the L-IML region (Krettek & Price, 1977; Brodal, 1992). In addition, L-IML thalamic lesions produced degeneration of specific thalamic projections (cortical layers 3 or 4) within the medial wall and rhinal sulcus of PFC, as well as nonspecific projections (cortical layers 1 and 6) in widespread areas of cortex (Mair, Zhang, & Koger, 1993). Therefore, behavioral effects following thalamic lesions may have resulted from the disruption of either specific or nonspecific thalamo-cortical projections, or both (Mair, Robinson, & Koger, 1992; Mair, Robinson et al., 1992; Mair, Zhang, & Koger, 1993).

The current results do not allow a conclusive statement on this matter. The lack of a sustained deficit following either medial wall or rhinal sulcal cortical lesions suggests that singular destruction of either of these specific MDn target regions cannot account for the L-IML effects. As suggested earlier, combined lesions of the medial wall and rhinal sulcal regions may clarify the involvement of these specific thalamo-cortical pathways. In fact, Harrison (1992) noted a correlation between the extent of encroachment on medial wall areas following rhinal sulcal lesions and the degree of impairment on spatial non-matching to sample. Although medial wall lesions were reported to impair spatial non-matching to sample, they did not produce the full range of impairments (including deficits on spatial reversal learning and the radial arm maze) (Harrison, 1992) that are exhibited
following L-IML lesions or PTD treatment (Mair et al., 1991; Robinson & Mair, 1992).

The MDn projections in the medial wall and rhinal sulcus were recently observed to remain intact, while axonal degeneration of nonspecific thalamic projections (layers 1 and 6) was noted in widespread areas of cortex following PTD treatment (Mair, Zhang, & Koger, 1993). Since L-IML lesions are associated with degeneration of both specific and nonspecific terminal degeneration (Mair, Zhang, & Koger, 1993), it was argued that nonspecific thalamic destruction could account for the impairments observed following L-IML lesions or PTD treatment which are not exhibited following MDn or PFC lesions (Harrison & Mair, 1993). Thus, disruption of nonspecific thalamo-cortical mechanisms may prove more critical to the L-IML deficit than the specific MDn-PFC pathways; however, more research is required before a definitive statement can be made.

Implications for Diencephalic Amnesia

In general, the current findings are consistent with the argument that medial thalamic lesions impair working, but not reference, memory, as assessed by delayed conditional discrimination tasks (Mair, Robinson, & Koger, 1992). As reviewed above (see Introduction), Korsakoff patients exhibit deficient performance on object delayed non-matching (Squire et al., 1988) and matching (Aggleton et al., 1988) to sample;
and PTD rats are impaired on spatial non-matching to sample (Knoth & Mair, 1991; Robinson & Mair, 1992). The current findings diverge from previous studies, however, with the lack of any effect of thalamic (L-IML) lesions on odor discrimination learning. Thalamic lesions were previously associated with odor recognition deficits in Korsakoff's patients (Jones et al., 1975a; Mair et al., 1980). Further, olfactory discrimination learning impairments were observed in PTD (Mair et al., 1991), and MDn lesioned rats (Eichenbaum et al., 1980; Lu & Slotnick, 1990; Slotnick & Risser, 1990), although all three populations eventually reached criterion performance. As noted previously, the ultimate attainment of criterion following thalamic lesions suggests a spared ability to perform the reference memory requirements of the tasks.

The present investigation was unique in two ways: First, performance on the CONMTS task was strictly dependent on olfactory discriminative stimuli, and no spatial cues were available; and second, a direct comparison was made between performance on non-matching to sample and discrimination in tasks with comparable, if not identical, procedural demands. Thalamic (L-IML) lesions significantly impaired CONMTS, while leaving odor discrimination learning intact, thereby substantiating the involvement of this region in performance of olfactory working memory, but not reference memory, tasks.
Conclusions

1. Lesions of either the medial wall or rhinal sulcal region of PFC produced a transient impairment in performance of go/no-go CONMTS trained prior to surgery, while thalamic lesions of the L-IML site produced a chronic CONMTS deficit. The effects of L-IML lesions persisted throughout manipulations of the number of odor stimuli and the ITI. The only subject in the L-IML group that did not exhibit a CONMTS impairment had a lesion which spared the most anterior portions of the L-IML site. This finding is in agreement with the demonstration that the entire anterior-posterior extent of the L-IML site must be destroyed to affect performance on spatial non-matching to sample (Mair, Robinson et al., 1992).

2. Control and cortical lesioned subjects exhibited susceptibility to proactive interference effects, produced by decreasing the number of odor stimuli utilized within each session. Analyses of within session performance demonstrated a similar interference effect, since performance decayed as the sessions progressed. In addition, accuracy tended to decrease in the control and cortical lesioned groups with training on the manipulations subsequent to the initial postsurgical retraining. The L-IML lesioned subjects were not differentially affected by increased proactive interference, apparently because of a floor effect in this group.

3. While deficient performance was exclusively characterized by elevated false alarm rates, an increase in responsivity was
unable to account for the lesion effects on performance since all animals acquired go/no-go odor discrimination tasks at equivalent rates. No group differences were observed in performance of two separate odor discrimination tasks.

4. Thus, although L-IML subjects exhibited a lasting deficit on CONMTS, this finding was not attributable to a) an inability to suppress responding to an odor stimulus; b) an odor discrimination impairment; or c) deficient acquisition or utilization of general rules and procedures inherent to both the CONMTS and discrimination tasks.

5. In sum, despite the direct innervation of thalamus and PFC by primary olfactory cortex, evidence is lacking for a distinctive contribution by specific thalamo-cortical pathways to olfactory processing. Rather, previously documented effects on olfactory learning following lesions to these areas may be more appropriately ascribed to general learning deficits which are not specific to the olfactory modality, and which resemble those observed in association with diencephalic amnesia.
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Table 1. List of abbreviations. Regions within the prefrontal cortex (PFC) of the rat (from Zilles, 1985).

<table>
<thead>
<tr>
<th>Abbreviation</th>
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</tr>
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<td>Cg</td>
<td>anterior cingulate</td>
</tr>
<tr>
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<td>dorsal anterior cingulate</td>
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</tr>
<tr>
<td>MO</td>
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</tr>
<tr>
<td>PL</td>
<td>prelimbic</td>
</tr>
<tr>
<td>VLO</td>
<td>ventrolateral orbital</td>
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<td>VO</td>
<td>ventral orbital</td>
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Table 2. List of odor stimuli.

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<td>phenethyl alcohol</td>
<td>transanethole</td>
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</tr>
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<td>cyclopentanone</td>
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Table 3. Average CONM TS performance (probability of false alarms). Each postsurgical block (Post-1 through 5) reflects performance during blocks of 200 trials following surgery.

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9 As noted previously with respect to the L-IML group: n = 7 for postsurgical blocks 1 - 4; n = 5 for block 5.
Table 4. The effects of manipulating the number of stimuli on the average probability of false alarms.

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Table 5. The effects of increasing the intertrial interval on the average probability of false alarms.

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Table 6a. Discrimination #1 (eugenol vs. amyl acetate). The average probability of false alarms during discrimination training. Sessions # 1-5 (50 trials/session).

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Table 6b. Sessions # 6-10.

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Table 7a. Discrimination #2 (geraniol vs. phenethyl alcohol). The average probability of false alarms. Sessions # 1-5.

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Table 7b. Sessions # 6-10.

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Figure 1: The behavioral chamber used for continuous olfactory non-matching to sample (CONMTS) and discrimination training.
Figure 2: The probability of responding on CONMTS during the final 2 blocks (400 trials) prior to surgery, and the 5 blocks (1000 trials) following treatment. Results are depicted for the control, medial wall (MW), rhinal sulcal (RS), and thalamic (L-IML) lesion groups (n = 7/group except for the L-IML group in the fifth block, n = 5). Performance is represented by the probability of responding to the drinking spout on the two types of trials: S+ (i.e., "Hit" responses); and S- (i.e., "False Alarm" responses). Error bars reflect the standard error of the mean.
Figure 3: The probability of responding on $S^+$ and $S^-$ trials as the number of sample stimuli (set size) is reduced within a session. Each point represents the aggregate of responses across three sessions (144 trials) at each of the four set sizes.
Figure 4: Within-session performance with varying stimulus set sizes. The probability of responding to S+ and S- trials is averaged across three sessions (144 trials) at each of the four stimulus set sizes.
Figure 5: The effect of increasing the intertrial interval on the probability of responding during S+ and S- trials. Two sessions, (100 trials) were run at each of the intertrial intervals.
Figure 6: A verification of stimulus control by odors on CONMTS. The tubing from the odor delivery flowmeter was disconnected, and the probability of responding was compared on S+ trials (i.e., in which a "change stimulus" or advance signal was generated) with the probability of responding on S- trials (i.e., in which a "change stimulus" or advance signal was not generated).
Figure 7: Training on discrimination #1, in which the presentation of one odor (eugenol) was associated with reinforcer availability (S+), while a second odor (amyl acetate) was not predictive of reinforcement (S-).
Figure 8: Training on discrimination #2, in which the presentation of one odor (geraniol) was associated with reinforcer availability (S+), while a second odor (phenethyl alcohol) was not predictive of reinforcement (S-).
Figure 9: Scatterplot of percent correct on CONMTS for individual animals during the first block of postsurgical training.
Figure 10: Scatterplot of percent correct on CONMTS for individual animals during the fourth block of postsurgical training.
Figure 11: The lesion sustained by the subject performing at the median in the medial wall (left panel), and in the rhinal sulcal (right panel) lesioned group. The numbers reflect distance (in mm) from bregma.
Figure 12: The lesion sustained by the subject performing at the median in the L-IML thalamic lesioned group.