COGNITIVE BEHAVIOR OF RATS WITH THALAMIC LESIONS

JO-ANNE B. TOMIE

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DEDICATION

To the loving memory of 2 special friends of mine who passed away shortly after I began graduate studies at the University of Lethbridge: My grandpa, Roy Alwin McMillan, and a cat I was very fond of and still miss a lot, Jake (meow meow).

ABSTRACT

The objective of this thesis was to test the idea that medial thalamic nuclei are part of a "memory circuit" in the brain. Rats received lesions of the anterior (ANT) or medial dorsal (MD) thalamic nuclei and were tested on two spatial tasks, a nonspatial configural task, and spontaneous and amphetamine-induced activity.

The thalamic rats were impaired on the spatial and configural tasks, and some of the thalamic groups were slightly hyperactive after administration of amphetamine. The deficits were not large and could not be unequivocally attributed to the ANT or MD damage. The results question the role of the ANT or MD in the behaviors studied. It is suggested that the deficits obtained after thalamic damage may be nonspecific and it is concluded that the results do not support the notion that thalamic structures have a primary role in memory.

ACKNOWLEDGEMENTS

It was a long time ago, but I still vaguely remember the day Ian Whishaw stopped coaching the swim club I was in to spend more time doing research and "swimming rats". If someone had told me at that time that, in the future, I would be doing research with Ian and would be "swimming rats", I would have told them they are nuts. But... guess what I've been up to lately...

I am indebted to Ian Whishaw, my supervisor, for believing I could do "graduate school stuff", for being encouraging to me with it, and for putting up with me as a graduate student, though sometimes this wasn't easy. And for not letting me give up easily when the thought of giving up crossed my mind. And for taking me under his wing as an undergraduate and then his technician, providing initial impetus and allowing me to develop skills I needed to complete the research I did. And for the invaluable help he gave with preparation of presentations I gave as a graduate student, and with the writing and "boiling down" of this thesis. I couldn't have done it without him. So, Thanks Ian!

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Thank you to Rob Sutherland, for coming up with the configural theory he did, which I initially set out testing, and for being the external examiner for this thesis. And for being, along with Whishaw and Kolb, a member of the trio of outstanding teachers and scientists who inspired me, and many others, to enjoy doing neuroscientific research.

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GENERAL INTRODUCTION

It is now realized that no one area of the brain is responsible for learning or memory. Rather, it is thought that memory is "distributed" across many brain areas, each of which may contribute in a different way. This distributed hypothesis has gained acceptance relatively recently over a number of theories that suggest that functions are localized in one or another brain area. The following will summarize some of the history of theorizing about the localization of memory and will describe some of the brain regions thought to be involved.

Historical Overview

How learning and memory take place seems to have always interested people. In the 4th century B.C., Aristotle thought the heart was responsible for mental function. The Prophets thought of the kidney and heart as "housing the soul" and thus, the brain is not mentioned once in the Bible (Dudai, 1990). Plato (4th century B.C.) introduced the notion of a 'tripartite soul', and suggested the rational part of this "three part soul" resides in the brain because this is the part of the body closest to the heavens. Hippocrates (4th century B.C.) thought that the brain housed all mental processes. In the 2nd century B.C., Galen experimentally demonstrated that nerves originate in the brain and that motor and sensory functions are abolished by brain injury. In the following centuries, despite continued belief by some that mental functions reside elsewhere, attempts to explain how people learn and remember via proposed brain function became common (Kolb and Whishaw, 1990).

Costa ben Luca (9th century, A.D.) suggested that a 'spiritus' flowing through brain ventricles causes memory. Variations of this theme were entertained by other scholars (Dudai, 1990). The idea that memories are stored in ventricles was finally discredited in

the mid 1500's by Andreas Vesalius. Vesalius dissected brains and noticed that the relative size of the ventricles in nonhuman and human brains was the same. He concluded that, since the largest brains belonged to "rational" humans, it is the brain itself, and not the ventricles, that mediates mental processes (Kolb and Whishaw, 1990).

Although Vesalius suggested that mental processes are mediated by nervous system tissue, it was Rene Descartes (1596-1650) who, by defining animals as 'reflex automatons', became the father of modern thinking about how learning and memory take place. An automaton is a theoretical machine consisting of input, computations and output. Descartes suggested that man is an automaton equipped with a rational soul, and that the pineal gland is the locus of "soul-body" interaction. In addition to introducing the intriguing problem of the relationship between "mind" and "body", Descartes' writings introduced the notion that memories are subserved by physical traces in the brain, and the notion that the mind is unified and is located in a single body structure. The following is a description written by Descartes on how information is remembered:

> *"Thus, when the soul wants to remember something...volition makes the gland lean first to one side and then to another, thus driving the spirits towards different regions of the brain until they come upon the one containing traces left by the object we want to remember. These traces consist simply of the fact that the pores of the brain through which the spirits previously made their way, owing to the presence of this object, have thereby become more apt than the others to be opened in the same way when the spirits again flow towards them. And so the spirits enter into these pores more easily when they come upon them, thereby producing in the gland that special movement which represents the same object to the soul, and makes it recognize the object as the one it wishes to remember." (Descartes, 1649 -- In Dudai, 1990).*

Following Descartes' accounts of reflexes and memory, the view that the brain mediates mental processes became widely accepted. Descartes' belief that the pineal gland is the "seat of mental processes" was incorrect, however, so questions addressing how the brain mediates mental processes and where in the brain "memory traces" are

located remained a point of inquiry. Today, the idea that the brain is the place where processes like learning and memory take place is treated as indisputable fact. How information is processed by the brain, however, though better understood than it was as recently as a decade ago, is still a puzzle.

After it was agreed that the brain mediates learning and memory processes, and before serious research on neural mechanisms underlying learning and memory could be conducted, technological barriers needed to be overcome. Objective ways to quantify learning and memory were needed, for example, and Ebbinghaus (1885) is the person credited with introduction of these. Experimenting on himself, Ebbinghaus found the number of 'consonant-vowel-consonant' nonsense syllables he could correctly recite after only once reading a list was approximately seven. A few years later Müller invented a memory drum that presented stimuli one at a time, at a standard rate. Müller's memory drum allowed for controlled studies and, via use of it, Müller discovered that memories are susceptible to interference immediately after their formation (Müller and Pilzecker, 1900). Müller is thus credited with the introduction of the phenomena of memory consolidation -- the idea that "memory traces" take time to fully form.

Techniques used to study human learning and memory by people like Ebbinghaus and Müller in the early 1900's resulted in concepts that are still widely accepted. Limitations inherent in the techniques, however, brought research on human learning and memory to a temporary halt. To gain full understanding of how learning and memory are subserved by central nervous system tissue, it was clear that treating the brain as a "black box" and inferring function from observed input-output relationships was not good enough. New methods for examination of neural substrates were needed.

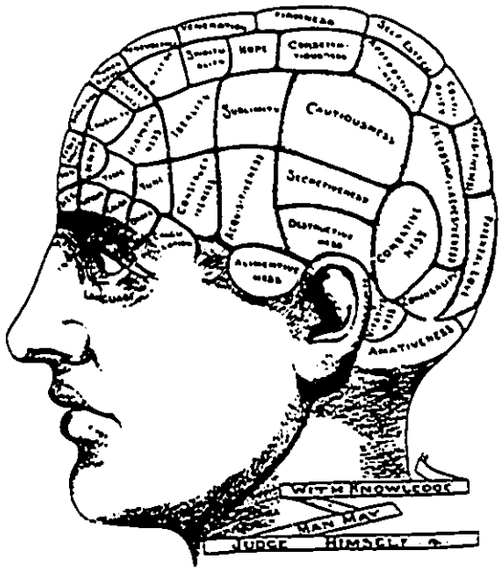
One source of information about neural foundations came from the study of

brain-injured people (Ribot, 1882; Korsakoff, 1887; Broca; 1878; Wernicke, 1874). Anatomical, electrophysiological, chemical and pharmacological methods for studying nervous system tissue also began to emerge. Most importantly, the techniques of classical and operant conditioning were developed. These techniques made controlled study of learning in nonhumans possible. An advantage to studying nonhumans is that confounding factors can be minimized so validity of conclusions about brain function can be maximized. A primary reason for studying nonhumans is to model human disorders so that mechanisms underlying them can be understood.

A question that emerged from brain studies was whether functions are localized in specific areas or whether they are distributed across the entire brain. The view today is that representation is highly localized. Each area of the brain is thought to have a distinct function. A particular function might be distributed across a particular area of the brain, but functions of the brain are not distributed across the entire brain. Also, some areas of the brain process information of specific kinds (e.g. visual, olfactory, auditory) whereas other areas are more associative, combining simple representations to form more complex ones.

The range of views about the extent of localized brain functions varied from extreme "localization" as expressed in the phrenological views of Gall (1835) and Spurzheim (1834) to the "equipotential" holistic views advocated by Fluorens (1824), Goltz (1960) and Lashley (1929, 1950). Phrenologists believed bumps on peoples' skulls indicated well developed underlying cortical gyri, and great capacity for particular behaviors, and that depressions in the same places on skulls indicated underdeveloped underlying cortical gyri, and reduced capacities for the behaviors. They thought every gyrus in the brain was responsible for storage and execution of a specific behavior (Figure 1). Equipotentiality

Figure 1. Functional organization of the human brain as advocated by the phrenologist, Spurzheim (From Kolb and Whishaw, 1990). This early view of brain function reflected the concept that each area of the brain had a specific function that could be executed without reference to other areas. In contrast, the idea examined in the present thesis is that functions are executed by the interaction of a number of separate brain areas.


Veneration
Hope
Conscientiousness
Sublimity
Cautiousness
Secretiveness
Destructiveness
Combativeness
Amativeness
WITH KNOWLEDGE
MAN MAY
JUDGE HIMSELF

advocates, on the other hand, used the technique of damaging the brains of animals to study changes in behavior and, from doing so, concluded that intellectual functions reside in the brain coextensively (Kolb and Whishaw, 1990).

The holistic view of brain organization advocated by Lashley was deduced from studies he conducted aimed at understanding where memories are stored. Lashley (1929, 1950) studied rats running through mazes. Cortical lesions of various sizes were made either prior to learning or after learning. Following cortical ablation, Lashley's rats were impaired. The degree of impairment was related to lesion size, but not to lesion location. Thus, Lashley concluded that reduction in learning ability is "the same, quantitatively and qualitatively, after equal lesions to diverse areas", and saw his findings as "pointing to the equivalence of function of all parts of the cerebral cortex for learning" (Lashley, 1929 -- In Squire, 1987). After hundreds of experiments aimed at identifying neural locations of learned habits, Lashley concluded that "it is not possible to demonstrate the isolated localization of a memory trace anywhere in the nervous system. Limited regions may be essential for learning or retention of a particular activity, but ... the engram is represented throughout the region" (Lashley, 1950 -- In Kolb and Whishaw, 1990).

A few years after Lashley's 1950 publication advocating equipotentiality, Dr. William Scoville operated on a 27 year-old man named H.M. To reduce severity of seizures H.M. suffered from, Scoville surgically excised H.M.'s medial temporal lobes. Following surgery, H.M.'s seizures were reduced but he was unable to learn any new information, and could not remember things from his recent past. In 1957, Scoville and Brenda Milner published a paper describing H.M.'s memory impairments. From Lashley's work, no one would have predicted that removal of a single structure, and especially a structure thought to have olfactory functions, would have impaired memory. Scoville and Milner's (1957) description

was thus a landmark.

For the past 37 years, every textbook on memory has included the story of H.M. and concluded that the hippocampus is the temporal lobe structure important for memory. A number of findings suggest that it is adjacent temporal lobe regions that are responsible for H.M.'s memory impairments, and not the hippocampus (Horel, 1978). Other work suggests the hippocampus is specifically involved in spatial functions (O'Keefe and Nadel, 1978). Notwithstanding these differing views, most major theories of learning and memory still include the hippocampus in memory circuits.

Contemporary Views

Most current hypotheses of the anatomy of memory propose that: (1) there are two memory systems, (2) learning of simple information is mediated by one system, and (3) learning of more complex information is mediated by the other.

Memory for complex information is thought to be mediated by a system involving connections between medial temporal structures, medial thalamic structures and the prefrontal cortex (Mishkin and Petri, 1984; Zola-Morgan and Squire, 1993). This system is thought to be comprised of two pathways, both of which originate in association cortex and both of which terminate in prefrontal cortex. One of these paths passes through the entorhinal cortex, hippocampus and anterior thalamic nucleus. The other passes through the amygdala and medial dorsal thalamic nucleus (Mishkin and Appenzeller, 1987; Ridley and Baker, 1991). On some kinds of tasks (e.g., visual recognition), damage to structures on both paths is required to impair performance. On other kinds of tasks, damage to the hippocampus is required to impair performance. Damage to structures on the other path does not lead to impairment if the hippocampus is intact and does not add to impairment induced by hippocampal damage (Mishkin and Appenzeller, 1987). Thus, it is thought that

there is more than one system for memory of complex information; one that is hippocampal dependent and one that is not (Tulving, 1985).

It should be noted here that there has been a recent rapid shift in thinking concerning the relative contributions of temporal lobe structures to learning and memory. Recent work in Mishkin's laboratory (Meunier, Bachevalier, Mishkin and Murray, 1993) and in Zola-Morgan's laboratory (Suzuki, Zola-Morgan, Squire and Amaral, 1993; Zola-Morgan, Squire, Clower and Rempel, 1993) emphasizes perirhinal cortex in learning and memory rather than the hippocampus. The recency of this work combined with the fact that it is based entirely on studies with monkeys presently prevents its generalization to rats.

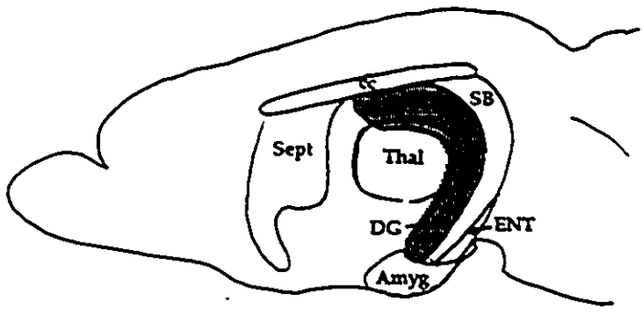
The Hippocampus

Of the structures comprising proposed memory systems, the hippocampus has received the most experimental attention. The word "hippocampus" comes from the Greek words "hippo" (horse) and "kampos" (sea monster). It is a seahorse shaped structure located on the medial surface of the temporal lobe in the mammalian brain. The anterior pole of the rat hippocampus is located dorsal to the thalamus and posterior to septum. The posterior pole is located dorsal and posterior to the amygdala, at the base of the brain (Figure 2).

When speaking of the "hippocampus", one is referring primarily to the hippocampus proper (i.e., Ammon's horn), and the dentate gyrus (Figure 3). The dentate gyrus and hippocampus proper are U shaped interlocking structures. The hippocampus proper is composed primarily of pyramidal cells and the dentate gyrus is composed primarily of tightly packed granule cells. On the basis of cell morphology and fiber projections, Cajal (1911) concluded that the hippocampus proper consists of 2 separate regions: a regio superior and a regio inferior. Upon further investigation, Lorenté de No (1934) proposed

Figure 2. Views of the rat brain depicting location of the hippocampus. (A) Saggital view. The hippocampus is the shaded area, which consists of Ammon's Horn (AH) and the dentate gyrus (DG). The hippocampus is bounded dorsally by the corpus callosum (cc), anteriorly by the septum (Sept), posteriorly by the subiculum (SB) and entorhinal cortex (ENT), and ventrally by the amygdala (Amyg). The thalamus (Thal) is located ventral to the anterior components of the hippocampus. (B) Coronal views. The four views are located 2.1 mm, 3.8 mm, 5.2 mm and 6.3 mm posterior to bregma, respectively (see Paxinos and Watson, 1985). The hippocampus is the shaded area that lies dorsomedially on the anterior views and ventrolaterally more posteriorly.

A



B

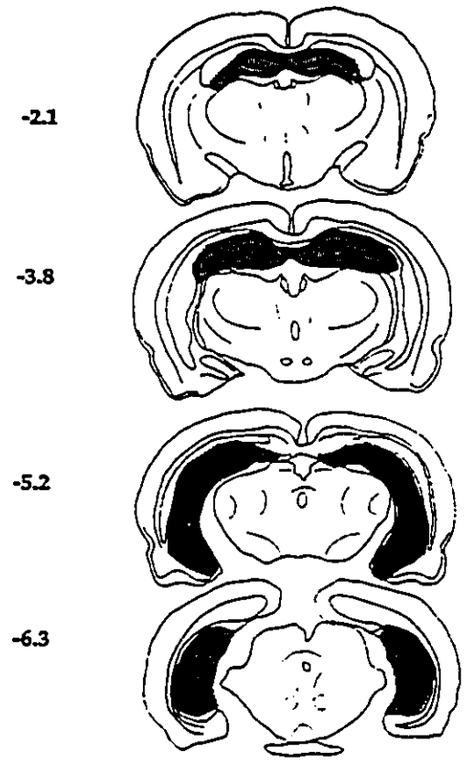
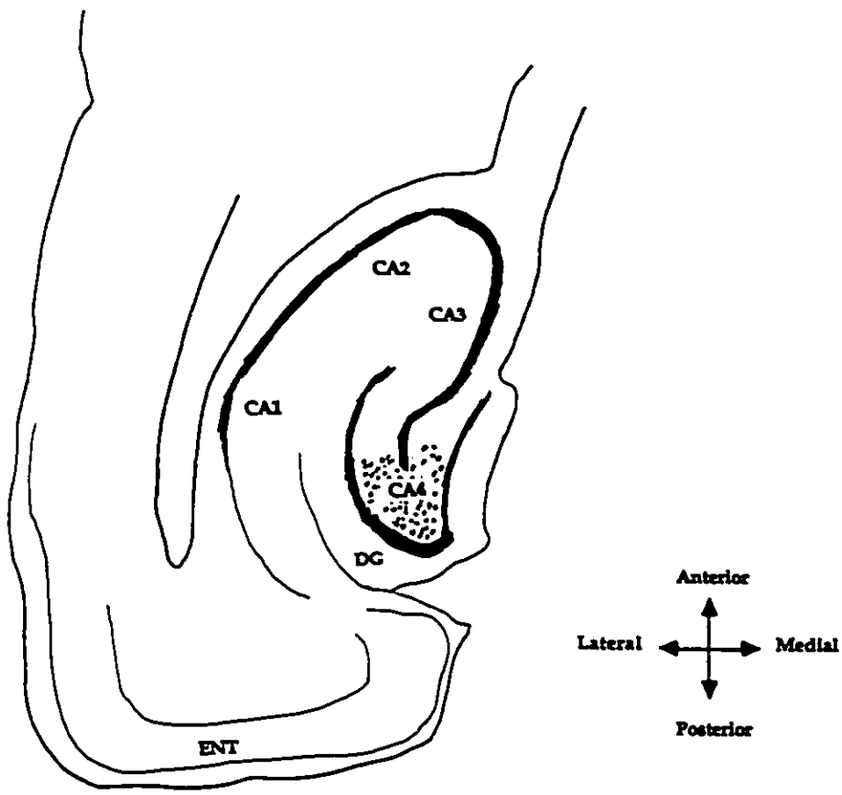


Figure 3. The left hippocampus and entorhinal cortex traced from a horizontal section of a rat brain. Note the locations of the dentate gryus (DG) and the CA1, CA2, CA3 and CA4 subfields of the hippocampus proper. Also note location of the entorhinal cortex (ENT). It is thought that information from the neocortex enters the entorhinal area and then is relayed sequentially through the DG, CA3 and CA1, and then returns to the neocortex via the entorhinal cortex. The dots between CA3 and the dentate gyrus are CA4 cells.


CA2
CA3
CA1
CA4
DG
ENT
Anterior
Lateral
Medial
Posterior

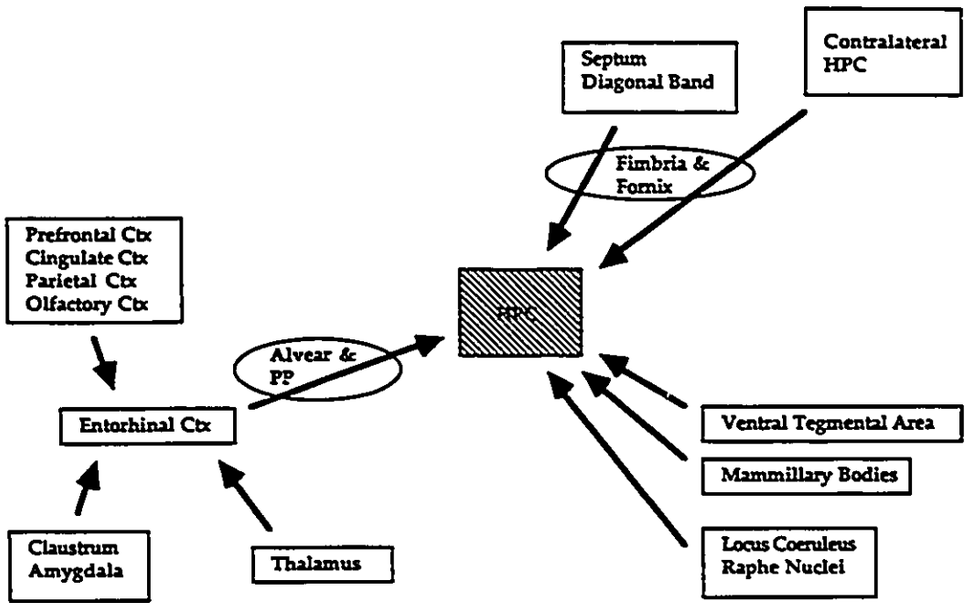
that the hippocampus proper actually consists of 4 regions. He assigned the term "Cornu Ammonus, field 1" (i.e., CA1) to the Cajal's regio superior, assigned the terms CA2 and CA3 to the Cajal's regio inferior, and assigned the term CA4 to the cells scattered in the area between CA3 and the dentate gyrus (Figure 3). The terms CA1, CA2, CA3 and CA4 are widely used today.

The main inputs to the hippocampus proper and dentate gyrus arise in the entorhinal cortex and the septum. There are also projections from the brainstem, hypothalamus, thalamus, amygdala, prefrontal cortex, contralateral hippocampus, locus coeruleus, raphe nuclei, dopaminergic cells of the ventral tegmental area, and cells in and near the mammillary bodies (Figure 4). Input to the hippocampus from the entorhinal cortex is via the fibers of the alvear and perforant pathways. The entorhinal cortex itself receives input from several association cortices (e.g., prefrontal cortex, cingulate cortex, parietal cortex), the olfactory cortex, several thalamic nuclei, the claustrum, and the amygdala. Input to the hippocampus from the septum and diagonal band enters the hippocampus via 4 routes: the fimbria, the dorsal fornix, the supracollosal stria, and the amygdaloid complex. The main route of entry is the fornix. Input to the hippocampus from the contralateral hippocampus comes through the fimbria and fornix and the hippocampal commissure (Shephard, 1990; O'Keefe and Nadel, 1978). Output from the hippocampus via the fornix projects to the lateral preoptic and lateral hypothalamic areas, the septum, the thalamus, the mammillary bodies and the rostral midbrain. Hippocampal efferents not directed through the fornix project to the subiculum and entorhinal cortex (O'Keefe and Nadel, 1978).

Dual System Theories of Hippocampal Function

Evidence for the hippocampus being a component of a memory system necessary for

Figure 4. Diagram depicting several afferents to the hippocampus (HPC) and to the entorhinal cortex. Most input to the HPC comes from the entorhinal cortex (Entorhinal Ctx) and from the septum. The entorhinal cortex receives input from several cortical areas (e.g., prefrontal, cingulate, parietal and olfactory), from the claustrum, from the amygdala and from the thalamus. Input to the HPC from the entorhinal cortex enters via fibers of the alvear and perforant pathways (Alvear and PP). Input to the HPC from the septum, diagonal band and contralateral HPC enters through the fimbria and fornix. There is also input to the HPC from the ventral tegmental area, mammillary bodies, locus coeruleus and raphé nuclei. This model of interacting structures suggests that functions such as memory are distributed across many brain structures.


Septum
Diagonal Band
Contralateral
HPC
Fimbria &
Fornix
Prefrontal Ctx
Cingulate Ctx
Parietal Ctx
Olfactory Ctx
HPC
Alvear &
PP
Entorhinal Ctx
Ventral Tegmental Area
Mammillary Bodies
Claustrum
Amygdala
Thalamus
Locus Coeruleus
Raphe Nuclei

learning only some kinds of complex information comes from two main sources: (1) clinical studies of people with hippocampal damage (e.g., H.M.), and (2) study of behavior of nonhumans with damage to the hippocampus or its afferents and efferents. Findings from these sources have led to the development of a number of dual system theories of hippocampal function, all of which claim that hippocampal damage impairs one class of memory and spares another (Table 1).

One of the first dual system theories of hippocampal function was proposed by Hirsh (1974). According to Hirsh, memory is normally stored in a specialized system. Environmental or motivational cues initiate transfer of information from this system to a "performance line" system. When presented with an external stimulus, information is associatively retrieved from performance line memory and an animal responds. If an animal is in conflict about how to respond to a given stimulus, information that might help it respond correctly is contextually retrieved from special memory. Hirsh claims that animals with the hippocampus ablated can associatively retrieve information from performance line memory but can not contextually retrieve information from special memory. He proposes that this explains why animals with hippocampal damage can learn simple stimulus-response information but have difficulty learning more complex information.

Other dual memory theories are similar to Hirsh's. Tulving (1972) distinguishes between episodic and semantic memory. Episodic memory is memory for particular events and semantic memory is memory that is built up over time and is not associated with any particular event. Tulving claims that episodic memory is lost after hippocampal damage and that semantic memory is spared. Gaffan (1972) distinguishes between recognition memory (i.e., memory for familiar items) and associative memory (i.e., memory

Table 1. A variety of terms used to describe two kinds of memory. Following hippocampal damage, those on the left are thought to be lost and those on the right are thought to be spared. (From Squire, 1987)

FACT MEMORY	SKILL MEMORY
DECLARATIVE	PROCEDURAL
MEMORY	HABIT
EXPLICIT	IMPLICIT
KNOWING THAT	KNOWING HOW
COGNITIVE MEDIATION	SEMANTIC
CONSCIOUS RECOLLECTION	SKILLS
ELABORATION	INTEGRATION
MEMORY WITH RECORD	MEMORY WITHOUT RECORD
AUTOBIOGRAPHICAL MEMORY	PERCEPTUAL MEMORY
REPRESENTATIONAL MEMORY	DISPOSITIONAL MEMORY
VERTICAL ASSOCIATION	HORIZONTAL ASSOCIATION
LOCALE	TAXON
EPISODIC	SEMANTIC
WORKING	REFERENCE

for what goes together with an item). He proposes that hippocampal lesions disrupt only the former. Olton, Becker and Handelmann (1979) distinguish between working memory (i.e., memory for information that changes from trial to trial on a given task) and reference memory (i.e., memory for information that remains stable across trials on a given task). They claim that working memory is sensitive to hippocampal damage. O'Keefe and Nadel (1978) distinguish between locale and taxon memory systems. The locale system is used for solving spatial problems. The hippocampus itself acts as a "map" serving as a framework for relating objects in the world but that is independent from the objects themselves. The taxon system allows the animal to recognize specific objects and allows it to orient to these objects. They propose that the locale system is the one disrupted when an animal receives hippocampal damage while the taxon system remains intact. Cohen and Squire (1980) distinguish between declarative and procedural memory. The former is memory directly accessible to conscious recollection and that can be declared, such as facts and time-place events. The latter is memory that is not accessible as facts and that can not be declared, such as skills. According to Cohen and Squire, declarative memory is lost following hippocampal damage while procedural memory is spared.

The most recent dual system theory of hippocampal function is Sutherland and Rudy's (1989) configural theory. Sutherland and Rudy distinguish between a "simple associative system" and a "configural associative system". They claim that the configural system is dependent on an intact hippocampus whereas the simple system is not. The simple associative system is involved in forming bonds between elementary stimulus events. For example, an animal learns that one size of tactile stimulus (T1) is paired with food (F1) and another size of tactile stimulus (T2) is not (F2) by forming an association between T1 and F1 and another between T2 and F2. In contrast, the configural associative system

combines features of a number of elementary stimuli to make unique representations. If the relationships of T1 and T2 to F1 and F2 varies, depending on presence or absence of an odor (O), so that in the presence of the odor (O1), T1 signals F1 and T2 signals F2 whereas in the absence of the odor (O2), the meanings of T1 and T2 are reversed, we have a configural task (Figure 5). No simple association allows an animal to behave appropriately to T1 and T2 in this task. T1 and T2 may each be associated with reward, but their relationship to O determines when (Whishaw, Tomie and Kolb, 1992). The beauty of Sutherland and Rudy's (1989) theory of hippocampal function lies in how easily testable it is. The consensus from a number of tests, however, is that animals without a hippocampus can solve some kinds of configural problems (Whishaw and Tomie, 1991; Gallagher and Holland, 1992; Jarrard, McKernan and Davidson, 1992; Davidson, McKernan and Jarrard, 1993).

Other Brain Areas Involved in Memory

The prefrontal cortex, the medial dorsal thalamic nucleus (MD) and the anterior thalamic nucleus (ANT) have direct and indirect connections with the temporal lobes, and thus, are also thought to play learning and memory roles. Figure 6 summarizes some of the connections of these structures. Note, however, that the pathways outlined are not exhaustive, and do not include the sensory pathways through which information enters into the circuitry (e.g., visual cortex and its connections to medial cingulate and retrosplenial cortex, etc.) or the motor pathways through which information leaves the circuit. Nor does Figure 6 include many other less relevant projections to thalamic structures.

The Prefrontal Cortex

Prefrontal cortex receives input from the MD. Unlike other areas of frontal cortex, it

Figure 5. Diagrammatic representation of a configural task. T1 signals F1 and T2 signals F2 in the presence of an odor (O1), and T1 signals F2 and T2 signals F1 in the absence of an odor (O2). This is a configural task. Without attending to both odor (O1 or O2) and the tactile stimulus (T1 or T2), an animal cannot predict whether F1 or F2 will occur. T1 and T2 signal both F1 and F2. It is their relationship to O1 and O2 that determines when. Thus, no simple association will allow an animal to solve such a task. Sutherland and Rudy (1989) suggest that the hippocampus is required to make configural associations.

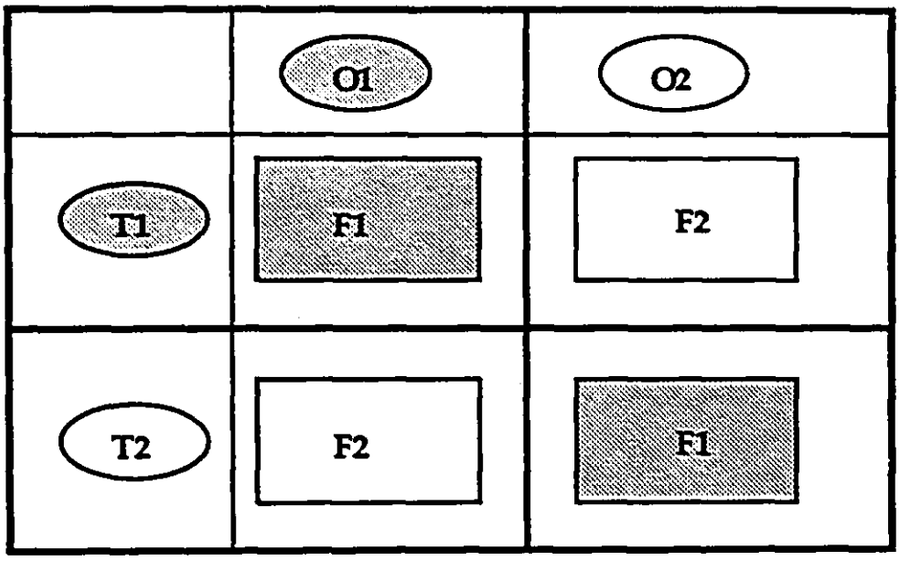
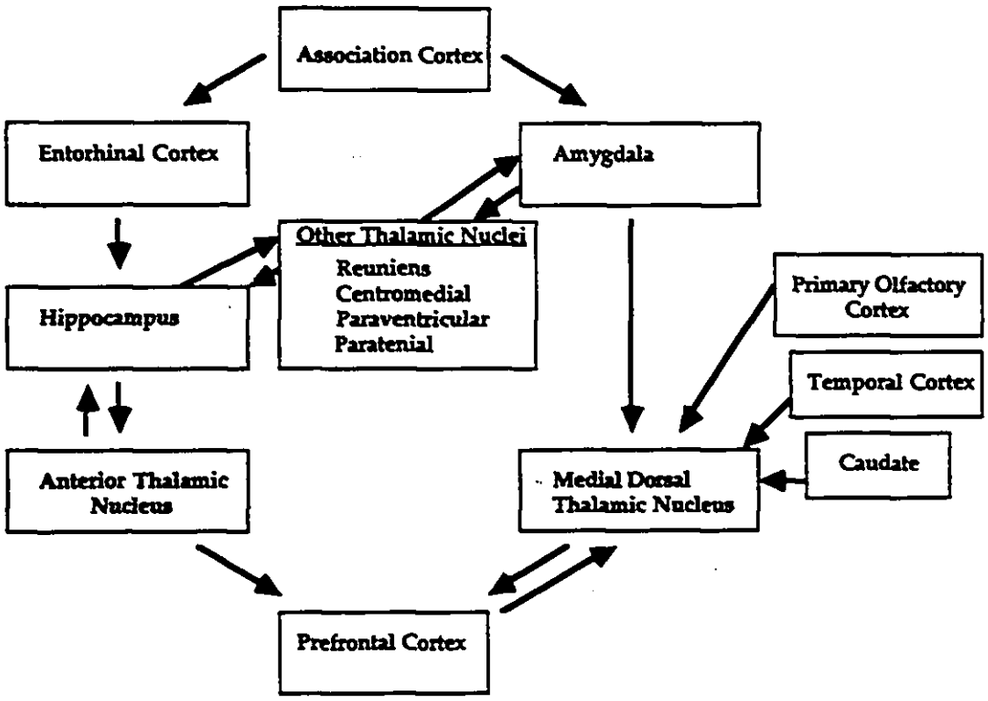

O1
O2
T1
F1
F2
T2
F2
F1

Figure 6. Diagram depicting connections between several brain areas presumed important for learning and memory. The two shaded structures, the ANT and the MD, are the areas of major interest in this thesis. Note that they have no direct connections with each other but that they both have special connections with the hippocampus and they both connect to prefrontal cortex.


Association Cortex
Entorhinal Cortex
Amygdala
Other Thalamic Nuclei
Reuniens
Centromedial
Paraventricular
Paratenial
Hippocampus
Primary Olfactory Cortex
Temporal Cortex
Caudate
Anterior Thalamic Nucleus
Medial Dorsal Thalamic Nucleus
Prefrontal Cortex

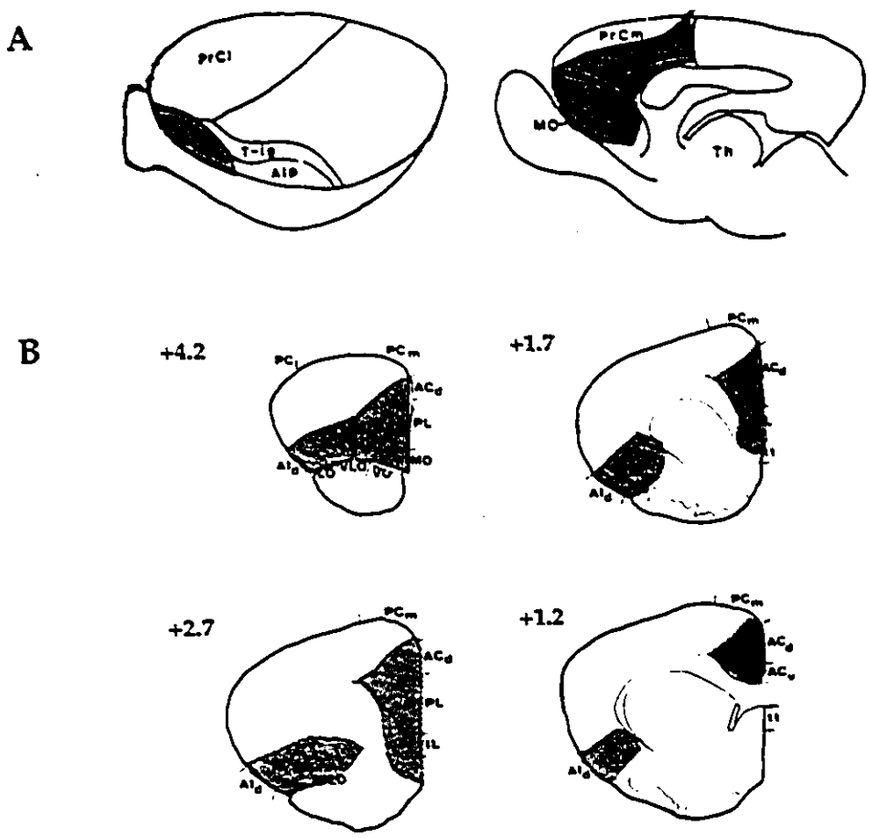
does not produce movements when electrically stimulated and does not produce gross motor or sensory deficits when removed (Kolb, 1984). The frontal cortex of the rat (Figure 7) consists of three major cytoarchitectonic areas: (i) medial frontal, (ii) ventral frontal and, (iii) motor and premotor. Medial frontal cortex consists of anterior cingulate cortex, prelimbic cortex and infralimbic cortex. Ventral frontal cortex consists of orbital cortex and agranular insular cortex. Medial and ventral frontal cortex constitute what is known as prefrontal cortex (Kolb, 1984). Though these areas receive input from the MD, they also receive input from other brain areas. Among these are other thalamic nuclei, the amygdala, pyriform cortex, the hippocampus, and the substantia nigra (Kolb, 1984).

Animals with frontal cortex damage have difficulty inhibiting various types of behavior (Kolb, 1984). They have difficulty shifting responses on reversal-type tests and have difficulty inhibiting components of complex chains of behavior. They have difficulty combining series of actions into organized sequences of movements, and are impaired on tasks in which reward is contingent on going to a particular place (i.e., spatial tasks). Frontal cortex damage affects social behavior and behavioral spontaneity of animals, along with ability of animals to discriminate between odors. Ability of animals to habituate to stimuli and to learn arbitrary associations between sets of stimuli and responses are also affected by frontal cortex damage (Kolb, 1984).

A number of studies suggest that frontal cortex is important for learning and memory. Kolb, Pittman, Sutherland and Whishaw (1982) found that rats with medial frontal cortex damage were impaired on two spatial tasks, the Morris water maze and the radial arm maze, for example. In the Morris water maze, rats swim through murky water to escape to a platform hidden just below the water's surface. In the radial arm maze, food is placed at the distal end of one or some of eight alleys that protrude from a central platform rats

Figure 7. Views of the rat brain depicting location of prefrontal cortex. (A) Lateral view (left) and Saggital view (right). Prefrontal cortex is the shaded area, which consists of anterior cingulate cortex (AC_d and AC_v), prelimbic cortex (PL) and infralimbic cortex (IL) along with medial orbital cortex (MO) and agranular insular cortex (AI_d). (B) Coronal views. The four views are located 4.2 mm, 2.7 mm, 1.7 mm and 1.2 mm anterior to bregma, respectively (see Paxinos and Watson, 1985). Prefrontal cortex is the shaded area consisting of anterior cingulate cortex (AC_d and AC_v), prelimbic cortex (PL), infralimbic cortex (IL), agranular insular cortex (AI_d and AI_v) and ventral orbital (VO), ventral lateral orbital (VLO) and lateral orbital (LO) cortex. Although prefrontal cortex is usually discussed as a single structure, it is actually composed of several different structures whose unique functions are not known.

(Additional abbreviations used: AI_p=agranular insular, posterior; PrCl and PC_l=lateral precentral cortex; PrCm and PC_m=medial precentral cortex; Th=thalamus; tt=tania tecta).


A
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ACd
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IL
AId
MO
+1.2
PCm
ACd
ACv
AId

are placed on, and the rats are to find the food. In both of these tasks, rats are to find the reward (i.e., the platform or food) as quickly and accurately as possible. It is thought that rats solve tasks like these using relational properties of surrounding room cues. Control rats learn these tasks rapidly but rats with medial frontal cortex damage do not. This suggests that medial frontal cortex is important for learning tasks of these kinds (Kolb et al., 1982).

Whishaw et al. (1992) found that rats with ventrolateral frontal cortex lesions were impaired at acquiring and retaining a configural string pulling task, a task requiring animals to combine olfactory and tactile information into unique representations. And Goldman-Rakic (1992) noted that monkeys with prefrontal cortex damage are impaired on delayed-response tasks, tasks in which, after a delay of several seconds, animals are signalled to respond to the location where a stimulus had briefly appeared. Goldman-Rakic (1992) also noted that strong correlations between electrical and metabolic activity of neurons in prefrontal cortex and performance of animals on delayed-response tasks exist. This further supports her claim that prefrontal cortex is important for memory.

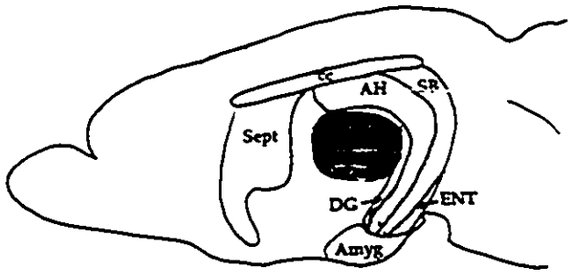
Goldman-Rakic (1992) claimed that prefrontal cortex is important for working memory. Working memory is memory that is of short-term importance and that needs to be rapidly and frequently updated with new and/or previously stored information. Goldman-Rakic claimed the hippocampus is also important for working memory (Olton et al., 1979), and claimed that its role is to rapidly consolidate new information whereas the role of prefrontal cortex is to rapidly retrieve stored information.

The Thalamus

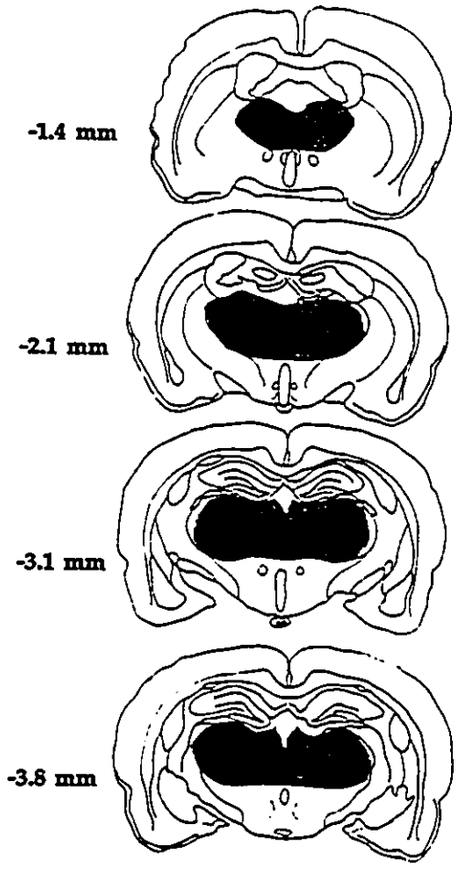
The thalamus is a diencephalic brain structure located in the middle of the forebrain (Figure 8). It is the principal terminal of sensory systems, excluding olfaction, and is

Figure 8. Views of the rat brain depicting location of the thalamus. (A) Saggital view. The thalamus is the shaded area (Thal). It is bounded above by the dentate gyrus (DG), Ammon's horn (AH) and the corpus callosum (cc). The septum (Sept) lies anterior to it, and the subiculum (SB), entorhinal cortex (ENT) and amygdala (Amyg) lie posterior and ventral to it. (B) Coronal views. The four views are located 1.4 mm, 2.1 mm, 3.1 mm and 3.8 mm posterior to bregma, respectively (see Paxinos and Watson, 1985). The thalamus is the shaded area in the middle in all the views. From its central location, its nuclei are uniquely positioned to serve as communication centers with surrounding brain areas.

A



B



sometimes called the "gateway to the cerebral cortex" (Angevine and Cotman, 1981). It is a complex of many nuclei that have different connections and, inevitably, different functions. It can be divided into anterior, medial and lateral groups of nuclei, and into dorsal and ventral groups of nuclei. Many thalamic nuclei are named by their topographical location (Jones, 1984). The MD is located medially in the dorsal nuclear group, and the ANT is located anteriorly in the dorsal nuclear group (Figure 9).

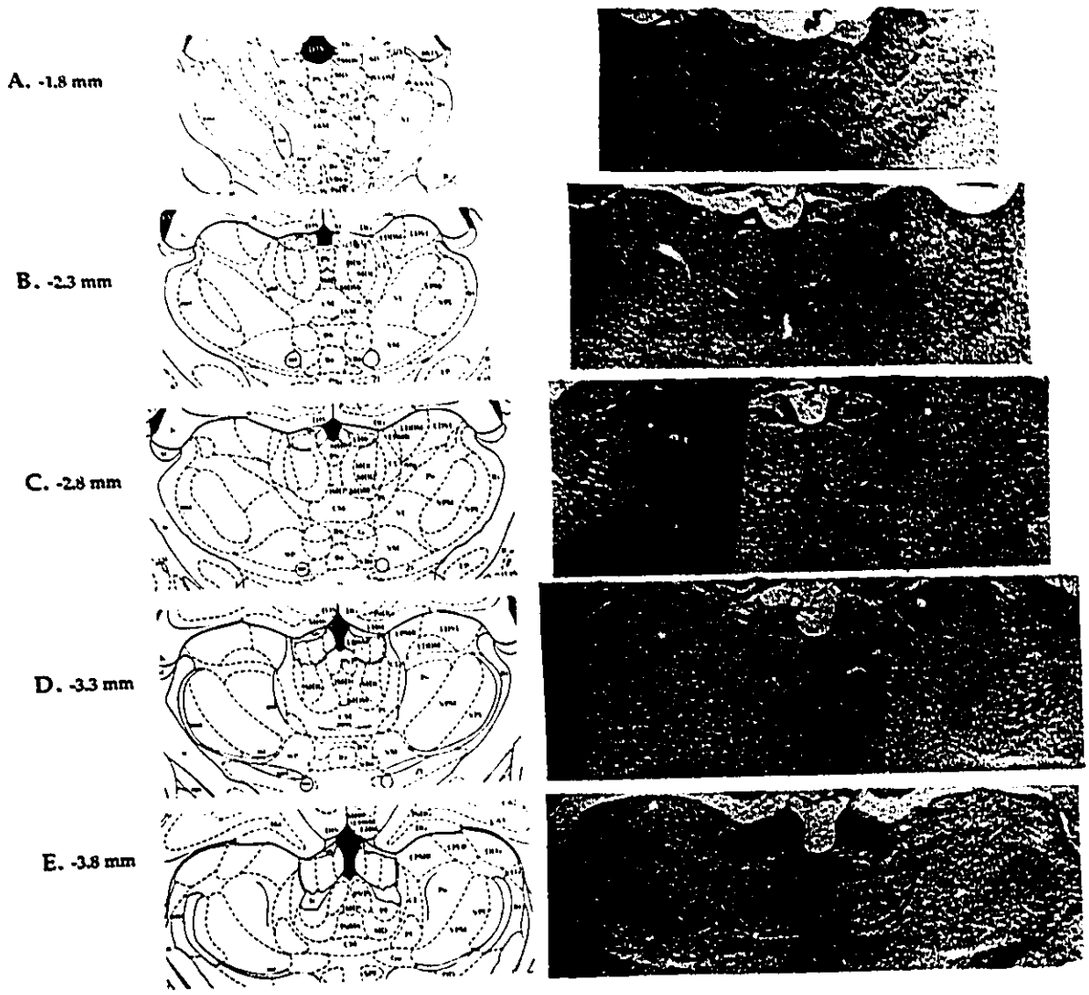
The ventral thalamus provides nonspecific input to the neocortex that might modulate its activity. The dorsal thalamus is composed of a number of nuclei, each of which projects to a specific area of the neocortex (Kolb and Whishaw, 1990). The ANT receives input from the hippocampus. The MD receives input from the amygdala, primary olfactory cortex, temporal cortex and the caudate. The ANT and MD both send input to prefrontal cortex (see Figure 6) and, as noted above, are thought to be involved in memory processes.

Evidence for role of the MD in memory processes comes from a number of sources; the patient N.A., people who suffer from thiamine deficiency induced amnesia, and people who suffer from Korsakoff's Syndrome. The thiamine deficency syndrome has been produced in rats through administration of thiamine deficient diets (Mair, Otto, Knoth, Rabchenuk and Langlais, 1991; Mair, Knoth, Rabchenuk and Langlais, 1991; Knoth and Mair, 1991). Memory impairments have also been produced in non-humans in which the MD is damaged experimentally (Slotnick and Kaneko, 1981; M'Harzi, Jarrard, Willig, Palacios and Delacour, 1991; Mumby, Pinel and Dastur, 1993).

One of the most interesting cases of thalamic-damage induced amnesia is N.A. In December, 1960, N.A. was stabbed with a fencing foil which penetrated through his right nostril and into his left forebrain. Severe memory impairment surfaced after his accident

Figure 9. Right. Coronal sections through the thalamus of a control rat's brain. The sections are located 1.8, 2.3, 2.8, 3.3 and 3.8 mm posterior to bregma, respectively (Paxinos and Watson, 1985). They are stained with Cresyl Violet, which stains Nissl substance in cells, and location of the ANT is outlined with dashed lines and location of the MD is outlined with solid lines on them. Left. Reproductions of the sections from the brain atlas of Paxinos and Watson (1985). Locations of several thalamic nuclei are shown on these reproductions.

(Abbreviations used in this figure (from Paxinos and Watson, 1985): 3V=3rd ventricle, AD=anterodorsal thalamic nucleus, al=ansa lenticularis, AM=anteromedial thalamic nucleus, Ang=angular thalamic nucleus, AVDM=anteroventral thalamic nucleus, dorsomedial part, AVVL=anteroventral thalamic nucleus, ventrolateral part, B=nucleus basalis of Meynert, BSTS=bed nucleus stria terminalus, supracapsular, CA2=field CA2 of Ammon's horn, CA3=field CA3 of Ammon's horn, CL=claustrum, CM=centromedial thalamic nucleus, cst=commissural stria terminalis, D3V=dorsal third ventricle, DG = dentate gyrus, DLG=dorsal lateral geniculate nucleus, eml=external medullary lamina, EP=entopeduncular nucleus, fi=fimbria hippocampus, fr=fasciculus retroflexus, G=gelatinosus thalamic nucleus, Gu=gustatory thalamic nucleus, Hil=hilus dentate gyrus, IAM=interanteromedial thalamic nucleus, ic=internal capsule, IMD=intermediodorsal thalamic nucleus, iml=internal medullary lamina, imvc=intermedioventral thalamic commissure, LDDM=laterodorsal thalamic nucleus, dorsomedial part, LDVL=laterodorsal thalamic nucleus, ventrolateral part, LHb=lateral habenular nucleus, LHbL=lateral habenular nucleus, lateral, LHbM=lateral habenular nucleus, medial, LPLR=lateral posterior thalamic nucleus, lateral rostral, LPMR=lateral posterior thalamic nucleus, medial rostral, LV=lateral ventricle, MD=mediodorsal thalamic nucleus, MDC=mediodorsal thalamic nucleus, central, MDL=mediodorsal thalamic nucleus, lateral, MDM=mediodorsal thalamic nucleus, medial, MHb=medial habenular nucleus, ml=medial lemniscus, mt=mammillothalamic tract, opt=optic tract, PaDC=paraventricular hypothalmic nucleus, dorsormedial cap, PC=paracentral thalamic nucleus, PF=parafascicular thalamic nucleus, Po=posterior thalamic nuclear group, PoDG=polymorph layer dentate gyrus, PoMN=posteromedian thalamic nucleus, PT=paratenial thalamic nucleus, PV=paraventricular thalamic nucleus, PVA=paraventricular thalamic nucleus, anterior part, PVP=paraventricular thalamic nucleus, posterior part, Re=reuniens thalamic nucleus, Rh=rhomboid thalamic nucleus, Rt=reticular thalamic nucleus, scp=superior cerebellar peduncle, sm=stria medullaris thalamus, st=stria terminalis, SPF=subparafascicular thalamic nucleus, VL=ventrolateral thalamic nucleus, VLG=ventral lateral geniculate nucleus, VM=ventromedial thalamic nucleus, VPL=ventral posterolateral thalamic nucleus, VPM=ventral posteromedial thalamic nucleus, VRe=ventral reuniens nucleus, Xi=xiphoid thalamic nucleus, ZI=zona incerta).


A. -1.8 mm
B. -2.3 mm
C. -2.8 mm
D. -3.3 mm
E. -3.8 mm

(Teuber, Milner and Vaughan, 1968). Computerized tomography scans revealed damage to the left MD in N.A. (Squire and Moore, 1979), and magnetic resonance imaging studies revealed more extensive left thalamic damage (Zola-Morgan and Squire, 1993). That N.A. has a severe memory defect and has left MD damage, however, is cited as evidence for a role of the MD in learning. Nevertheless, the presence of damage in other brain areas in N.A. can be used to question this conclusion.

Long-term alcoholism, especially when accompanied with malnutrition, has long been known to produce defects of memory (Kolb and Whishaw, 1990). In 1887, a Russian physician, Korsakoff, wrote about the syndrome that accompanies chronic alcoholism, which is now widely known by his name. There is controversy over exactly what brain areas are damaged in Korsakoff's patients (Kolb and Whishaw, 1990), but the bulk of evidence suggests that damage to the MD produces the memory loss (Victor, Adams and Collins, 1971; Mair, Warrington and Weiskrantz, 1979).

In studies involving non-humans, some claim learning deficits surface after induction of MD damage, and some claim that they do not (Kolb, 1977; Kolb et al., 1982; Mumby et al., 1993; Slotnick and Kaneko, 1981; Aggleton and Mishkin, 1983; Hunt and Aggleton, 1991). Differences in the techniques used to induce MD damage could partly account for variable conclusions, as could amount of damage inadvertently induced to surrounding structures and differences in tasks employed. Nevertheless, the number of studies suggesting behavioral impairments follow thalamic damage is impressive (Table 2).

When the MD is damaged, other midline nuclei such as the paraventricular, paratenial and reuniens thalamic nuclei are typically damaged as well. Some of these have reciprocal connections with both the amygdala and hippocampus and thus, are "strong candidates for inclusion in the circuitry subserving memory" (Amaral, 1987). Other areas

Table 2. Summary of findings in previous research on effect of medial dorsal thalamic nucleus lesions on behavior of rats.

Task	Lesion Type	Result	Reference
Delayed Non Matching to Sample	Ibotenic	not impaired	Neave et al., 1992
	Electrolytic	impaired	Mumby et al., 1993
	Electrolytic	impaired	Hunt & Aggleton, 1991
	Ibotenic	impaired	Hunt & Aggleton, 1991
Radial Arm Maze	Ibotenic	not impaired	Beracochea et al., 1989
	Electrolytic	not impaired	Kolb et al., 1982
	Electrolytic	impaired	M'Harzi et al., 1991
	Ibotenic	impaired	Stokes & Best, 1990
	Electrolytic	impaired	Stokes & Best, 1990
	Electrolytic	impaired (less cues)	Stokes & Best, 1988
	Ibotenic	impaired (more difficult version)	Kessler et al., 1982
Water Maze	Electrolytic	not impaired	Kolb et al., 1982
Hebb-William complex mazes	Electrolytic	variable (some rats impaired)	Gross et al., 1965
Alternation Tasks			
Delayed Alternation		not impaired	Greene & Naranjo, 1986
		not impaired	Brito et al., 1982
	Electrolytic	not impaired	Tigner, 1974
		impaired	Winocur, 1985
	Kainic acid	impaired	Kessler & Markowitsch, 1981
Spontaneous Spatial Alternation	Electrolytic	impaired	Weis & Means, 1980
Spatial Delayed Alternation	Electrolytic	impaired	Vicedomini et al., 1982
Spatial Reversal	Electrolytic	impaired	Kolb, 1977
	Electrolytic	not impaired (depends)	Means et al., 1975b
Spatial Reversal Extinction	Electrolytic	impaired	Kolb, 1977
Serial Spatial Reversal	Ibotenic	not impaired	Beracochea et al., 1989
Temporal Spatial Reversal	Ibotenic	impaired	Beracochea et al., 1989
Forced Alternation	Ibotenic	impaired	Hunt & Aggleton, 1991
	Electrolytic	not impaired	Hunt & Aggleton, 1991
Spontaneous Alternation (in T maze)	Electrolytic	impaired	Means et al., 1974
Spontaneous Alternation (bar press)	Electrolytic	impaired	Gross et al., 1965
Go/No-Go Alternation	Heating	impaired	Sakurai & Sugimoto, 1985
	Electrolytic	impaired	Means et al., 1973a
Discrimination Tasks			
Visual Discrimination	Electrolytic	not impaired	Slotnick & Kaneko, 1981
Olfactory Discrimination	Electrolytic	not impaired	Slotnick & Kaneko, 1981
	Electrolytic	impaired (but depends on factors)	Eichenbaum et al., 1980
	Electrolytic	impaired	Staubli et al., 1987
Olfactory Discrimination Reversals	Electrolytic	impaired	Slotnick & Kaneko, 1981
Brightness Discrimination	Electrolytic	not impaired	Vanderwolf, 1969
	Kainic acid	impaired	Tigner, 1974
Place Discrimination & Reversal	Kainic acid	not impaired	Tigner, 1974
Roughness Discrimination & Reversal	Kainic acid	impaired	Tigner, 1974
Visual-Tactile Discrimination	Electrolytic	impaired	Means et. al., 1973b

	Electrolytic	impaired	Waring & Means, 1976
	Electrolytic	impaired	Weis & Means, 1980
Activity Measures			
Running Wheels	Electrolytic	increase (but not significant)	Kolb, 1977
Activity	Ibotenic	increase (at night)	Beracochea et al., 1989
	Electrolytic	increase (but not significant)	Waring & Means, 1976
Maze Activity (in T maze)	Electrolytic	increase	Means et al., 1974
	Electrolytic	no change	Means et al., 1973b
Recognition and Detection			
Olfactory Detection	Electrolytic	not impaired	Slotnick & Kaneko, 1981
Object Recognition	Electrolytic	not impaired	M'Harzi et al., 1991
Place Recognition	Electrolytic	not impaired	M'Harzi et al., 1991
Environment Familiarity			
Unfamilar Environment	Electrolytic	rear more; freeze less	Vanderwolf, 1969
Platform Test	Electrolytic	slow to initiate	Vanderwolf, 1969
Response to Novel Alley	Electrolytic	impaired	Means et al., 1974
Shock-Induced Behaviors			
Avoidance Responses	Electrolytic	impaired	Vanderwolf, 1962
	Electrolytic	impaired	Vanderwolf, 1963
	Electrolytic	impaired	Vanderwolf, 1969
		impaired	Olton & Isaacson, 1967
Conditioned Fear	Electrolytic	not impaired	Vanderwolf, 1962
Conditioned Defication	Electrolytic	impaired	Vanderwolf, 1963
Shock-Induced Agression	Electrolytic	increase	Kolb, 1977
Other Behaviors			
Hoarding	Electrolytic	decrease	Kolb, 1977
Male-Male Interactions	Electrolytic	increase	Kolb, 1977
Water Intake	Ibotenic	increase	Beracochea et al., 1989
Food Intake	Ibotenic	increase	Beracochea et al., 1989
	Electrolytic	no change	Means et al., 1973b
Exploring	Electrolytic	slow to initiate	Vanderwolf, 1969
Runway Speed	Electrolytic	not impaired	Means et al., 1974
Runway Speed Extinction	Electrolytic	impaired	Means et al., 1974
Visual Placing	Electrolytic	not impaired	Means et al., 1973b
Emotionality (response to stimuli)	Electrolytic	not impaired	Means et al., 1973b
	Electrolytic	decrease	Waring & Means, 1976

important for learning and memory include the fimbria, the mammillothalamic tract, and the anterior nuclear complex (Amaral, 1987). All of these can receive inadvertent damage so the idea that the MD is responsible for memory deficits can be questioned. Hunt and Aggleton (1991), based on their finding that rats with MD lesions that extend into the ANT exhibit clearer deficits than rats with damage confined to the MD, claim that some impairments attributed to the MD nucleus might reflect damage to the adjacent ANT instead. Sutherland and Rodriguez (1989) found that rats with ANT damage were impaired on a spatial learning task, and Mishkin and Appenzeller (1987) claim that combined damage to thalamic targets of the hippocampus and amygdala severely impair monkeys' recognition memory whereas damage to either target alone has only slight effects. Thus, the ANT may well share a role in learning with the MD.

PROPOSED RESEARCH

Several lines of evidence suggest that the ANT and MD are involved in learning. They are connected to structures thought to be involved in memory and learning, they are found to be damaged in humans with memory disorders and when they are damaged in nonhumans, memory impairments are found (Mishkin and Appenzeller, 1987; Whishaw, 1987; Kolb, 1984; Kolb et al., 1982). The purpose of the present work was to examine the effects of damage to these two thalamic nuclei on memory and learning tasks.

Three tasks were selected for the behavioral analyses: a spatial task, a configural task, and amphetamine-induced locomotion. Each of these tasks has been shown to be sensitive to frontal cortex and hippocampal damage (Whishaw, 1987; Kolb et al., 1982; Whishaw and Tomie, 1991; Whishaw et al., 1992; Whishaw and Mittleman, 1991). Each also taps a different feature of behavior. It was expected that if the ANT and MD share functions with the frontal cortex and hippocampus then animals with damage to the ANT and MD should be impaired on one or more of these tasks.

The Morris water task was the spatial task. In it, rats swim through murky water to escape to a platform hidden just below the water's surface. It is thought that rats solve water maze tasks using relational properties of room cues. Two versions of the water maze task were used. In one version, the platform was in a different location each day. This is sometimes referred to as a working memory task since once a rat finds the platform, it must use that information for the rest of that day's trials but then give up the information the next day. In the other version, the platform was in the same location each day. This is sometimes referred to as a reference memory task since information the rats use across trials and days does not change.

An olfactory-tactile string pulling task was the configural task. In it, rats are presented

with two strings simultaneously, one that has food tied on its distal end and one that does not. The rats are to pull up the string containing food. The task consists of three stages. On Stage 1, the rats must select a string based on its odor. On Stage 2, the rats must reverse the response learned in Stage 1. On Stage 3, the rats have to take both tactile and olfactory information into account. Thus, the task tests ability of rats to form a simple association, a reversal, and a configural association.

Activity was assessed by placing the rats in wire mesh cages and counting how often beams between light sources and photocells attached to the cages were broken by the rats in a given length of time. Administration of a low dose of amphetamine (0.25-1.0 mg/kg) to normal rats results in general activation consisting of sniffing, locomotion and rearing. Medium doses result in initial locomotor activity followed by stereotyped sniffing behavior. With high enough doses (2.5-7.5 mg/kg) behavior largely consists of stereotyped activity (Feldman and Quenzer, 1984; Whishaw and Mittleman, 1991). To maximize the chance of finding between group differences, rats were tested twice, first with a low dose and second with a medium-high dose of amphetamine.

Thalamic lesions were made electrolytically or via infusion of the neurotoxins ibotenic acid or quinolinic acid. The electrolytic technique damages cell bodies and fibers of passage whereas the neurotoxins that were used kill cell bodies and spare fibers of passage. By comparing changes induced by the electrolytic lesions with changes induced by the neurotoxin lesions, the relative contributions of cell bodies versus fibers of passage could thus be assessed. Some neurotoxins are toxic to only certain cells, and thus, the relative potency of the two neurotoxins could also be assessed.

EXPERIMENT I

Introduction

The purpose of the first experiment was to investigate the role of the ANT and the MD in spatial navigation and amphetamine-induced activity. Rats received lesions of the ANT or MD either electrolytically or via intrathalamic infusion of ibotenic acid or quinolinic acid. To study spatial navigating ability of the rats, two versions of a water maze task were administered. A changing platform version was administered first and, on the possibility that the rats in one of the groups might not be able to do it, a same place platform version was then administered. At the completion of spatial navigation testing, amphetamine induced activity was examined (Whishaw and Mittleman, 1991). To maximize the chance of finding between group differences, the rats were tested twice, first with a low dose and second, with a medium-high dose of amphetamine.

Method and Procedures

Animals

Adult female Long-Evans hooded rats, from the University of Lethbridge (Lethbridge, Alberta, Canada) vivarium and weighing 200-250 g when the study began, were used. They lived in groups in hanging wire mesh cages in an animal colony that was maintained on a 12:12 hr light-dark cycle. Testing was done during the light portion of the cycle. Prior to surgery, the rats were divided into groups receiving the treatments summarized in Table 3.

Table 3. Lesion groups, number of animals and lesion coordinates for animals used in Experiment I.

	Groups			
	n	Anterior	n	Medial Dorsal
Small Electrolytic	7	1.5 mA for 5 secs (1.4 P, 1.0 L, 5.0 V)	7	1.5 mA for 5 secs (2.7 P, 1.0 L, 5.0 V)
Large Electrolytic	7	1.5 mA for 10 secs (1.4 P, 1.0 L, 5.0 V)	7	1.5 mA for 10 secs (2.7 P, 1.0 L, 5.0 V)
Ibotenic	8	0.3 µl over 3 mins (1.5 P, 1.0 L, 5.2 V) or (1.3 P, 1.0 L, 5.0 V)	7	0.5 µl over 5 mins (2.7 P, 1.0 L, 5.0 V)
Quinolinic	7	0.3 µl over 3 mins (1.5 P, 1.0 L, 5.2 V)	7	0.5 µl over 5 mins (2.7 P, 1.0 L, 5.0 V)
Controls	13			

n=number of animals, P=mm posterior to bregma, L=mm lateral from the midline, V=mm ventral to dura

Surgery

The rats were anesthetized with intraperitoneal injections of sodium pentobarbital (40 mg/kg) and atropine methylnitrate (5 mg/kg). Thalamic lesions were made electrolytically or via intrathalamic infusions of either ibotenic acid (10 µg/µl dissolved in 1 M Phosphate buffered saline, pH = 7.4) or quinolinic acid (2% solution dissolved in phosphate buffered saline, pH = 7.4). For electrolytic lesions, 00 insect pins insulated with epoxylite were used. They were attached to a Grass D.C. constant current lesion maker. Before being lowered into the brain, the insulated electrode was cut to expose the tip. After being lowered, a 1.5 mA anodal electric current was passed through the electrode. For the neurotoxic lesions, ibotenic acid or quinolinic acid was infused through a 30 gauge stainless steel cannula attached, via polyethyline tubing, to a 10 µl Hamilton microsyringe. The microsyringe was attached to a motorized infusion pump, and the pump speed was set so that the solution would be infused at a rate of 0.1 µl/min.

With bregma and lambda on the same horizontal plane, coordinates for electrode and cannula placements (Table 3) were measured in relation to bregma, the midline and dura, respectively. Current was passed through the electrodes for either 5 sec or 10 sec, and neurotoxins were infused through the cannula for either 3 min or 5 min (Table 3). After neurotoxin infusions, the cannula were left in place for 5 min to allow for diffusion of the neurotoxin away from the cannula tips. Control animals were anesthetized. Behavioral testing began approximately one week after surgery.

Water Maze Tasks

Apparatus. The water maze was a circular tank, 146 cm in diameter and 46 cm high, that was painted white and filled to a height of 25 cm with 18° C water. Approximately 1500 ml of skim milk powder was dissolved in the water to make it opaque. A clear

Plexiglas platform (14 x 14 cm) was submerged 14 mm below the water surface and was invisible to rats when they were inside the pool (Figure 10).

Procedure and Performance Rating. Rats were placed in the pool facing the wall at one of four starting positions (east, north, south or west). The latency to find the platform on each trial, which was timed with a stopwatch, and the swim path, drawn on a map of the pool, were used to assess performance. A trial terminated when a rat found the platform or after 60 sec elapsed. Rats were left on the platform for 10 sec, and were removed from the pool after each trial. Swim paths were rated on a 2 point scale. If a rat's swim path remained within an 18 cm alley, it was considered correct and received a score of '0', and if it did not remain within the 18 cm alley, it was considered incorrect, and received a score of '1' (Figure 11, Top). Rats were tested in the changing platform task first, and then were tested in the same platform task. Rats were brought into the test room in groups of seven. Each group consisted of a mix of control rats and thalamic rats. Rats were tested individually.

Changing Platform Task. Rats were tested on 10 consecutive days. The platform was in a different location each day and 8 different locations were used (Figure 11, Bottom). Rats received 8 trials per day, 2 from each of the four starting positions. Order of the starting positions was pseudorandom, but once a rat received a trial from a particular position it immediately received its second trial from that position. It was then removed from the pool for approximately 5 min while the other rats were tested.

Same Platform Water Maze Task. Rats were tested on 5 consecutive days. The platform was in the same location each day. Rats received 8 trials per day, 2 from each of the four starting positions. Order of the starting positions was pseudorandom. After each trial, rats were removed from the pool for approximately 5 min while the other rats

Figure 10. Photograph of a rat sitting on the hidden platform in the water maze. The water maze is a circular tank, 146 cm in diameter and 46 cm high that is painted white and filled to a height of 25 cm with 18°C water. Approximately 1500 ml of skim milk powder is dissolved in the water to make it opaque. A clear plexiglas platform (14 x 14 cm) is submerged 14 mm below the water surface so that it is invisible to rats when they are in the pool. Rats are excellent swimmers and in the wild live along the edges of water ways. They can swim from the edge of the pool to the platform in this maze within three sec.

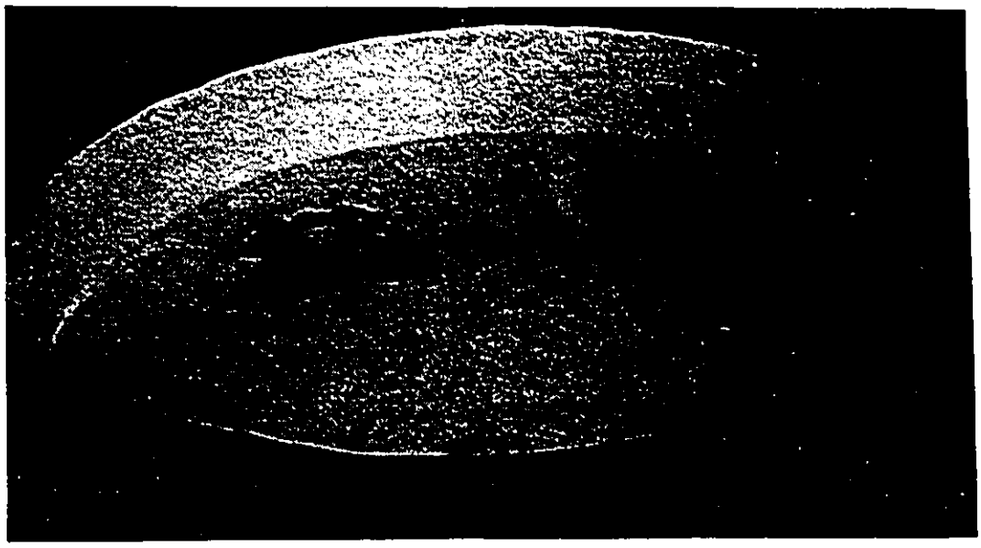
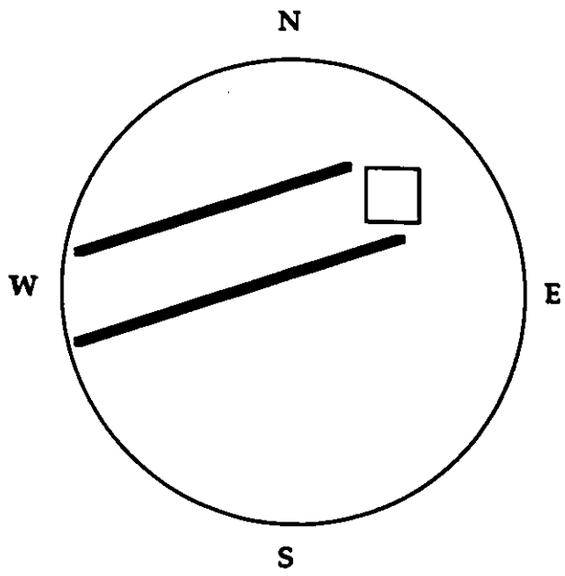
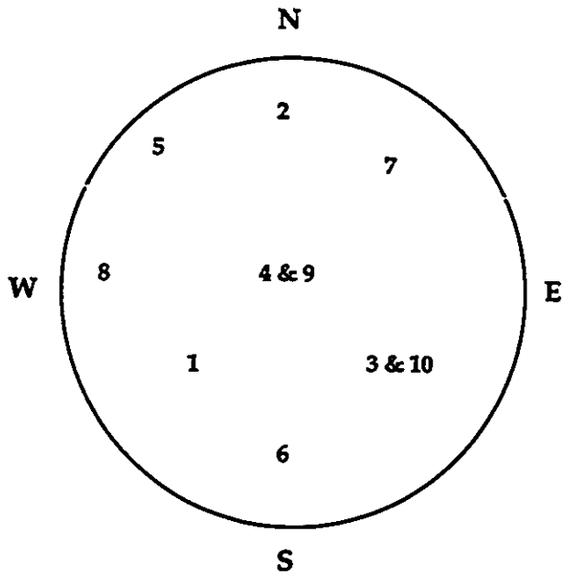


Figure 11. Schematic illustration of the water maze task. The large circle represents the pool. (A) Rats are placed in the pool facing the wall at one of four starting positions (north (N), south (S), east (E) or west (W)). On each trial, rats are given 60 sec to find the hidden platform (shaded box). The time to find the hidden platform is measured with a stopwatch. The path swam is manually drawn. If rats find the platform before 60 sec elapses, they are left on the platform for 10 sec. Rats are removed from the pool after each trial. If rats deviate from swimming directly to the platform by a noticeable amount (e.g., by swimming outside the alley between the west (W) starting point and the platform shown by the thick lines on the diagram), they are given an error for that trial. If the rats swim directly to the platform on a given trial, they are not given an error for the trial. The procedures just described were used in both the changing platform and same platform water maze tasks. (B) In the changing platform task, the platform was in a different location each day. Eight different platform locations were used and the rats were tested on ten days. Daily locations of the platform are depicted. On day one, for example, the platform was located in the middle of the south-west quadrant of the pool, and on day ten, it was located in the middle of the south-east quadrant of the pool.

A



B



were tested.

Activity Task

Apparatus. Activity cages were 15 hanging wire mesh cages, which measured 40.5 cm long by 24.5 cm wide by 18.0 cm high (Figure 12). Fibre-optic light sources were attached to the front of each cage, approximately 5 cm from each side and approximately 4 cm from the floor, and photocells were attached to the back. The photocells were connected to an Apple IIe computer. Breaks in the beam between the light sources and the photocells induced by movement of rats were recorded by the computer as being right or left beam breaks. Cage crosses, abstracted from the beam break counts, were used as the measure of activity. A cross comprised a return trip along the length of the cage and consisted of three alternating beam breaks (e.g., right, left, right).

Drug Injections. Rats received subcutaneous injections of d-amphetamine, which was dissolved in saline. They received 1.25 mg/kg on the first test and 2.5 mg/kg on the second.

Procedure. Data were collected in the activity cages after water maze testing was over. Rats were placed in the activity cages individually for two sessions, and 3 to 5 days elapsed between sessions. During the first 2 hr of each session baseline activity measures were recorded. The rats were then injected with d-amphetamine, and another 2 hr of data were collected.

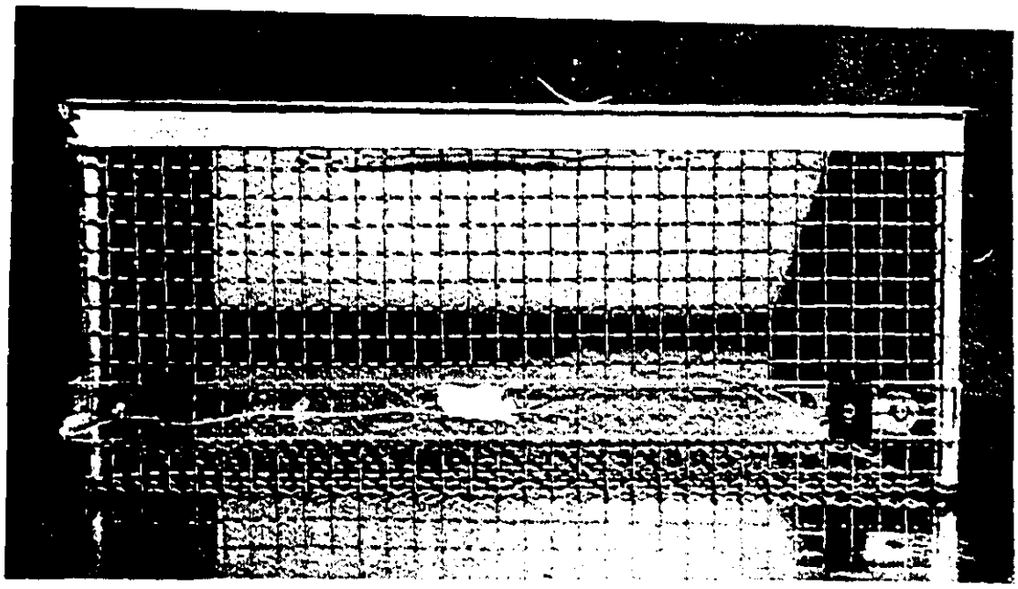
Data Analysis

The results were analyzed using analysis of variance, descriptive statistics and correlation features of the statistical software package BMDP (Dixon, 1985).

Histology

At the completion of behavioral testing, the rats were deeply anesthetized with sodium

Figure 12. Photograph (front view) of one of the activity cages. The activity cages were hanging wire mesh cages, 40.5 cm long by 24.5 cm wide by 18.0 cm high. Fibre-optic light sources were attached to the front of each cage, approximately 5 cm from each side and approximately 4 cm from the floor, and photocells were attached to the back. On the photograph, the pieces of black tape indicate the locations of the light sources, and the small holes at the back of the cage indicate locations of the photocells. The photocells were attached to an Apple IIe computer. Breaks in the beam between the light sources and photocells, induced by movement of the rats, were recorded by the computer as being right or left beam breaks. Cage crosses, abstracted from the beam break counts, were used as the measure of activity. A cross comprised a return trip along the length of the cage and consisted of three alternating beam breaks (e.g., right, left, right).



pentobarbital (100 mg/kg ip) and were transcardially perfused with a 0.9% saline solution followed by 10% formal-saline. The brains were removed and stored in a 30% sucrose and 10% formal-saline solution. They were sectioned at -20° C using a cryostat. Every 3rd to 5th 40 µm thick section throughout the thalamus was mounted on gelatin coated glass slides. The sections were stained with cresyl violet and were examined microscopically.

Results

Histology

The rats had large lesions that destroyed extensive areas of the thalamus. Details of the histological findings for each group of rats will be presented in sequence.

Electrolytic Anterior. In most of the rats, the small lesions were too dorsal, producing moderate to severe damage to the anterior dorsal and anterior ventral thalamic nuclei, and only mild damage to the anterior medial thalamic nucleus (Figure 13). The rats all had some damage to the MD, the stria medullaris, the paraventricular nucleus and the paratenial nucleus. Three rats had mild lateral dorsal thalamic nucleus damage, two rats had mild ventral anterior lateral thalamic damage and one rat had moderate habenula damage and mild damage to the lateral posterior thalamic nucleus. The fornix was damaged in many of the rats, as were anterior parts of the hippocampus.

The large electrolytic lesions damaged the anterior dorsal thalamic nucleus completely in four of the rats and severely in the other three (Figure 14). Damage to the anterior ventral thalamic nucleus was complete in five of the rats and was severe in the remaining two. Damage to the anterior medial thalamic nucleus was moderate to severe, but not complete, in all the rats. In addition to the ANT, the stria medullaris, paraventricular and

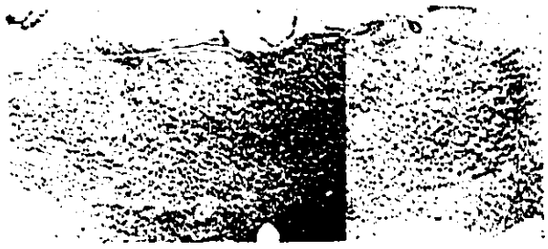
Figure 13. Coronal sections through the thalamus of a rat that received a small electrolytic lesion of the ANT. The shading on the overlay on sections A and B shows where damaged tissue is. The ANT is partially destroyed. The shaded fragments located dorsally on section A are remnants of the fornix, which was inadvertently damaged. In addition to ANT, the anterior components of the habenula, stria medullaris and paraventricular thalamic nucleus were damaged (see Figure 9 for reference).

Electrolytic Anterior
(Small)

A

B

C

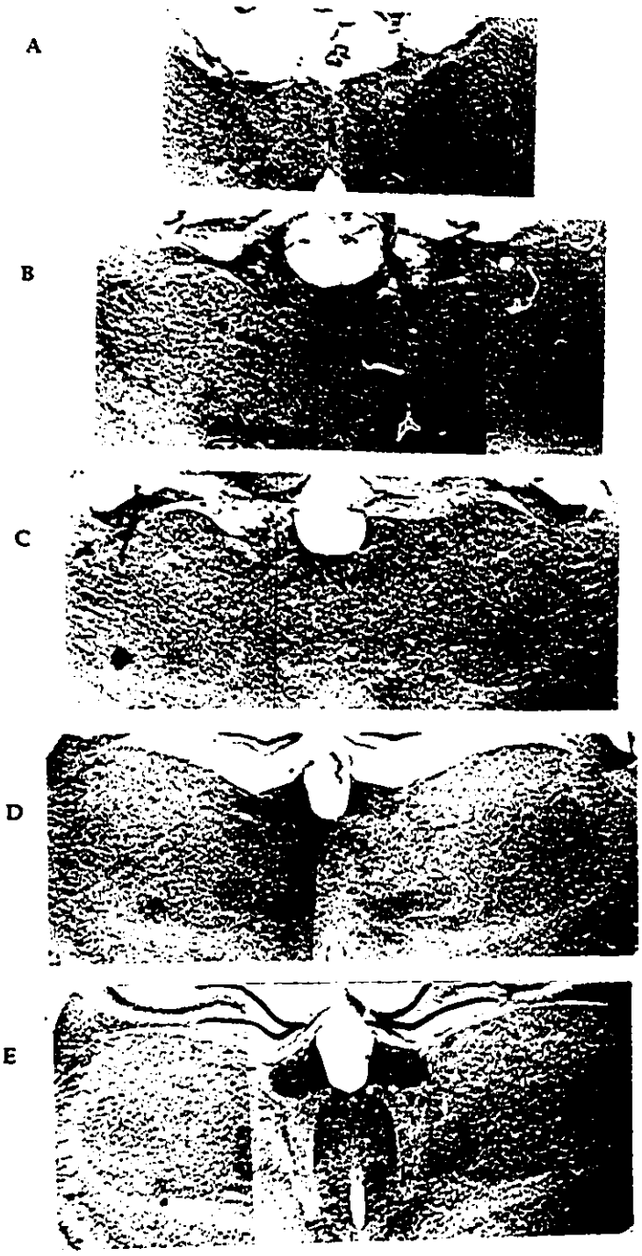


D

E

Figure 14. Coronal sections through the thalamus of a rat that received a large electrolytic lesion of the ANT. The shading on the overlay on sections A, B and C show where damaged tissue is. Note the damage located dorsally in sections A and B, and the mild amount of damage located dorsally on the left in section C (see Figure 9 for reference).

Electrolytic Anterior
(Large)



paratenial thalamic nuclei were moderately to severely damaged in all of the rats. The habenula, lateral dorsal thalamic nucleus and MD received variable amounts of damage, as did the lateral posterior, ventral anterior lateral, centromedial and paracentral thalamic nuclei. The ventrobasal, rhomboid, reuniens and ventromedial thalamic nuclei were severely destroyed in one rat. The fornix and anterior hippocampus also received inadvertent damage.

Ibotenic Anterior. The anterior dorsal and anterior ventral thalamic nuclei were completely damaged in two rats, severely damaged in three rats, mildly damaged in two rats and not damaged in one rat (Figure 15). The anterior medial thalamic nucleus was moderately damaged in three rats, mildly damaged in four rats and was not damaged in one rat. Nuclei receiving varying amounts of inadvertent damage included the MD, the stria medullaris, the paraventricular thalamic nucleus, the paratenial thalamic nucleus, and the centromedial thalamic nucleus. The lateral dorsal thalamic nucleus and rhomboid thalamic nucleus were mildly damaged in a few rats and one rat had mild damage to the ventral lateral, reuniens, submedial and ventromedial thalamic nuclei.

Quinolinic Anterior. Quinolinic acid completely destroyed the ANT in one rat, but the other rats had moderate to mild damage of the ANT (Figure 16). Nuclei inadvertently damaged included the MD, the habenula, the lateral dorsal and lateral posterior thalamic nuclei, the ventral anterior lateral and ventrobasal thalamic nuclei, the stria medullaris, the paraventricular and paratenial thalamic nuclei, the centromedial thalamic nucleus, the rhomboid, reuniens and submedial thalamic nuclei, the ventromedial thalamic nucleus, the paracentral thalamic nucleus and the claustrum. A few of the rats had calcification in the thalamus, also (see Figure 16).

Electrolytic Medial Dorsal. Three of the small electrolytic rats had moderate and four

Figure 15. Coronal sections through the thalamus of a rat that received an ibotenic acid lesion of the ANT. The shading on the overlay on sections A, B, C and D indicates where damaged tissue is located. There is quite a bit of cell loss located medially and extending dorsolaterally in sections A, B and C, and there is some cell loss located medially in section D. The ANT is extensively damaged, and the damage spreads posteriorly into the MD. As is clear on section C, the damage is somewhat asymmetrical. Fewer cells are spared on the right than on the left. (See Figure 9 for reference)

Ibotenic Anterior

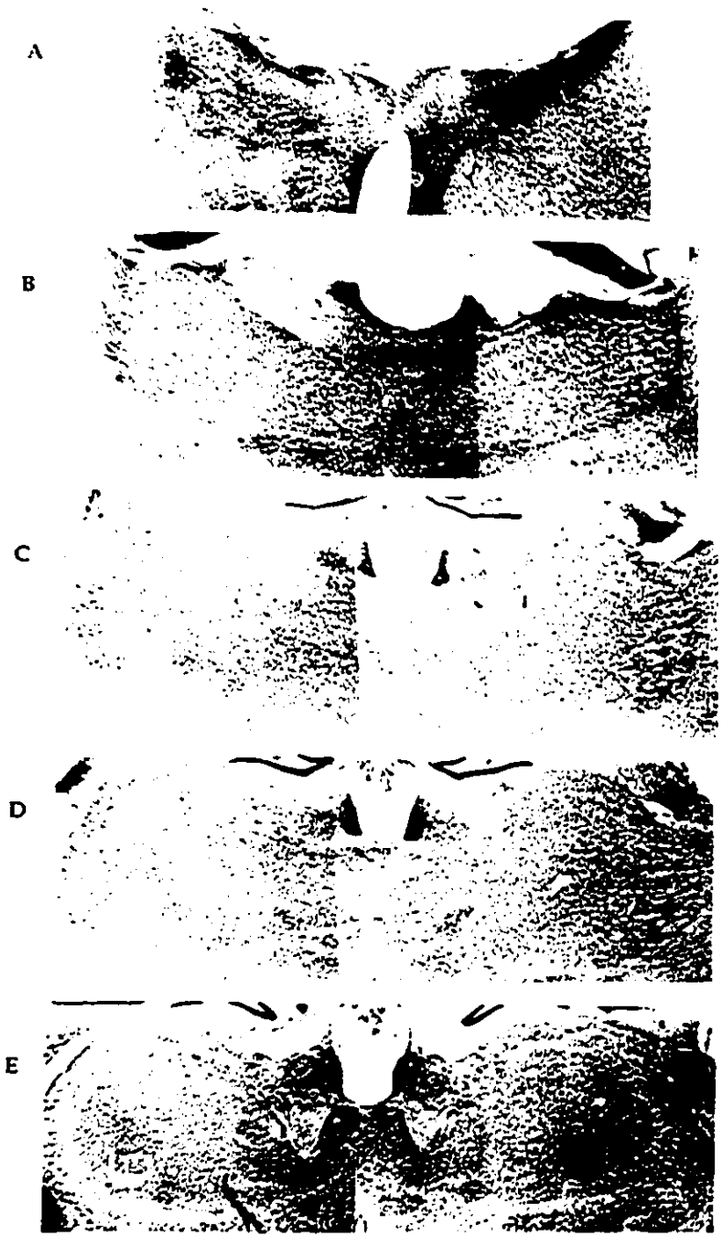


Figure 16. Coronal sections through the thalamus of a rat that received a quinolinic acid lesion of the ANT. The shading on the overlay indicates where damaged tissue is. There is cell loss medially and laterally in sections A, B, C and D, and there is some cell loss located medially in section E. The ANT is damaged, as are the MD and several other thalamic nuclei (see Figure 9 for reference). The black dots located medially in section B and more laterally in sections C and D are calcium deposits. Most of the quinolinic thalamic rats had calicification in the thalamus.

Quinolinic Anterior

A

B

C

D

E

had severe damage to the MD (Figure 17). Nuclei that received inadvertent damage, that ranged from being mild to severe, included the ANT, the habenula, the lateral dorsal and lateral posterior nuclei, the ventral anterior lateral nucleus, the stria medullaris, the paraventricular, paratenial, centromedial, rhomboid, reuniens and submedial thalamic nuclei, the paracentral thalamic nucleus, the claustrum, the ventromedial thalamic nucleus and the ventrobasal thalamic nucleus.

All the large electrolytic rats had either complete or severe damage to the MD (Figure 18). Nuclei inadvertently damaged moderately to severely included the habenula, the stria medullaris, the paraventricular, paratenial, centromedial, rhomboid, reuniens and paracentral thalamic nuclei and the claustrum. Nuclei inadvertently damaged mildly to moderately included the ANT, the lateral dorsal and lateral posterior thalamic nuclei, the ventral anterior lateral and ventrobasal nuclei and the ventromedial thalamic nucleus.

Ibotenic Medial Dorsal. The MD was moderately to severely damaged in all of the ibotenic rats (Figure 19). Several other thalamic nuclei were also damaged. The anterior dorsal and anterior ventral thalamic nuclei were moderately to severely damaged, as were the stria medullaris, the paraventricular and paratenial thalamic nuclei, the centromedial thalamic nucleus, the paracentral thalamic nucleus and the claustrum. The anterior medial thalamic nucleus was mildly to moderately damaged, as were the habenula, the lateral dorsal and lateral posterior thalamic nuclei, the ventral anterior lateral and ventrobasal thalamic nuclei, the rhomboid, reuniens and submedial thalamic nuclei and the ventromedial thalamic nucleus.

Quinolinic Medial Dorsal. The quinolinic lesions were large and were full of calcification (Figure 20). The MD was completely damaged in three rats, severely damaged in three rats and moderately damaged in one rat. Nuclei that received

Figure 17. Coronal sections through the thalamus of a rat that received a small electrolytic lesion of the MD. The shading on the overlay on sections A, B and C indicate where damaged tissue is. The MD is clearly damaged in sections A and B, and there is loss of cells in the MD in section C. Some MD cells are spared in sections B and C, and other thalamic nuclei are damaged (e.g., the habenula, the stria medullaris and the paraventricular nucleus) (see Figure 9 for reference).

Electrolytic Medial Dorsal
(Small)

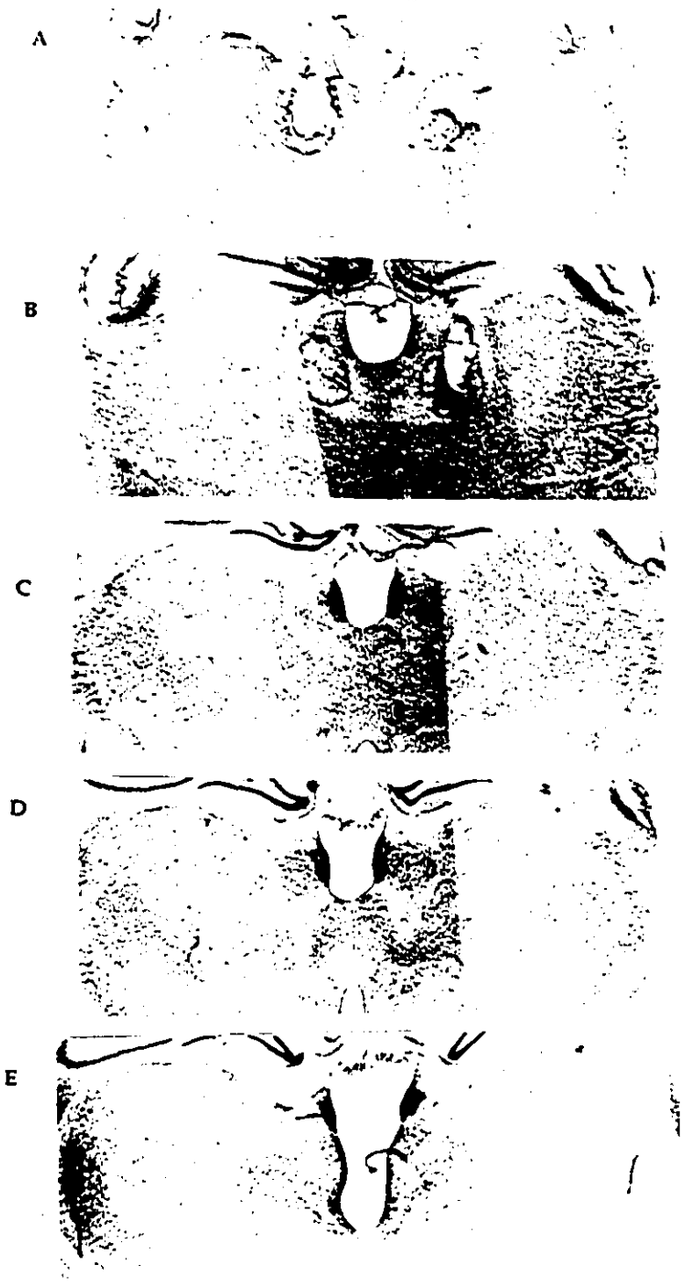


Figure 18. Coronal sections through the thalamus of a rat that received a large electrolytic lesion of the MD. Clearly, the MD is damaged in sections B, C and D, and the lesion is not confined to the MD (see Figure 9 for reference). The shading on the overlay indicates where damaged tissue is. In addition to extensive damage in sections B, C and D, there is some cell thinning in section A and there is some tissue damage in section E. The large circular areas in sections B, C, and D are composed of necrotic tissue and glial cells.

Electrolytic Medial Dorsal
(Large)

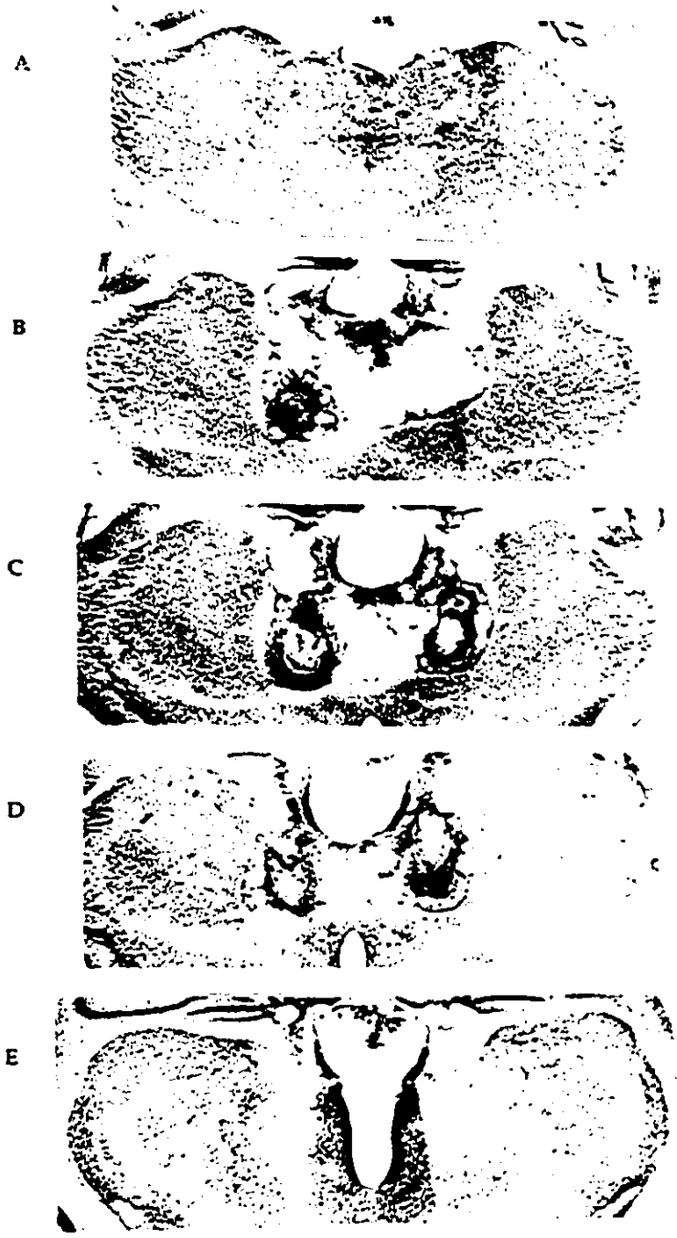


Figure 19. Coronal sections through the thalamus of a rat that received an ibotenic acid lesion of the MD. The shading on the overlay indicates location of damaged tissue. There clearly is cell loss located medially in sections B and C. There is also cell loss in the left dorsolateral thalamus in sections B and C. The MD is damaged, but there are cells spared in ventrolateral parts of it (see section C).

Ibotenic Medial Dorsal

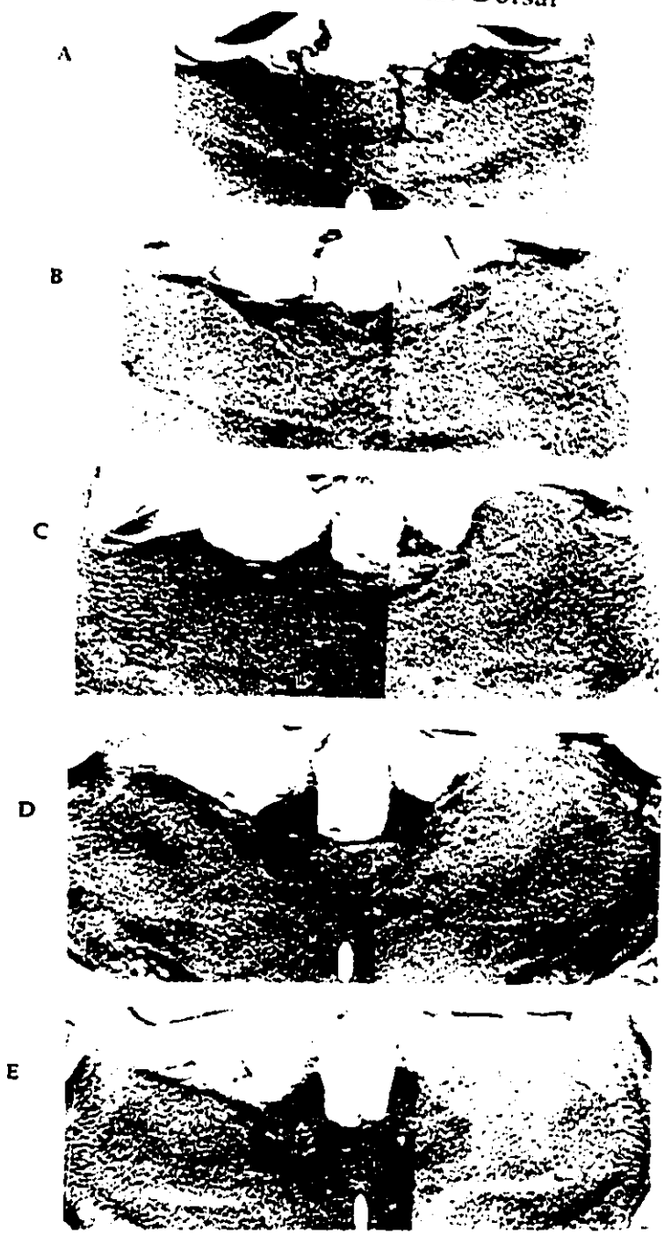
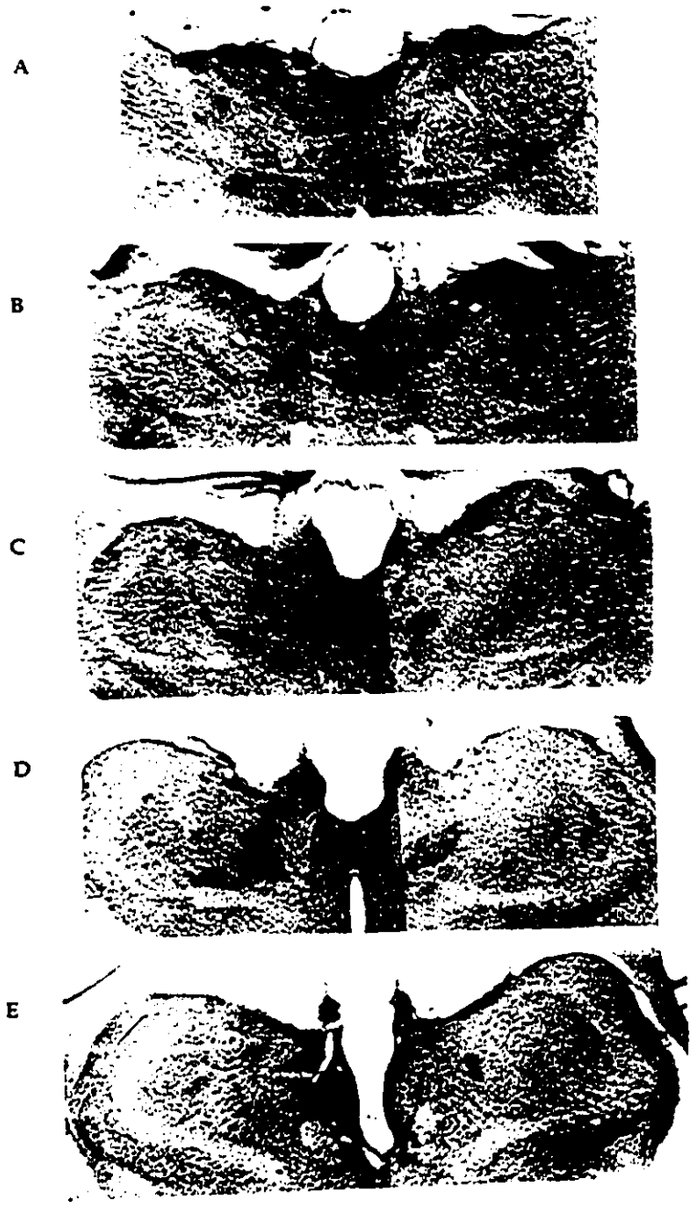


Figure 20. Coronal sections through the thalamus of a rat that received a quinolinic acid lesion of the MD. Shading on the overlay shows where damaged tissued is. The MD is clearly damaged (see sections B and C), as are a lot of other thalamic nuclei (see sections A through E). The black dots located medially in sections A through C and more laterally in sections D and E are calcium deposits. Nearly all of the neuronal areas surrounding the calcium deposits consist of dead neurons.

Quinolinic Medial Dorsal



inadvertent damage that was mild in two rats and moderate to severe in the others included the ANT, the habenula, the lateral dorsal and lateral posterior nuclei, the ventral anterior lateral and ventrobasal nuclei, the stria medullaris, the paraventricular and paratenial nuclei, the centromedial, rhomboid, reuniens and submedial thalamic nucleus, the ventromedial nucleus, the paracentral nucleus and the claustrum.

Changing Platform Task

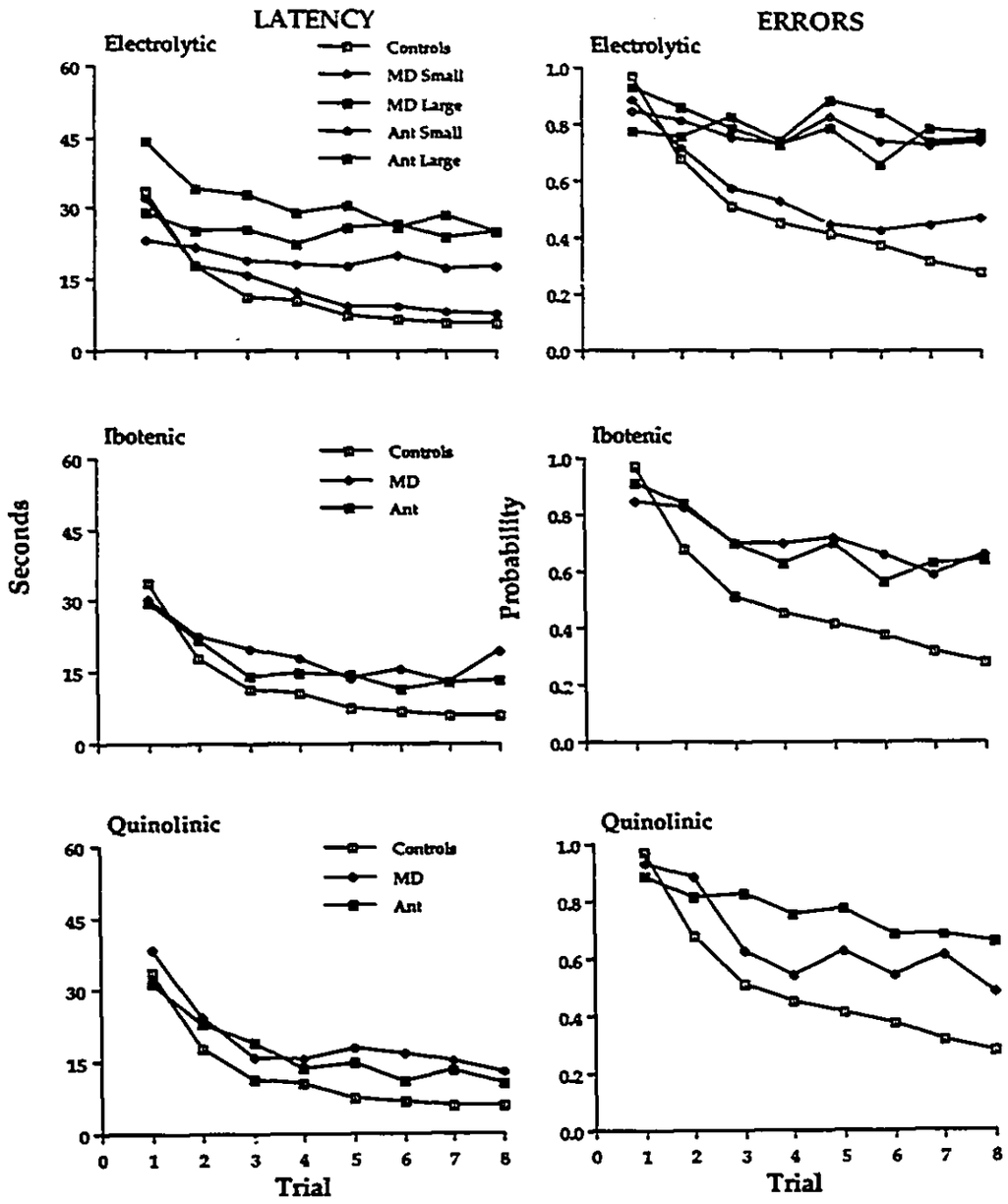
On the first trial, control rats took 33 sec to find the platform (Figure 21). They swam to the previous day's location frequently, thus making an error. They rapidly learned where the platform was, however, and found the platform quicker and more accurately on subsequent trials. The thalamic groups did not perform as well as the control group.

The electrolytic groups took longer to find the platform ($F(4,36) = 8.66$, $p<0.001$) and made more errors ($F(4,36) = 28.87$, $p<0.001$) than the control group (Figure 21, Top). Follow-up tests showed that all the electrolytic groups made more errors than the controls and that all but the small MD group took longer to find the platform than controls (Table A-1). All of the groups improved across trials, but some of the groups improved less than others (Group by Trial Latency: $F(28,252) = 5.77$, $p<0.001$; Group by Trial Errors: $F(28,252) = 5.239$, $p<0.001$).

The ibotenic groups took longer to find the platform ($F(2,25) = 4.98$, $p=0.015$) and made more errors ($F(2,25) = 18.07$, $p<0.001$) than the control group (Figure 21, Middle). Follow-up tests showed that this was true for both the MD and the ANT groups (Table A-2). All the groups improved across trials, but the control group improved more than the thalamic groups (Group by Trial Latency: $F(7,175) = 62.42$, $p<0.001$; Group by Trial Errors: $F(7,175) = 26.24$, $p<0.001$).

The quinolinic groups took longer to find the platform ($F(2,24) = 9.19$, $p=0.001$) and

Figure 21. Latencies (Left) and errors (Right), averaged across the 10 days of testing for each of the 8 trials rats received in the changing platform water maze task. Top. *Electrolytic thalamic rats versus controls.* Note that latencies and errors of the rats with small MD lesions (MD Small) are not much different from the controls. The rats with large MD lesions (MD Large), small ANT lesions (Ant Small) and large ANT lesions (Ant Large) all have higher latencies and make more errors than the controls. Middle. *Ibotenic acid thalamic rats versus controls.* The rats that received ibotenic acid MD lesions (MD) and the rats that received ibotenic acid ANT lesions (Ant) had higher latencies and made more errors than the controls. Bottom. *Quinolinic acid thalamic rats versus controls.* The rats that received quinolinic acid MD lesions (MD) were impaired relative to the controls, and so were the rats that received quinolinic acid ANT lesions (Ant).


LATENCY
ERRORS
Electrolytic
Controls
MD Small
MD Large
Ant Small
Ant Large
Ibotenic
Controls
MD
Ant
Quinolinic
Controls
MD
Ant
Seconds
Probability
Trial
Trial

made more errors ($F(2,24) = 28.25$, $p<0.001$) than the control group (Figure 21, Bottom). Follow-up tests showed that this was true for both the MD and the ANT groups (Table A-3). All the groups improved across trials, but the control group improved more than the thalamic groups (Group by Trial Latency, $F(14,168) = 2.12$, $p=0.013$; Group by Trial Errors: $F(14,168) = 3.66$, $p<0.001$).

Same Platform Task

Control rats quickly learned to swim to the platform whereas the thalamic groups were impaired.

The electrolytic groups took longer to find the platform ($F(4,36) = 3.6$, $p=0.014$) and made more errors ($F(4,36) = 15.48$, $p<0.001$) than the control group (Figure 22, Top). Follow-up tests showed that all but the small MD group differed from the control group (Table A-3). All of the groups improved across trials, but some of the groups improved more than others (Group by Trial Latency, $F(36,324) = 1.48$, $p=0.043$; Group by Trial Errors: $F(36,324) = 0.66$, $p=0.937$).

The ibotenic groups took longer to find the platform ($F(2,25) = 6.66$, $p=0.005$) and made more errors ($F(2,25) = 15.68$, $p<0.001$) than the control group (Figure 22, Middle). Follow-up tests showed that this was true for both the MD and ANT groups (Table A-3). Group by trial effects were not significant.

The quinolinic groups took longer to find the platform ($F(2,24) = 14.49$, $p<0.001$) and made more errors ($F(2,24) = 16.20$, $p<0.001$) than the control group (Figure 22, Bottom). Follow-up tests showed that this was true for both the MD and ANT groups (Table A-3). Group by trial effects were not significant.

Activity Task

During baseline testing, the rats were not very active (Figures 23, 24 and 25, Top).

Figure 22. Latencies (Left) and errors (Right), averaged across the four trials comprising each of the ten trial blocks rats received in the same place water maze task. Top. *Electrolytic thalamic rats versus controls.* Note that latencies and errors of the rats with small MD lesions (MD Small) differ only slightly from the controls. The rats with large MD lesions (MD Large), small ANT lesions (Ant Small) and large ANT lesions (Ant Large) all have higher latencies and make more errors than controls. Middle. *Ibotenic acid thalamic rats versus controls.* The rats that received ibotenic acid MD lesions (MD) had slightly higher latencies than the controls and made quite a few more errors than the controls. The rats that received ibotenic acid ANT lesions (Ant) had slightly higher latencies than the controls and made quite a few more errors than the controls also. Bottom. *Quinolinic acid thalamic rats versus controls.* Both the MD and the ANT groups had higher latencies and made more errors than the controls.

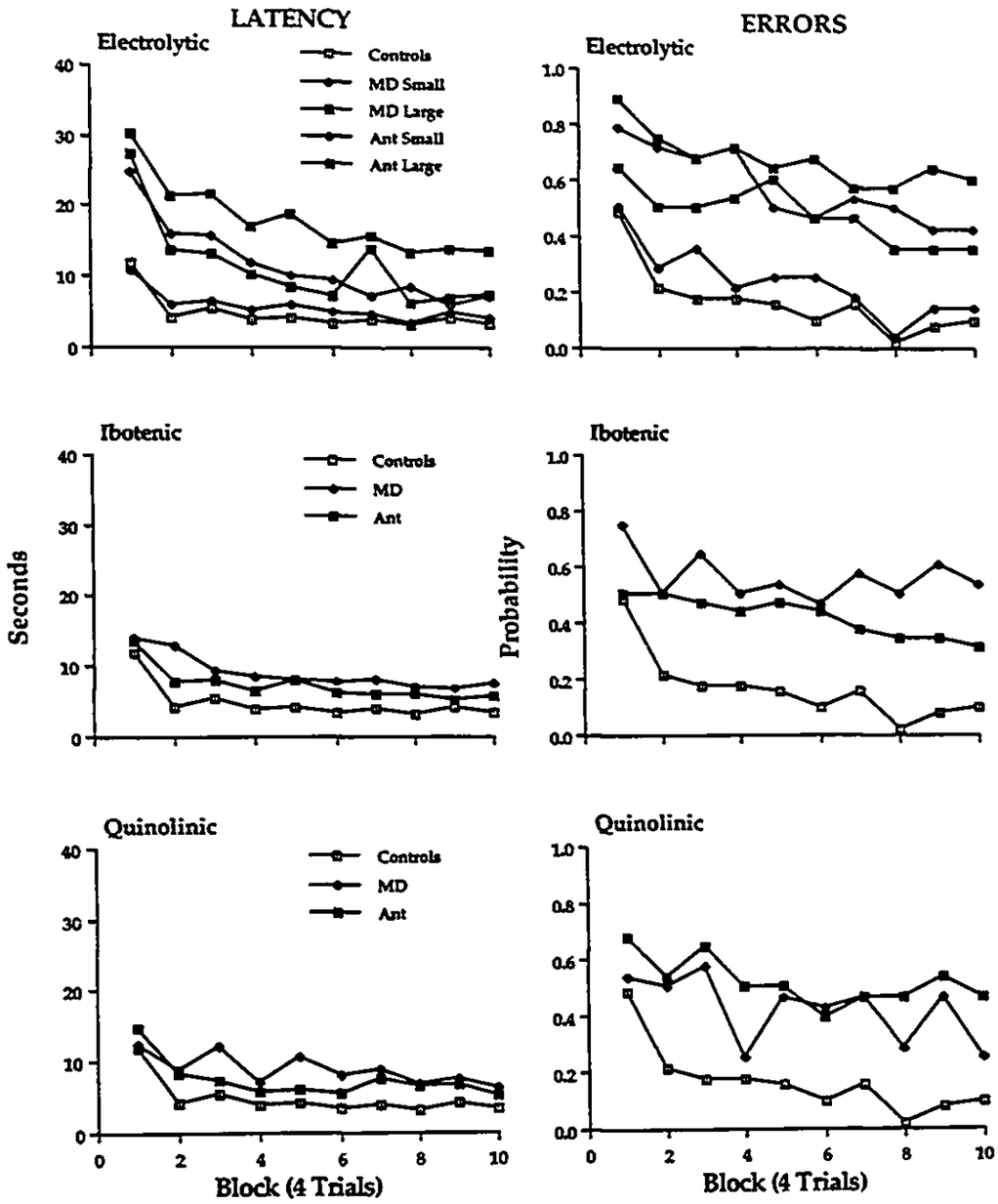

LATENCY
ERRORS
Electrolytic
Controls
MD Small
MD Large
Ant Small
Ant Large
Ibotenic
Controls
MD
Ant
Quinolinic
Controls
MD
Ant
Seconds
Probability
Block (4 Trials)
Block (4 Trials)

Figure 23. Crosses in the activity cages averaged across rats for each of the twelve ten minute long time bins before drug administration (top), after administration of 1.25 mg/kg d-amphetamine (middle) or after administration of 2.5 mg/kg d-amphetamine (bottom). Rats had either no thalamic lesions (controls) or had small electrolytic lesions of the MD (MD Small), large electrolytic lesions of the MD (MD Large), small electrolytic lesions of the ANT (Ant Small) or large electrolytic lesions of the ANT (Ant Large). Before drug administration, differences between groups were small. Amphetamine-induced locomotion of the thalamic rats was greater than that of the controls and was related both to dose and to lesion size.

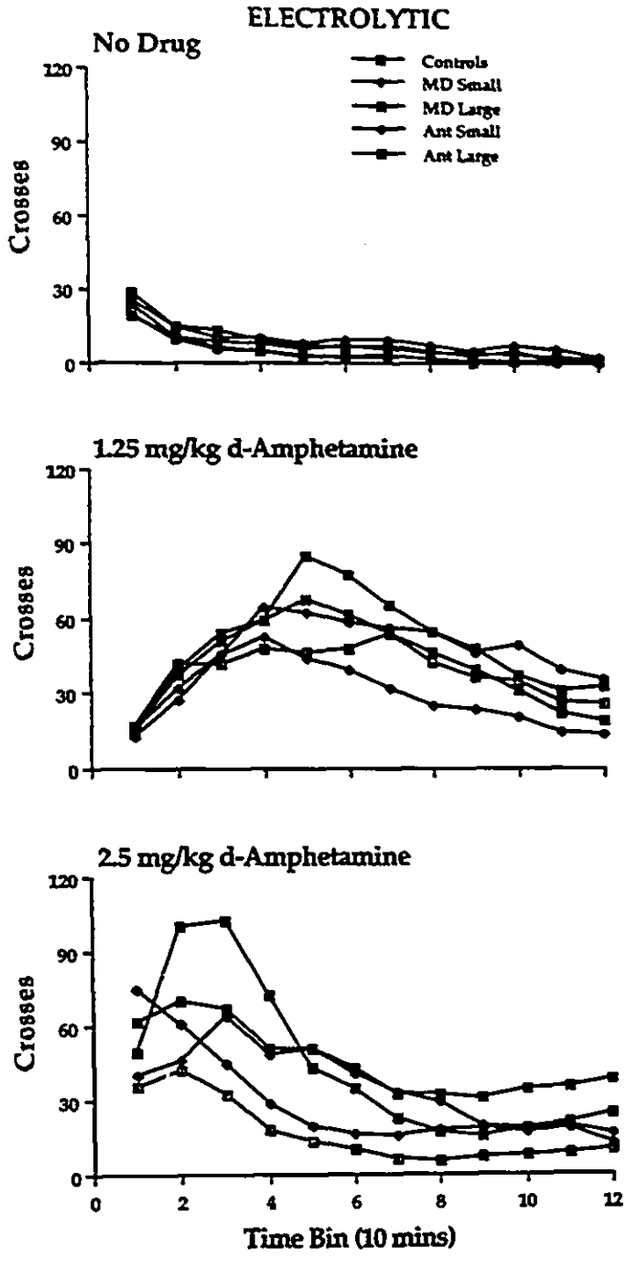

ELECTROLYTIC
No Drug
Controls
MD Small
MD Large
Ant Small
Ant Large
Crosses
120
90
60
30
0
1.25 mg/kg d-Amphetamine
Crosses
120
90
60
30
0
2.5 mg/kg d-Amphetamine
Crosses
120
90
60
30
0
0
2
4
6
8
10
12
Time Bin (10 mins)

Figure 24. Crosses made in the activity cages averaged across rats for each of the twelve ten minute long time bins before drug administration (top), after administration of 1.25 mg/kg d-amphetamine (middle) or after administration of 2.5 mg/kg d-amphetamine (bottom). Rats had either no thalamic lesions (controls) or had ibotenic acid lesions of the MD (MD) or ANT (Ant).

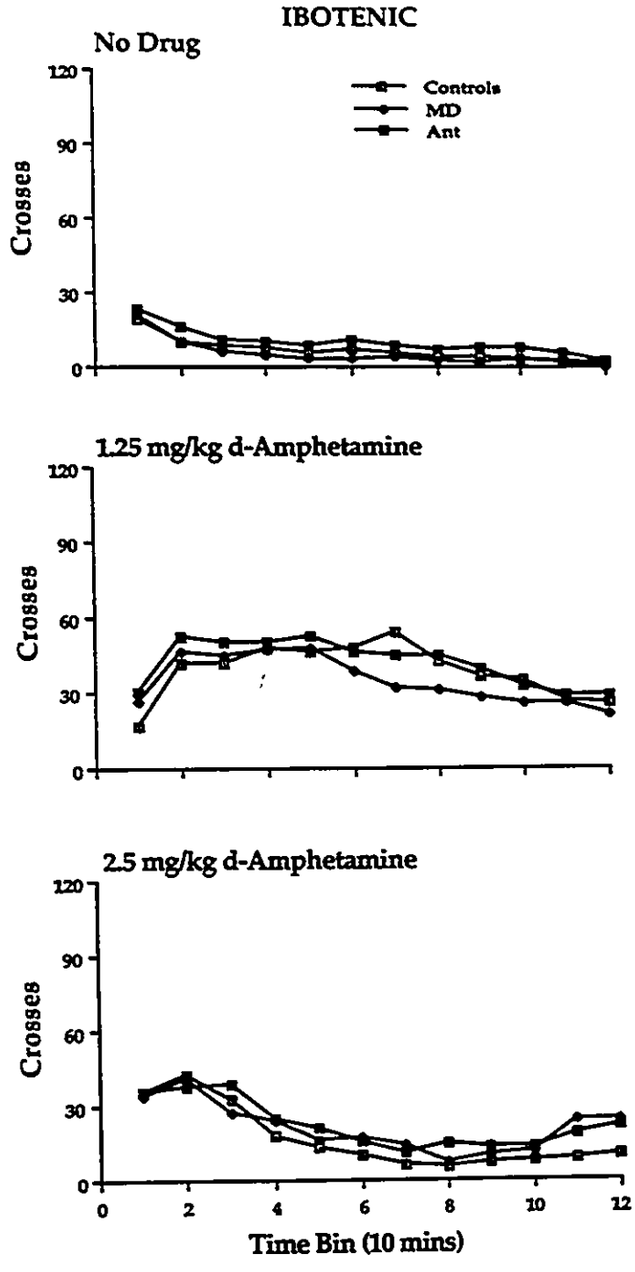
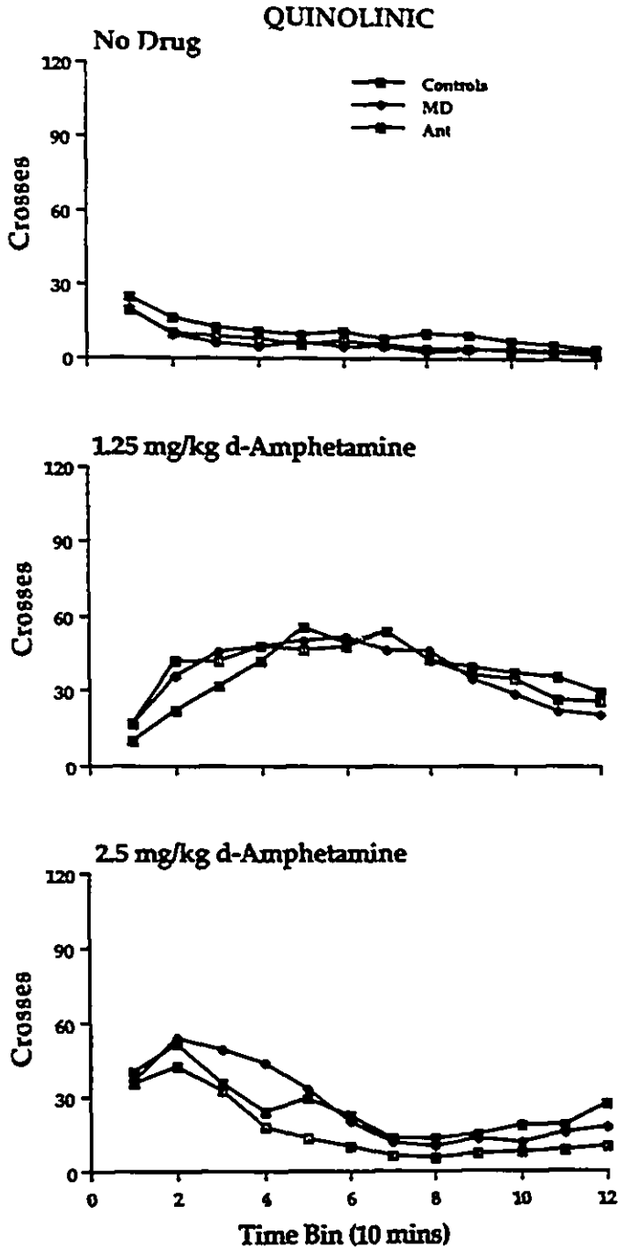

IBOTENIC
No Drug
Controls
MD
Ant
Crosses
120
90
60
30
0
1.25 mg/kg d-Amphetamine
Crosses
120
90
60
30
0
2.5 mg/kg d-Amphetamine
Crosses
120
90
60
30
0
0
2
4
6
8
10
12
Time Bin (10 mins)

Figure 25. Crosses made in the activity cages averaged across rats for each of the twelve ten minute long time bins before drug administration (top), after administration of 1.25 mg/kg d-amphetamine (middle) or after administration of 2.5 mg/kg d-amphetamine (bottom). Rats had either no thalamic lesions (controls) or had quinolinic acid lesions of the MD (MD) or ANT (Ant).


QUINOLINIC
No Drug
Controls
MD
Ant
Crosses
120
90
60
30
0
1.25 mg/kg d-Amphetamine
Crosses
120
90
60
30
0
2.5 mg/kg d-Amphetamine
Crosses
120
90
60
30
0
0
2
4
6
8
10
12
Time Bin (10 mins)

There were significant differences between the groups ($F(8,61) = 3.38$, $p=0.003$), however (Table A-5). Follow-up tests showed that the small electrolytic MD and the ibotenic MD groups were significantly less active and the quinolinic ANT group was significantly more active than the controls (Table A-4). They also showed that the electrolytic and ibotenic MD groups were less active than the electrolytic and ibotenic ANT groups (Table A-6), and that differences between the thalamic groups and the controls were confined to particular time bins (Table A-6).

After administration of amphetamine, all the groups showed significant increases in activity ($F(2,122) = 109.85$, $p<0.001$). After administration of 1.25 mg/kg d-amphetamine (Figures 23, 24 and 25, Middle), between group differences were not significant ($F(8,61) = 0.74$, $p=0.6540$), but after administration of 2.5 mg/kg d-amphetamine (Figures 23, 24 and 25, Bottom), they were ($F(8,61) = 3.7$, $p=0.001$). Follow-up tests indicated that only the electrolytic groups were significantly more active than the control group (see Tables A-4 to A-7).

Relation Between Lesions and Performance

Due to between rat variation in performance, the following analyses were done to see if lesion size and location were related to performance: (i) The area of the thalamus at three coronal planes was calculated using an image analyzing system ("The Microcomputer Imaging Device"). The planes were located 1.4 mm, 2.3 mm and 3.8 mm posterior to bregma, respectively (Paxinos and Watson, 1985). Correlations between the area measurements and behavior of the rats were then calculated. (ii) Amount of damage to various thalamic nuclei was rated on the following scale: 0 = completely gone, 0.5 = very severe, 1 = severe, 1.5 = moderate, 2 = mild, 2.5 = very mild, and 3 = not damaged. The rated nuclei included: the anterior dorsal, anterior ventral and anterior

medial thalamic nuclei, the habenula, the lateral dorsal and lateral posterior thalamic nuclei, the medial dorsal thalamic nucleus, the ventral anterior lateral thalamic nucleus, the ventrobasal thalamic nuclei (i.e., the ventral posterior medial nucleus, the ventral posterior lateral nucleus and the posterior thalamic complex), the stria medullaris, the paraventricular and paratenial thalamic nuclei, the centromedial, rhomboid and reuniens thalamic nuclei, the submedial thalamic nucleus, the paracentral thalamic nucleus and the claustrum. Correlations between the damage ratings and behavior of the rats were then calculated.

Some rats in this study had small amounts of damage to extrathalamic structures such as the anterior hippocampus and the fimbria/fornix. This damage was not included when examining relations between lesions and performance because only the electrolytic groups had more than just very mild extrathalamic damage. Additionally, damage to structures such as the hippocampus and fimbria/fornix must be extensive to impair behavior of animals (Sutherland and Rudy, 1989; Eichenbaum, Otto and Cohen, 1992).

Correlations Between Thalamic Area and Behavior

Water Maze Tasks. Data from the changing platform task and from the same platform task were averaged across both days and trials so that each rat had one number representing latency and one number representing errors for each task. Correlations between these numbers and the thalamic area measurements were then calculated. Several significant correlation coefficients were obtained, and most were negative, implying that larger thalamic lesions produced greater impairments on both the changing and same platform water maze tasks (see Tables A-8 and A-9).

Activity Task. Total crosses made by the rats during baseline and amphetamine tests were calculated. Correlations between these and area of the thalamus at the three

different planes revealed no significant effects (see Table A-10).

Correlations Between Nuclei Ratings and Behavior

The amount of damage to several thalamic nuclei significantly correlated with performance of the rats on the water maze tasks (Tables A-11 to A-14), implying that damage to certain structures was more closely related to behavioral impairments than damage to others. Very few of the correlations between thalamic nuclei ratings and amphetamine-induced activity of the rats were significant, and, of those that were, some were positive and some were negative (Tables A-15 and A-16). Thus, amphetamine-induced activity did not correlate with lesion size in any meaningful way.

Figures 26 and 27 summarize the main relationships found when comparing thalamic nuclei ratings to spatial learning. For the ANT groups, damage to the ANT and to thalamic nuclei in close proximity to the ANT (Figure 26), was closely correlated with impairments. For the MD groups, damage to the MD and to nuclei in close proximity to it, as well as to some nuclei located quite far ventral and lateral to it (Figure 27), was most closely related to behavioral impaiments.

Discussion

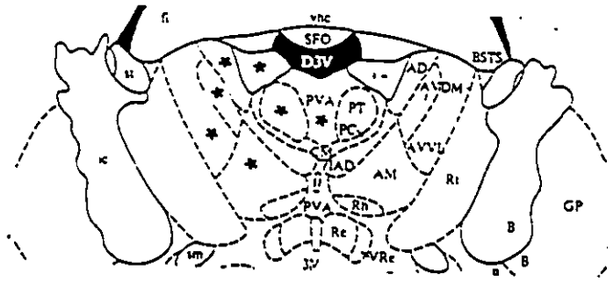
The main findings in this experiment are that rats with thalamic lesions were impaired on the spatial tasks and more extensive damage gave greater impairments. For the ANT rats, damage to the ANT correlated with spatial task performance, as did damage to adjacent thalamic nuclei. Similarly, for the MD rats, damage to the MD correlated with water maze performance, as did inadvertent damage to several adjacent nuclei as well as to some more distal nuclei. The MD groups were spontaneously less active and the

Figure 26. Reproductions of coronal sections through the thalamus of a rat. The sections are located 1.4, 1.8, 2.3 and 2.8 mm posterior to bregma (see Paxinos and Watson, 1985). Stars are placed on the nuclei whose damage ratings correlated significantly with behavior of the rats who received lesions of the ANT. These nuclei included: the paraventricular nucleus, the paratenial nucleus, the stria medullaris, the anterior dorsal thalamic nucleus, the dorsal medial part of the anterior ventral thalamic nucleus, the ventrolateral part of the anterior ventral thalamic nucleus and the anterior medial thalamic nucleus. In general, the more damage rats had to these nuclei, which are all located close to the ANT, the more impaired the ANT rats were on the behavioral tasks in this study.

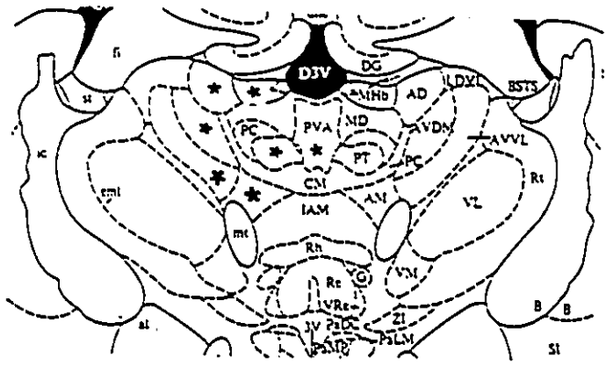
(Abbreviations used in this figure (from Paxinos and Watson, 1985): 3V=3rd ventricle, AD=anterodorsal thalamic nucleus, al=ansa lenticularis, AM=anteromedial thalamic nucleus, Ang=angular thalamic nucleus, AVDM=anteroventral thalamic nucleus, dorsomedial part, AVVL=anteroventral thalamic nucleus, ventrolateral part, B=nucleus basalis of Meynert, BSTS=bed nucleus stria terminalus, supracapsular, CA3=field CA3 of Ammon's horn, CL=claustrum, CM=centromedial thalamic nucleus, D3V=dorsal third ventricle, DG = dentate gyrus, DHC=nucleus dorsal hippocampal commissure, eml=external medullary lamina, EP=entopeduncular nucleus, fi=fimbria hippocampus, G=gelatinosus thalamic nucleus, GP=globus pallidus, IAD=interanterodorsal thalamic nucleus, IAM=interanteromedial thalamic nucleus, ic=internal capsule, IMD=intermediodorsal thalamic nucleus, iml=internal medullary lamina, LDDM=laterodorsal thalamic nucleus, dorsomedial part, LDVL=laterodorsal thalamic nucleus, ventrolateral part, LHb=lateral habenular nucleus, LV=lateral ventricle, MD=mediodorsal thalamic nucleus, MDC=mediodorsal thalamic nucleus, central, MDL=mediodorsal thalamic nucleus, lateral, MDM=mediodorsal thalamic nucleus, medial, MHb=medial habenular nucleus, mt=mammillothalamic tract, PaDC=paraventricular hypothalmic nucleus, dorsormedial cap, PaLM=paraventricular hypothalamic nucleus, lat magnocell, PaMP=paraventricular hypothalamic nucleus, med parvocell, PC=paracentral thalamic nucleus, Po=posterior thalamic nuclear group, PoDG=polymorph layer dentate gyrus, PT=paratenial thalamic nucleus, PV=paraventricular thalamic nucleus, PVA=paraventricular thalamic nucleus, anterior part, Re=reuniens thalamic nucleus, Rh=rhomboid thalamic nucleus, Rt=reticular thalamic nucleus, scp=superior cerebellar peduncle, SFO=subfornical organ, SI=substantia innominata, sm=stria medullaris thalamus, st=stria terminalis, vhc=ventral hippocampal commissure, VL=ventrolateral thalamic nucleus, VM=ventromedial thalamic nucleus, VPL=ventral posterolateral thalamic nucleus, VPM=ventral posteromedial thalamic nucleus, VRe=ventral reuniens nucleus, ZI=zona incerta).

Anterior

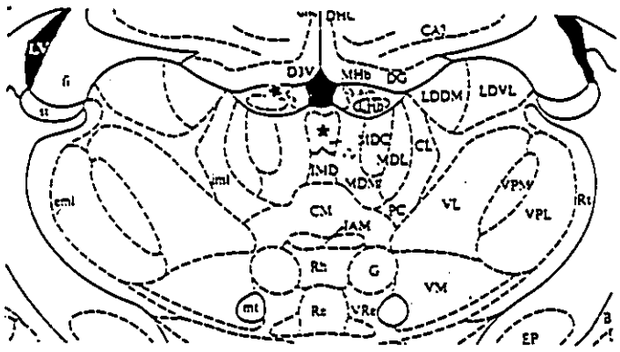
-1.4 mm



-1.8 mm



-2.3 mm



-2.8 mm

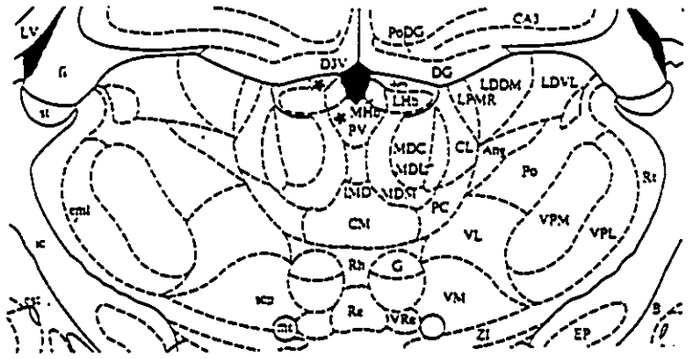
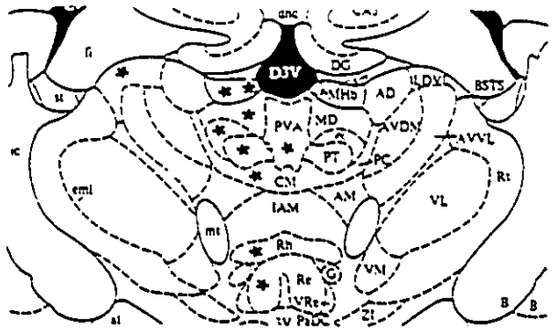


Figure 27. Reproductions of coronal sections through the thalamus of a rat. The sections are located 1.8, 2.3, 2.8 and 3.8 mm posterior to bregma (see Paxinos and Watson, 1985). Stars are placed on the nuclei whose damage ratings correlated significantly with behavior of the rats who received lesions of the MD. Among these were: the paraventricular nucleus, the paratenial nucleus, the paracentral thalamic nucleus, the claustrum, the stria medullaris, the medial habenula, the lateral habenula, the centromedial thalamic nucleus, the MD, the lateral dorsal thalamic nucleus, the rhomboid thalamic nucleus and the reuniens thalamic nucleus. The more damage the MD rats had to these nuclei, most of which are located close to the MD, the more impaired they were on the behavioral tasks in this study.

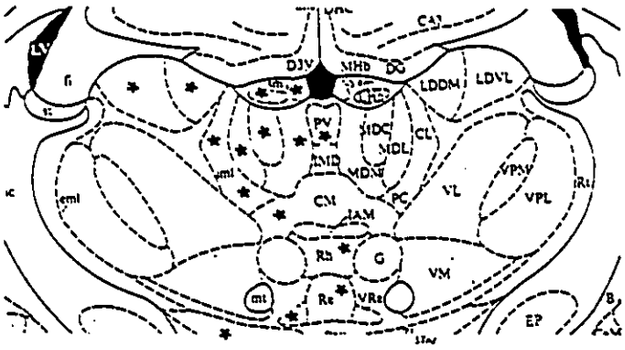
(Abbreviations used in this figure (from Paxinos and Watson, 1985): See Figure 26 for most. Also: DLG=dorsal lateral geniculate nucleus, fr=fasciculus retroflexus, Gu=gustatory thalamic nucleus, LHbL= lateral habenular nucleus, lateral part, LHbM=lateral habenular nucleus, medial part, LPLR=lateral posterior thalamic nucleus, laterorostral, LPMR=lateral posterior thalamic nucleus, mediorostral, ml=medial lemniscus, PF=parafascicular thalamic nucleus, PoMn=posteromedian thalamic nucleus, PVP=paraventricular thalamic nucleus, posterior part, STN=subthalamic nucleus, VLG=ventral lateral geniculate nucleus).

Medial Dorsal

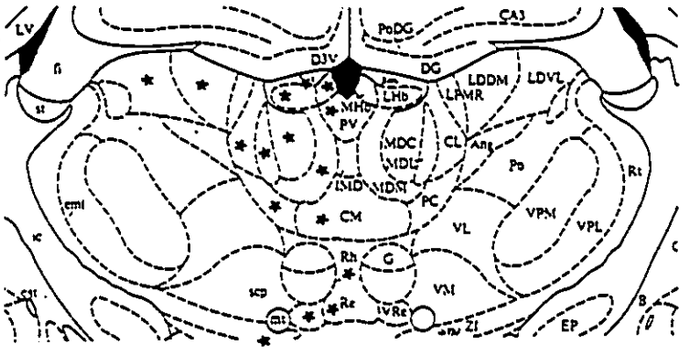
-1.8 mm



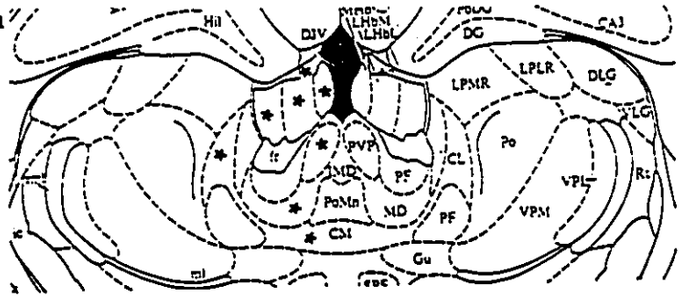
-2.3 mm



-2.8 mm



-3.8 mm



ANT groups were spontaneously more active than the controls, and after administration of amphetamine, the electrolytic groups locomoted more than the control group. Thalamic damage did not correlate significantly with spontaneous and amphetamine-induced activity.

There is controversy in literature over how MD damage affects behavior (see Table 2). The factor brought up most often by researchers when discussing variable behavior of rats with MD damage is lesion size and location. In no study on function of the MD have lesions been confined to the MD. Reccgnizing this, several researchers claim that larger lesions produce greater impairments (Slotnick and Kaneko, 1981; Hunt and Aggleton, 1991; Kessler and Markowitsch, 1981; Waring and Means, 1976; Kessler, Markowitsch and Otto, 1982). Other researchers claim that critical areas such as the ANT, the centromedial and parafascicular nuclei or the mammillary bodies need to be damaged to obtain impairments (Hunt and Aggleton, 1991; Delacour, 1971). The finding that impairments of rats in this study were related to lesion size suggests lesion size could explain some of the variability in literature. Additionally, the present findings of significant correlations between certain thalamic nuclei and behavior support claims that critical areas might need to be damaged to produce impairments.

One study (Kolb et al., 1982) reported that rats with small electrolytic lesions of the MD are not impaired on a water maze task. This result was confirmed. Rats with small electrolytic lesions of the MD in the present study were the only group not impaired on the spatial tasks. This result seems most consistent with the idea that large lesions, including more than any single structure, are required to obtain impairments.

On the surface, the finding that rats with thalamic damage were impaired on the spatial tasks seems to support claims about importance of thalamic nuclei in learning.

The changing platform task does not measure unitary function, however, and can be thought of as consisting of the following components (Figure 28). (1) *Retention component.* Since the platform is placed in a new location each day, the first trial given each day tests ability to remember the previous day's platform location and, thus, can be considered to be a measure of retention. Rats who remember the previous platform location swim to it before searching for the new location (Whishaw, 1987). Thus, rats with "good retention" should take longer to find the platform on the first trial than other rats. (2) *One-trial learning component.* A "good rat", after finding the platform in its new location on the first trial, will immediately return to it. Its time to find the platform on the second trial will be less than its time to find the platform on the first trial, the difference indicating how much it has learned. Thus, the second trial given each day can be considered the one-trial learning component. (3) *Performance component.* The third to eighth trials given each day can be considered to be a performance component of the changing platform task. "Good rats", after learning where the platform is located, swim to it correctly on subsequent trials. Thus, latencies and errors on trials three to eight are indices of how well rats can perform the response they acquired on the second trial.

Statistical analyses (see Table A-17) indicated that the thalamic rats were impaired on all three components of the changing platform task (see Figure 29). Lesion size does not correlate well with behavior on all three components, however (see Tables A-18, A-19 and Table 4). Correlations between thalamic area and behavior on the performance component are more abundant and stronger than correlations between thalamic area and behavior on the retention and one-trial learning components. Thus, the spatial task impairment exhibited by the thalamic rats seems to be more in performance than in retention or learning.

Figure 28. Figure depicting the three components of the changing platform water maze task. On trial one each day, a "good rat" will remember the previous day's platform location and will search there for it, so will have a high latency and a high probability of making an error. Thus, trial one is the retention component, reflecting memory for the location of the platform on the previous day. After finding the platform on the first trial, a "good rat" will rapidly learn where the platform is located, so its latency to find the platform on trial two will be much lower than its latency on trial one, as will its probability of making an error. Thus, the change from trial one to trial two, reflected in trial two latencies and errors, is the one-trial learning component of the changing platform task. Finally, the latencies and errors of the rats on trials three to eight each day reflect how well the rats know where the hidden platform is located. Thus, trials three to eight are the performance component of the changing platform task.

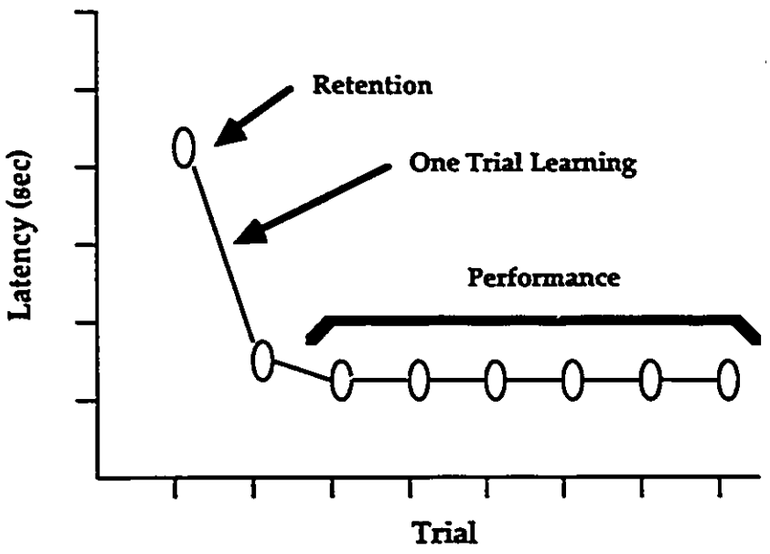

Retention
One Trial Learning
Performance
Latency (sec)
Trial

Figure 29. Summary of the main findings in the first experiment. Thalamic rats were impaired on the water maze tasks. They were more impaired on the performance component of the changing platform task than on the retention or one-trial learning components. Top. In the retention component of the changing platform task, the rats that received lesions of the ANT (Anterior) had lower latencies (vertical axis on graph) and made fewer errors (horizontal axis on graph) than the controls. The rats that received lesions of the MD had latencies not significantly different from controls, but made significantly fewer errors than controls. Thus, both the ANT and the MD rats had a retention deficit on the place alternation task, but the size of the deficit was small. Middle. On the one-trial learning component of the changing platform task, the controls had lower latencies and made fewer errors than did the MD and ANT rats. Clearly, the thalamic rats did not learn the new location of the platform as quickly as the controls. Bottom. On the performance component of the changing platform task, the controls had lower latencies and made fewer errors than both the MD and the ANT rats.

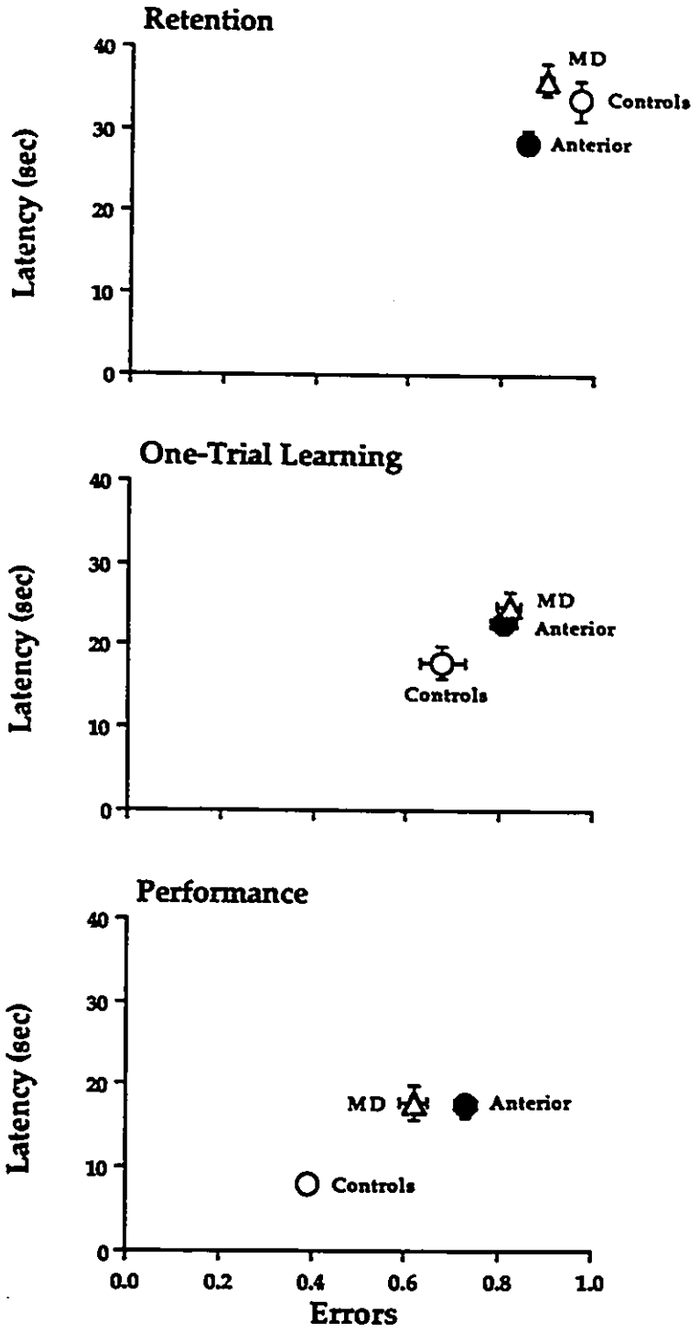

Retention
Latency (sec)
40
30
20
10
0
MD
Controls
Anterior
One-Trial Learning
Latency (sec)
40
30
20
10
0
MD
Anterior
Controls
Performance
Latency (sec)
40
30
20
10
0
MD
Anterior
Controls
0.0
0.2
0.4
0.6
0.8
1.0
Errors

Table 4. Summary of correlations between thalamic area and latency and errors of the ANT and MD rats on the retention, one-trial learning and performance components of the changing place water maze task.

	Retention		One-Trial		Performance		Overall	
	Latency	Errors	Latency	Errors	Latency	Errors	Latency	Errors
Anterior								
Electrolytic	-	-	-	-	-	-	-	-
Ibotenic	-	*	-	-	-	-	-	-
Quinolinic	-	-	-	-	-	-	-	-
All	-	-	-	-	-	*	-	*
Medial Dorsal								
Electrolytic	-	-	-	-	-	*	-	*
Ibotenic	-	*	-	-	-	-	-	-
Quinolinic	-	-	-	-	-	*	-	*
All	-	-	-	-	*	**	-	*

* = different from controls, $p<0.05$
** = different from controls, $p<0.01$

This finding is interesting. The belief that the MD is important for learning and memory is widely held (Mishkin and Appenzeller, 1987, Zola-Morgan and Squire, 1993; Victor et al., 1971). In literature on function of the MD in the rat, however, researchers rarely claim that MD damage impairs memory without acknowledging the fact that their data could be interpreted in terms of some "nonspecific, non-memory dysfunction". The majority of researchers claim that deficits of rats with MD lesions are probably not with memory, in fact, and claim that damage to the MD results in attentional deficits, emotional deficits, motor deficits, or reduced ability to initiate proper and inhibit improper motor acts (Stokes and Best, 1990; Kolb, 1977; Kolb et al., 1982; Beracochea et al., 1989; Vanderwolf, 1962; Vanderwolf, 1969; Means et al., 1974; Kessler and Markowitsch, 1981; Gross, Chorover and Cohen, 1965; Waring and Means, 1976). The findings in this study support such claims and suggest that the thalamus is less involved with primary components of learning and is more involved with how learned information is used.

EXPERIMENT II

Introduction

In Experiment I it was found that rats with thalamic damage were impaired on spatial tasks, but their impairment was mainly on performance features of the tasks. This result differs from findings that have been reported following frontal cortex (Kolb et al., 1982) and hippocampal lesions (Whishaw, 1987), where deficits are found on acquisition and retention. It was also found that amphetamine-induced locomotion of the quinolinic and ibotenic groups was not significantly different from that of controls. After amphetamine, rats with frontal cortex lesions (Lynch, Ballantine and Campbell, 1971) or hippocampal lesions (Whishaw and Mittleman, 1991) do show increased activity relative to control rats. Thus, on two important features of behavior, learning and activity, rats with thalamic lesions are not like rats with frontal cortex or hippocampal lesions. Finally, in Experiment I it was found that the effects of ANT lesions did not differ greatly from those of MD lesions. Together, these results suggest that although impairments do follow thalamic lesions, the tests used in Experiment I were not specifically sensitive to thalamic functions or to the different functions of these nuclei.

The purpose of Experiment II was to see whether a different kind of test might be more sensitive to thalamic damage. To this end, rats were tested on a configural string pulling task (Tomie and Whishaw, 1990). As described previously, this task has three features. It tests animals' ability to form a simple association, a reversal, and a configural association. Ability to perform the first two features is not affected by frontal cortex or

hippocampal lesions. Hippocampal lesions mildly affect acquisition and do not affect retention of the configural feature of the task (Whishaw and Tomie, 1991), whereas prefrontal lesions restricted to the orbital frontal cortex can block both acquisition and retention (Whishaw et al., 1992). Thus, it seemed reasonable to ask whether this task might be sensitive to thalamic damage.

Since in Experiment I, the behavior of the rats with ANT and MD lesions was similar, and since the MD is preferentially connected to the frontal cortex, only rats with MD lesions were used in the second experiment. In addition, since the electrolytic lesions and the neurotoxic lesions produced similar deficits, and since neurotoxins are selective for cell bodies and spare fibers of passage, only neurotoxic lesions were used. Finally, in order to replicate some of the results of the first experiment, the rats received testing on the changing platform water maze task and then were tested in the amphetamine-induced activity task.

Methods and Procedure

Animals

Adult female Long-Evans hooded rats, from the University of Lethbridge (Lethbridge, Alberta, Canada) vivarium and weighing 200-250 g when the study began, were used. They were housed in an animal colony maintained on a 12:12 hr light-dark cycle. Testing was done during the light portion of the cycle. Before testing began feeding was restricted so that the rats were gradually reduced to and maintained at 80-90% of expected body weight. Wayne Rodent pellets were used for supplemental feeding to maintain body weight throughout the test period.

Surgery

The rats received ibotenic or quinolinic acid lesions of the MD via techniques similar to those described in Experiment I. The only change in technique was that 0.3 µl of ibotenic acid was infused. Behavioral testing began a few days after surgery.

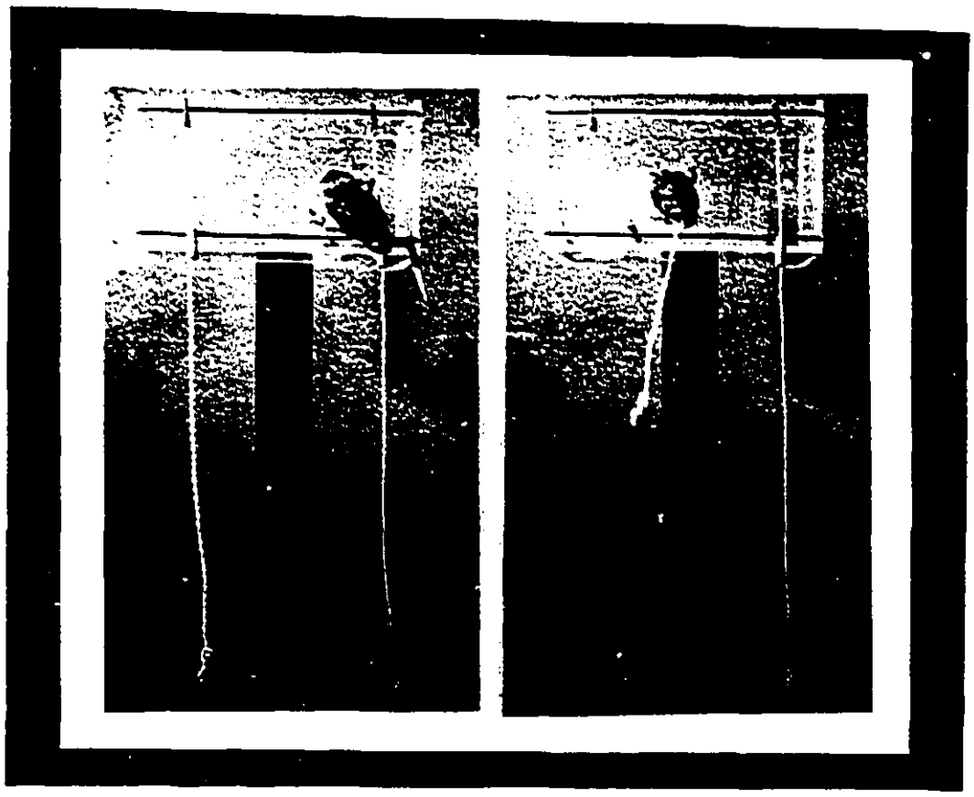
Configural Task

Apparatus. The rats were tested on a stand (Tomie & Whishaw, 1990), which was a 24 x 15.5 cm Plexiglas platform with walls, 13 cm high, lining its sides and back. The platform was mounted on a 41 cm high pedestal. A 3 mm diameter metal bar was attached to the front of the platform, 12 cm above its floor. Strings with food pellets tied onto their distal end could be attached with alligator clips to the metal bar (see Figure 30).

Tactile Stimuli. Small and large diameter strings, 50 cm long, were the tactile stimuli. The strings were made using a simple fringe method (Harvey, 1967) of twisting strands of fine cotton household twine together in one direction, folding the twisted strands in half, and then twisting the folded strands together in the opposite direction. One end was knotted with an overhand knot and an alligator clip was attached to the other end. The number of strands of twine twisted together determined string size with small strings (T1) consisting of 2 strands and large strings (T2) consisting of 10 strands. Uniform string sizes were obtained by using premeasured lengths of strings and equivalent numbers of wraps. This method produced strings with an average width of 1 mm for small strings and 5 mm for large strings.

When a rat pulled up a string it received a food pellet that was inserted into a loosely tied overhand knot at the end of the string. Food pellets were 190 mg dustless precision rodent pellets (Bio-Serv, Incorporated, Frenchtown, NJ). This size of pellet was used because it kept the rats occupied while the strings were being changed for the next trial.

Figure 30. Configural string pulling test apparatus. Strings were hung by clips, odor was painted onto the tape pads on the strings, and food was attached to the end of one string. The rat is to pull up the string containing food. It chooses the correct string by attending to how thick the string is and to odor painted on the tape attached to the string. (Left) A rat sniffs the tape and inspects the incorrect string. (Right) The rat pulls up the correct string.



A large number of strings were used throughout pretraining and testing so that the strings could be changed every few days. This procedure was used to ensure that the rats were not using some nonrelevant feature of an individual string as a cue to direct their choices.

Olfactory Stimuli. Almond extract was used as an odor cue, and the odor was either present (O1) or absent (O2). A piece of Elastoplast fabric adhesive tape, 2.5 cm wide and 5 cm long (Smith and Nephew, Inc., Lachine, Quebec, Canada, Ref. 1001), was wrapped around the strings. The length of the tape was varied slightly so that the exposed surface of the tape was the same for each string size. The tape was either painted lightly with almond extract or was left unpainted. The extract evaporates overnight so the same string could be either an odor-positive or odor-negative cue, depending on whether the odor was freshly painted onto the tape.

Pretraining. The rats were pretrained by being placed individually on the test stand for 10 to 15 min each day. Using a successive approximation operant conditioning procedure the rats were trained to pull up a medium size (2.5 mm wide) string to obtain food. After each correct response, the string was removed, another food pellet was placed on its end, and the string was replaced. Within 7 days rats were adept at string pulling. During the next week the rats were required to pull up a variety of different size strings, presented in random order. This procedure was used because rats pretrained with only one size of string subsequently reject novel sizes when a discrimination problem is first presented.

Response Criteria and Analysis. A trial consisted of simultaneous presentation of two strings, which were separated by 15 cm. Only one string had food tied to it. When a rat pulled up the string with food, its response was scored as correct. When a rat pulled up the string without food, its response was scored as incorrect. A response was also scored

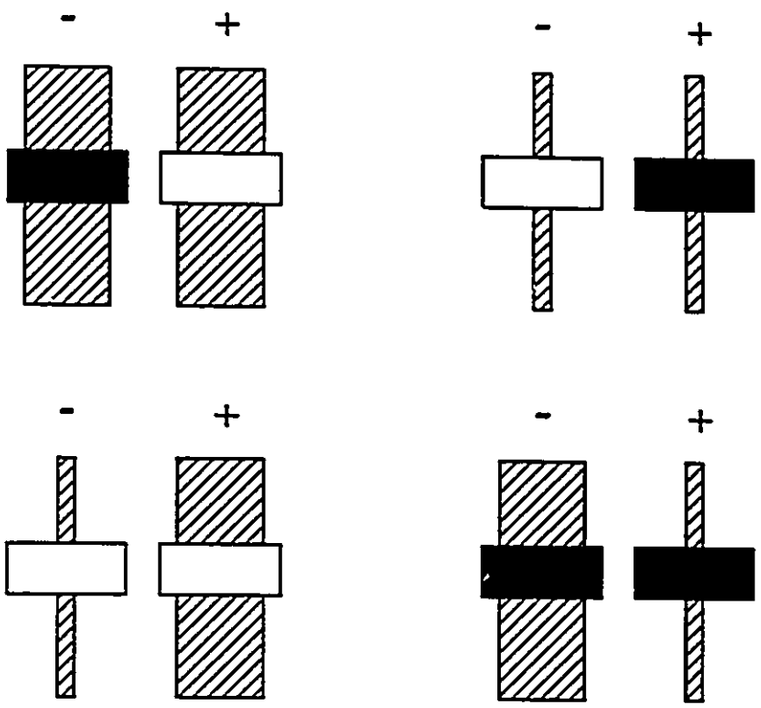
as incorrect if a rat pulled up the incorrect string at least half way. Both strings were removed at the end of each trial. Rats received 20 trials per day, and testing was stopped when rats achieved a performance score of at least 90% (18 out of 20 trials) on two consecutive days.

Acquisition. Fourteen control, seven ibotenic acid thalamic rats and seven quinolinic acid thalamic rats were used. The rats were presented with two strings simultaneously on each trial, one of which contained food. Rats were to identify the string containing food using a compound of two separate cues; string size and string odor (Figure 31). String sizes were T1 and T2, and odors were almond extract present (O1) and almond extract absent (O2). Four stimulus compounds were thus possible (<T1-O1>, <T1-O2>, <T2-O1> and <T2-O2>) and four pairings of these stimulus compounds were possible (<T1-01><T1-O2>, <T1-O1><T2-O1>, <T2-O2><T2-O1> and <T2-O2><T1-O2>). For half the rats in each group the positive compounds were <T1-O1> and <T2-O2> and the negative compounds were <T1-O2> and <T2-O1>. For the remaining rats the positive compounds were <T1-O2> and <T2-O1> and the negative compounds were <T1-O1> and <T2-O2>. The rats received 20 trials per day, five of each of the four compound pairings.

Training took place in three stages. In Stage 1, two strings of the same size were used. The tape on one of the two strings was freshly coated with almond extract and this cue indicated that the string was reinforced. The position of the reinforced string was varied from left to right via a pseudorandom, balanced sequence. In Stage 2, two strings of the other size were used; the negative string contained odor and the positive string contained no odor. The full complement of string pairings were given in Stage 3.

Retention after a Break. After acquisition of the task, the 14 control rats received a seven day no-training break. They were then retrained on Stage 3.

Figure 31. Schematic illustration of the configural task used in the present study. The hatched rectangles indicate the two diameters of string. The shaded boxes indicate the almond-scented tape [black] or plain tape [white]. In a simple association and its reversal, the animal learns that scented is either correct or incorrect [e.g., learn top left then top right or the reverse sequence]. In the configural task, an animal must perform all of the discriminations concurrently [e.g., the nonscented thick string is correct [+], as is the scented thin string]. By definition, the elements of odor and string size must be positively and negatively reinforced equally.



Post-Surgical Retention. The control rats tested for acquisition received thalamic lesions. Seven received lesions with quinolinic acid and seven received lesions with ibotenic acid. Beginnning a few days after surgery, the rats were retrained on Stage 3.

Changing Platform Task

The apparatus and procedure were the same as those used in Experiment I (see Figure 10). Twenty-eight thalamic rats and 24 control rats were used. The thalamic rats were the string pullers described above. They were tested in the water maze after they completed the string pulling task. The controls were rats used in pilot string pulling tasks or naive rats that weighed the same and were the same age as the string pullers.

Activity Task

The apparatus and procedure were the same as that used in Experiment I (see Figure 12). Twenty-eight thalamic rats and 21 controls were used. The thalamic rats were the rats used in the string pulling and water maze components of this study. The controls were a subset of the control rats used in the water maze task. Data were collected from rats in the activity cages after termination of water maze testing.

Histology

The histological procedures were the same as those used in Experiment I.

Data Analysis

Data were analyzed as they were in Experiment I.

Results

Histology

In most of the quinolinic rats, the only thalamic nuclei not completely damaged were

the paraventricular and centromedial thalamic nuclei, which are midline nuclei that had some cells spared, and the reticular, ventral posterolateral, lateral edge of the ventral posteromedial and lateral edge of the lateral dorsal thalamic nuclei, which are located far laterally and were entirely spared (Figure 32). Most of the quinolinic rats had widespread calcification (Figures 34 to 37). Two quinolinic rats had lesions confined to the MD and other medial nuclei, and one quinolinic rat had only anterior thalamic damage.

Typically, the ibotenic rats had extensive MD damage (Figure 33), as well as damage to adjacent nuclei. These included the stria medullaris, the lateral habenula, the medial edge of the central lateral nucleus, the paraventricular nucleus, the intermediodorsal nucleus, medial parts of the anterior dorsal and anterior ventral nuclei, the paratenial nucleus, the interanterodorsal nucleus, medial parts of the central medial and anteromedial nuclei and dorsal parts of the rhomboid nucleus. Some of the rats' lesions spread further laterally and ventrally to include medial parts of the lateral dorsal thalamic nucleus along with parts of the paracentral, ventral medial, submedial and reuniens nuclei. Two of the rats had mild calcification. The medial habenula was intact in most rats. In most rats, damage was asymmetrical and lateral components of the mediodorsal nucleus were spared on one side or the other. Posterior and anterior poles of the mediodorsal thalamic nucleus were often partly spared.

Configural Task

Acquisition. Differences between the thalamic groups and the control group on Stages 1 and 2 were not significant (Stage 1: Trials - $F(2,25) = 1.69$, $p=0.210$; Errors - $F(2,25) = 1.50$, $p=0.240$; Stage 2: Trials - $F(2,25) = 2.60$, $p=0.090$; Errors - $F(2,25) = 1.74$, $p=0.196$). There were significant group differences on Stage 3, however (Trials: $F(2,25) = 4.45$, $p=0.022$; Errors: $F(2,25) = 5.26$, $p=0.012$). Follow-up tests indicated that the thalamic

Figure 32. Coronal sections through the thalamus of a rat that received a quinolinic acid lesion of the MD. Shading on the overlay shows where damaged tissue is. The MD is clearly damaged (see sections B, C, D and E), as are several other thalamic nuclei (see sections A through E). The lesions were large. The black dots located medially in sections C, D and E are calcium deposits, which most of the quinolinic rats had.

Quinolinic

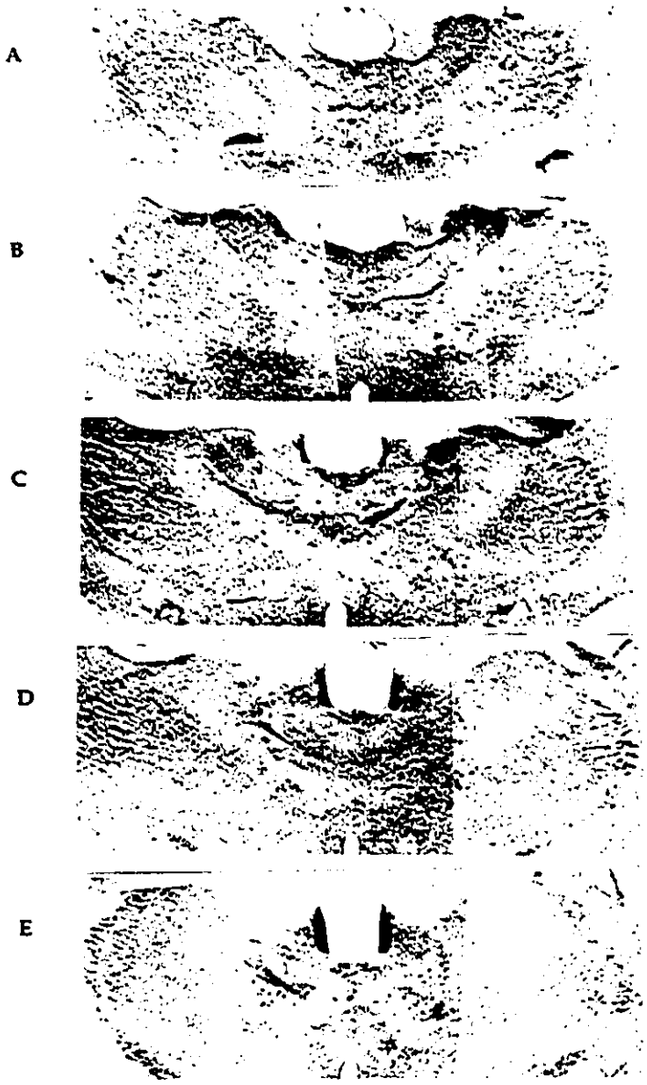


Figure 33. Coronal sections through the thalamus of a rat that received an ibotenic acid lesion of the MD. Shading on the overlay shows where damaged tissue is. The MD is clearly damaged (see sections B, C and D). Ventrolateral parts of the MD are spared, particularly in section D, and the lesion is not confined to the MD. Other medial thalamic nuclei are damaged (e.g., the paraventricular thalamic nucleus), and the lesion spreads anteriorly to include part of the ANT (section A). For reference purposes, see Figure 9.

Ibotenic

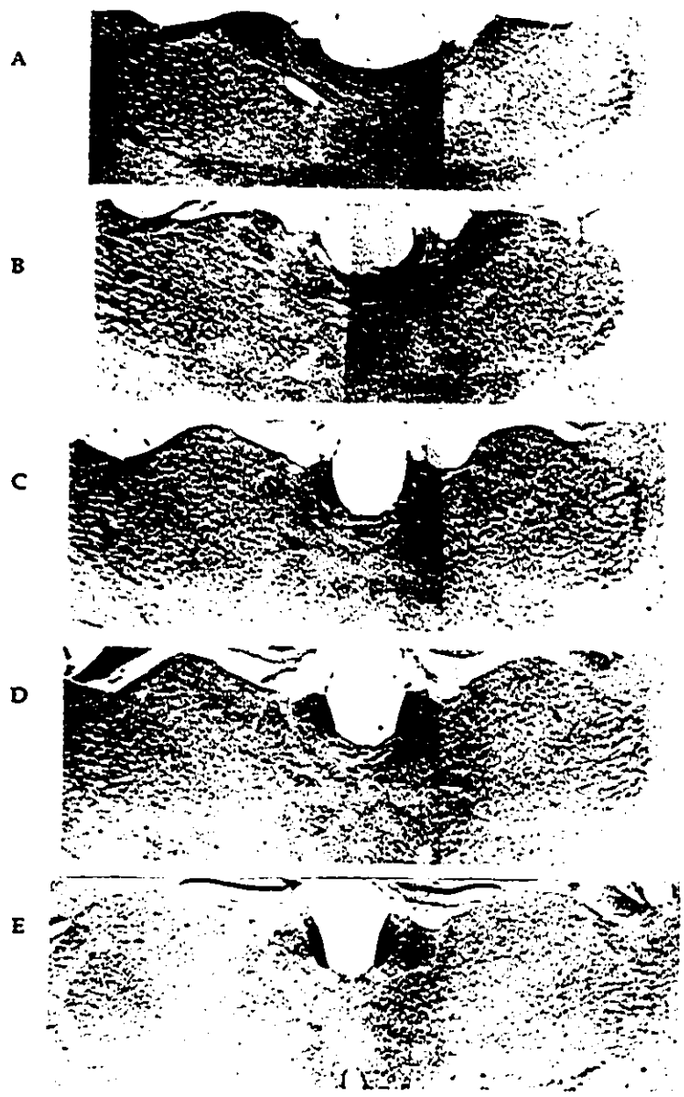
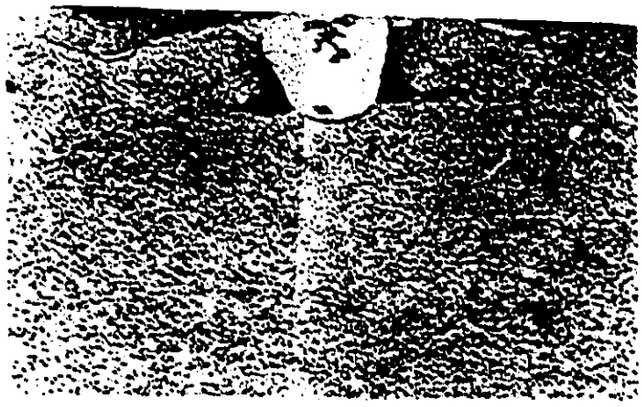
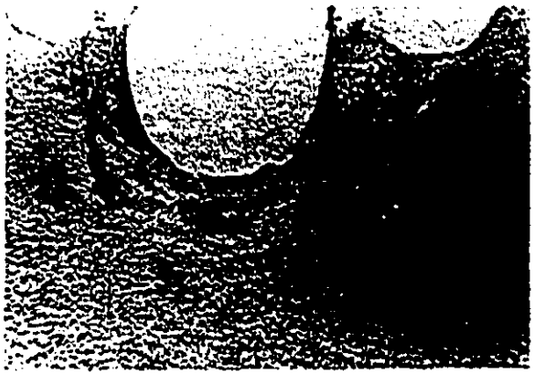


Figure 34. Photomicrographs (magnification = 50X) of the MD of a control, ibotenic and quinolinic rat. Note the loss of cells in the ibotenic and quinolinic rats and the spared cells located ventrolaterally in the ibotenic rat. The black patch and large black dots in the quinolinic rat are calcium deposits.

Control



Ibotenic



Quinolinic

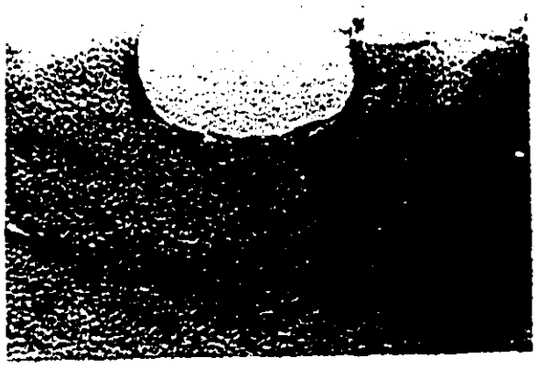


Figure 35. Photomicrographs (magnification = 100X) of part of the MD of a control, ibotenic and quinolinic rat. Note the cell loss in the ibotenic and quinolinic rats. Also, note the spared cells located ventrally in the ibotenic rat and the calcification (large black patches that are clearly not cells) in the quinolinic rat.

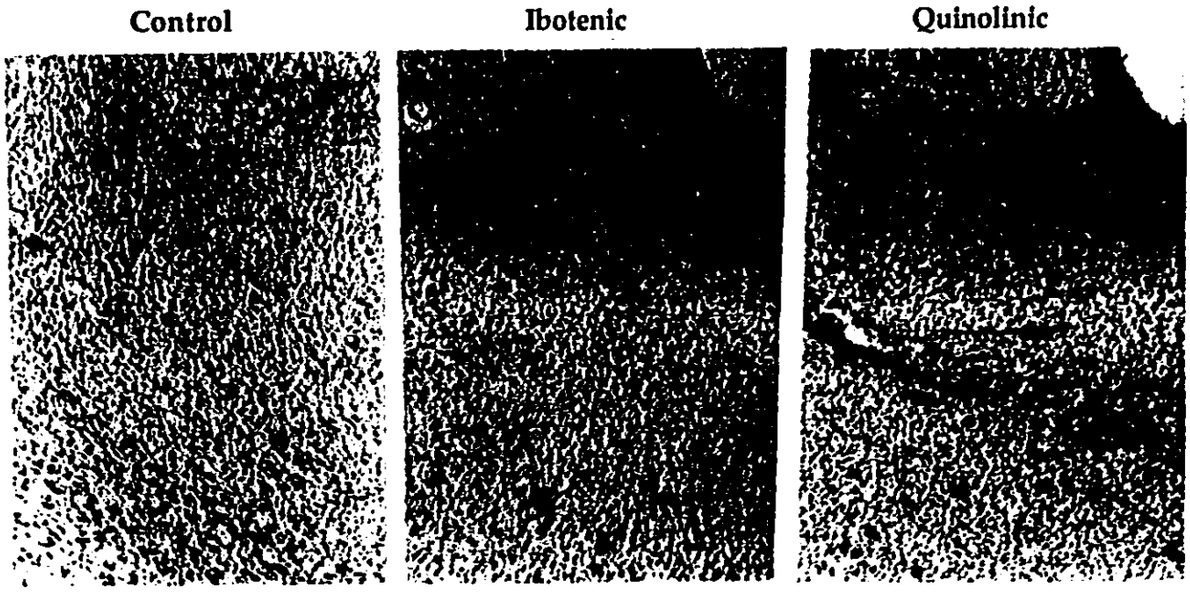
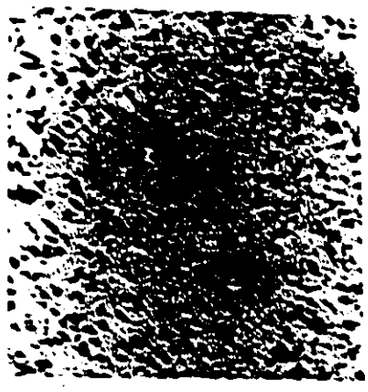
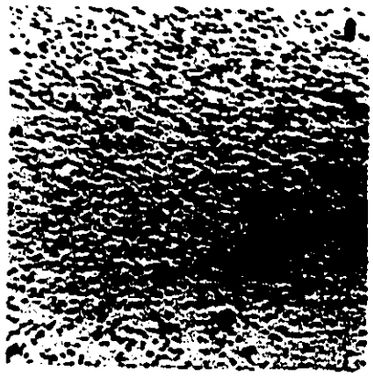

Control
Ibotenic
Quinolinic

Figure 36. Photomicrographs (magnification = 200X) of part of the MD of a control, ibotenic and quinolinic rat. Note the cell loss and gliosis (accumulation of small round cells which are glia) in the ibotenic and quinolinic rats. Note that gliosis in the quinolinic rat is greater than that in the ibotenic rat. Also note the calcification (large black patches) in the quinolinic rat.

Control



Ibotenic



Quinolinic

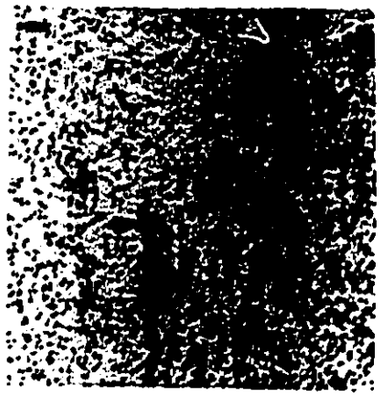
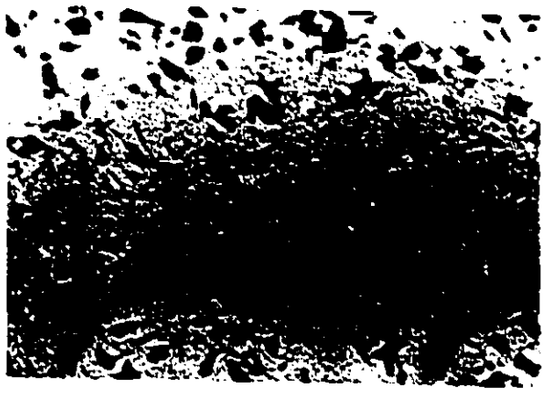
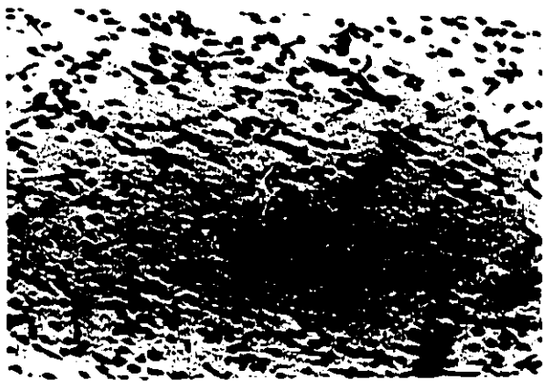


Figure 37. Photomicrographs (magnification = 400X) of part of the MD of a control, ibotenic and quinolinic rat. Note the loss of cells and abundance of glia (small round cells) in the ibotenic and quinolinic rats. Also, note the calcification (large black patches) in the quinolinic rat.

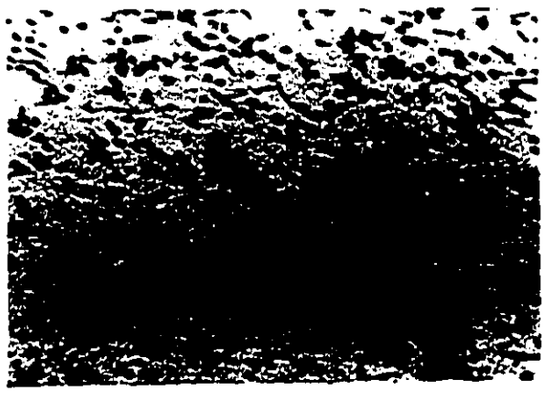
Control



Ibotenic



Quinolinic



groups were impaired relative to the control group and that differences between the thalamic groups were not significant (Figure 38).

Retention. When comparing pre-operative to post-operative retention of Stage 3, significant differences were found (Trials: $F(1,13) = 8.66$, $p=0.011$; Errors: $F(1,13) = 9.27$, $p=0.009$). Follow-up tests indicated that both the ibotenic and quinolinic groups were impaired post-operatively, and that the quinolinic group was more impaired than the ibotenic group (Figure 39).

Changing Platform Water Maze Task

The thalamic groups took longer to find the platform ($F(2,49) = 6.06$, $p=0.005$) and made more errors ($F(2,49) = 5.67$, $p=0.006$) than the control group (Figure 40). Follow-up tests indicated that latencies and errors of the quinolinic group and only the errors of the ibotenic group differed significantly from the control group. Differences between the ibotenic and quinolinic groups were not significant.

Activity Task

During baseline testing, the rats were not very active (Figure 41, Top) and there were no group differences ($F(2,46) = 0.04$, $p=0.961$). After administration of amphetamine, all the groups became significantly more active ($F(2,49) = 5.67$, $p=0.006$).

After administration of 1.25 mg/kg d-amphetamine (Figure 41, Middle), between group differences were not significant ($F(2,46) = 1.91$, $p=0.160$), but after administration of 2.5 mg/kg d-amphetamine (Figure 41, Bottom), they were ($F(2,46) = 6.59$, $p=0.003$). Follow-up tests indicated that the quinolinic group locomoted more than the ibotenic group and the control group.

Relation Between Lesions and Performance

The following analyses were done to see if lesion size was related to performance: (i)

Figure 38. Total trials (left) and errors (right) accumulated by individual rats while learning Stages 1 (top), 2 (middle) and 3 (bottom) of the configural string pulling task. Rats either had no lesion (CON), thalamic damage induced by ibotenic acid infusion (IBO) or thalamic damage induced by quinolinic acid infusion (QUIN). Stage 1 was a simple odor discrimination. In Stage 2 the odor discrimination was reversed, and in Stage 3 the stimuli were given in four different combinations and the rats were required to select the correct stimulus compound on each trial. Thalamic rats did not differ from controls on Stage 1 and 2, but were impaired relative to controls at acquiring Stage 3. Quinolinic thalamic rats were more impaired than ibotenic thalamic rats. The bars on the graphs are aligned by rat (i.e., the first bar on each graph is the same rat, the second bar on each graph is the same rat, etc.).

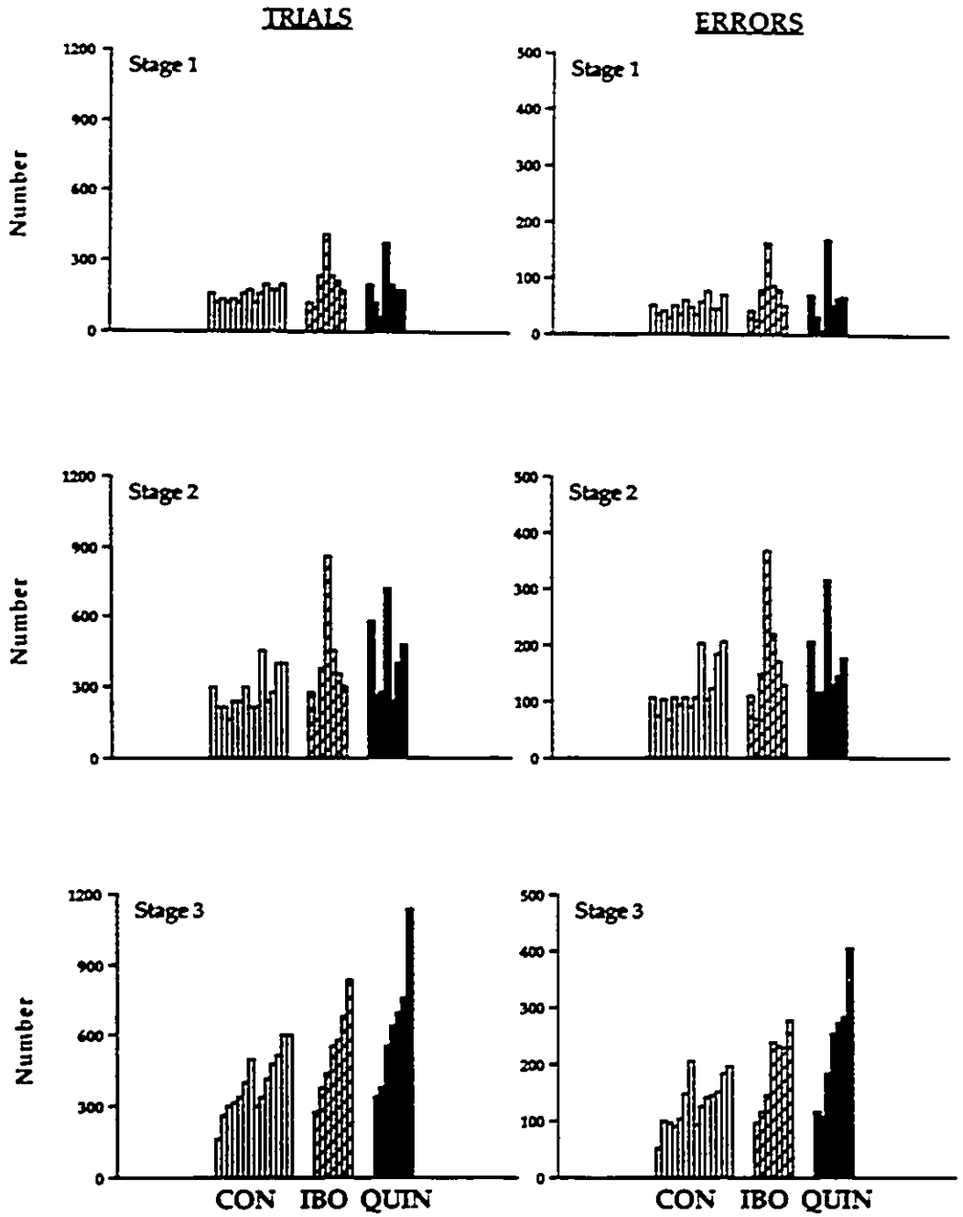

TRIALS
ERRORS
Stage 1
Stage 2
Stage 3
Number
1200
900
600
300
0
500
400
300
200
100
0
CON IBO QUIN

Figure 39. Total trials (top) and errors (bottom) accumulated by individual rats on Stage 3 of the configural string pulling task pre-operatively (Pre-Op), after a seven day no-training break, and post-operatively (Post-Op), after intra-thalamic infusions of ibotenic acid (IBO) or quinolinic acid (QUIN). Note the impaired post-operative performance of the rats and, in particular, the impaired performance of the quinolinic rats. The bars on the graphs are aligned by rat (i.e., the first bar on each graph is the same rat, the second bar on each graph is data from the same rat, etc.).

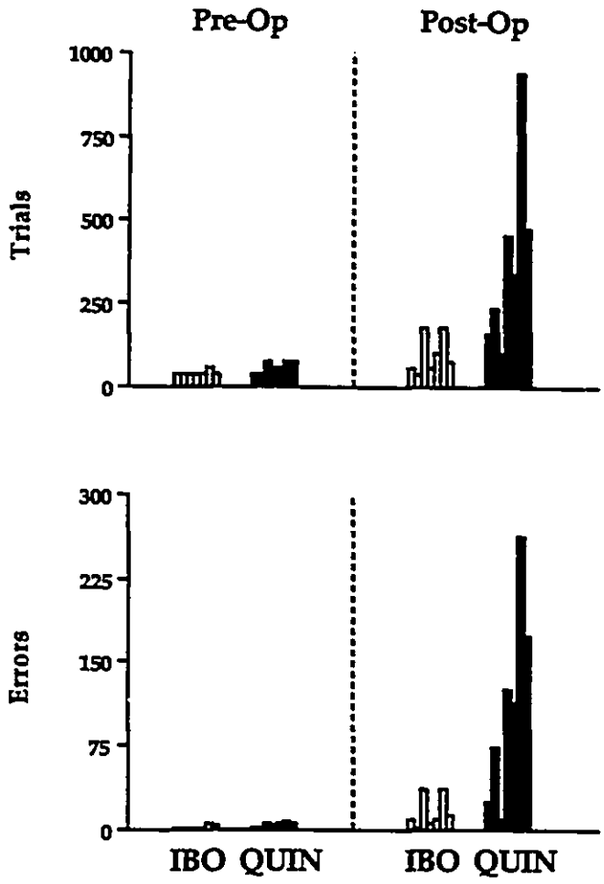

Pre-Op
Post-Op
Trials
1000
750
500
250
0
Errors
300
225
150
75
0
IBO QUIN
IBO QUIN

Figure 40. Trial by trial mean (and standard errors) latencies (top) and errors (bottom) in the changing platform water maze task. Each point on the graphs is the average over the 10 days of testing for the control rats (Controls), the rats with ibotenic acid induced thalamic damage (Ibotenic) or the rats with quinolinic acid induced thalamic damage (Quinolinic). Note the impaired performance of the thalamic rats and, in particular, that of the quinolinic rats.

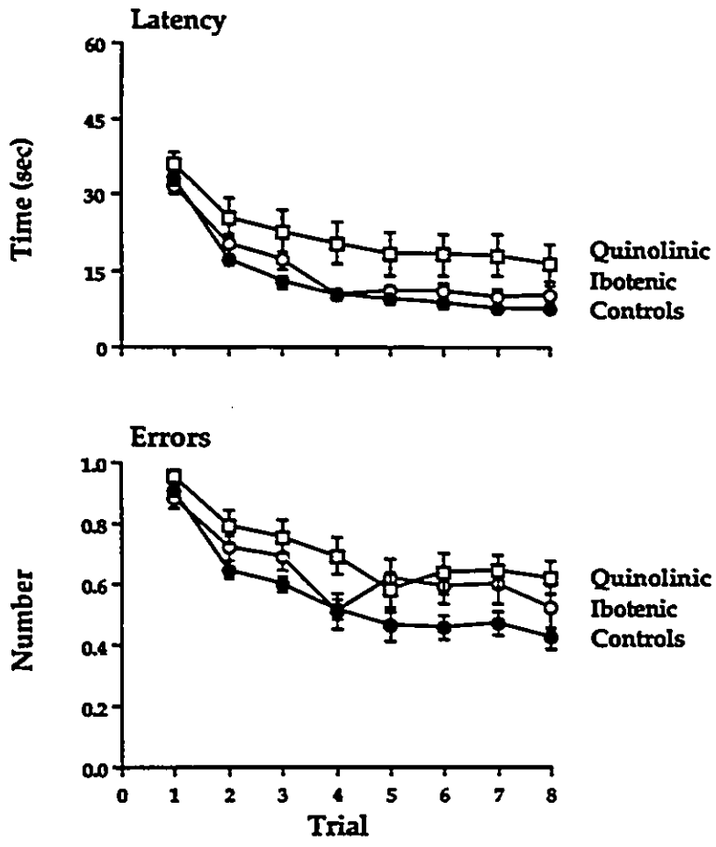
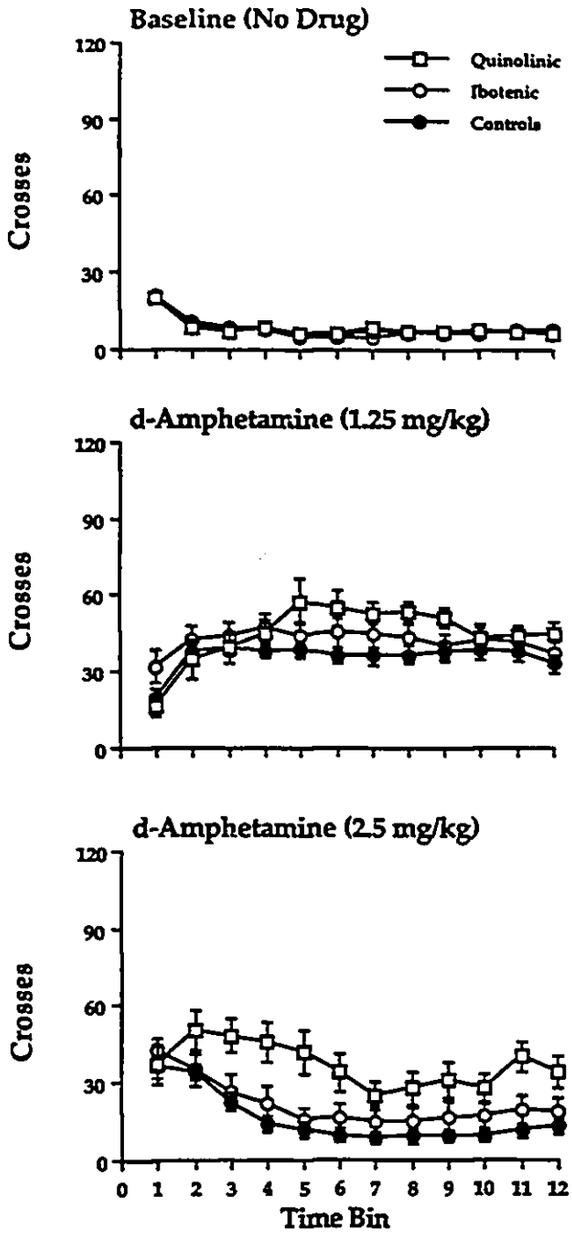

Latency
Time (sec)
60
45
30
15
0
Quinolinic
Ibotenic
Controls
Errors
Number
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
6
7
8
Trial
Quinolinic
Ibotenic
Controls

Figure 41. Crosses (means and standard errors) made by rats in the activity cages during each of the twelve 10 minute long time bins before drug administration (top), after administration of 1.25 mg/kg d-amphetamine (middle) and after administration of 2.5 mg/kg d-amphetamine (bottom). Rats had either no thalamic damage (Controls), thalamic damage induced by ibotenic acid infusion (Ibotenic) or thalamic damage induced by quinolinic acid infusion (Quinolinic). Note the elevated activity levels of rats after administration of both doses of amphetamine. Note that elevated activity is more marked for quinolinic thalamic rats than for ibotenic thalamic rats or controls, also, and that quinolinic thalamic rat activity is more marked after administration of 2.5 mg/kg d-amphetamine than after 1.25 mg/kg d-amphetamine.


Baseline (No Drug)
Quinolinic
Ibotenic
Controls
Crosses
120
90
60
30
0
d-Amphetamine (1.25 mg/kg)
Crosses
120
90
60
30
0
d-Amphetamine (2.5 mg/kg)
Crosses
120
90
60
30
0
0 1 2 3 4 5 6 7 8 9 10 11 12
Time Bin

The area of the thalamus at three different planes was calculated using an image analyzing system. The planes measured were the same as those measured in Experiment I. Correlations between thalamic area measurements and behavior were then calculated. (ii) The amount of damage to various thalamic nuclei was rated using the same scale used in Experiment I. The nuclei rated were the same as those rated in Experiment I. Correlations between the damage ratings and behavior of the rats were then calculated.

Correlations Between Thalamic Area and Behavior

Several of the correlation coefficients obtained when comparing thalamic area to configural task performance were significant and negative (see Table A-20), implying a direct relation between lesion size and impairment. The water maze data were averaged across both days and trials so that each rat had one number representing latency and one number representing errors. Correlations between some of these scores and thalamic area were significant (see Table A-21). Finally, there were no significant correlations between spontaneous or amphetamine-induced activity and lesion size (see Table A-22).

Correlations Between Nuclei Ratings and Behavior

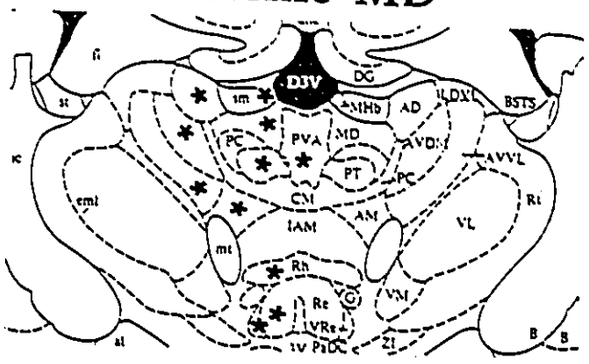
When comparing thalamic nuclei ratings to configural and water maze task performance, several of the correlation coefficients obtained were significant (see Tables A-23 and A-24). Most of the significant correlations were negative, implying that greater damage to specific nuclei produced greater impairments. For the ibotenic rats (Figure 42), ratings of damage to the MD and to surrounding midline nuclei correlated significantly with behavior. For the quinolinic rats (Figure 43), ratings of damage to the MD, to surrounding midline nuclei and to nuclei located more laterally and ventrally correlated significantly with behavior.

Figure 42. Reproductions of coronal sections through the thalamus of a rat. The sections are located 1.8, 2.3, 2.8 and 3.8 mm posterior to bregma (see Paxinos and Watson, 1985). Stars are placed on the nuclei whose damage ratings correlated significantly with behavior of the rats who received lesions of the MD via ibotenic acid infusions in this study. The nuclei whose damage ratings correlated with behavior of the ibotenic thalamic rats included: the ANT, the MD, the paraventricular nucleus, the paratenial nucleus, the habenula, the rhomboid thalamic nucleus, the reuniens thalamic nucleus and the subthalamic nucleus. In general, the more damage the MD rats had to these nuclei, which are primarily located close to the medial dorsal thalamic nucleus, the more impaired they were on the behavioral tasks in this study.

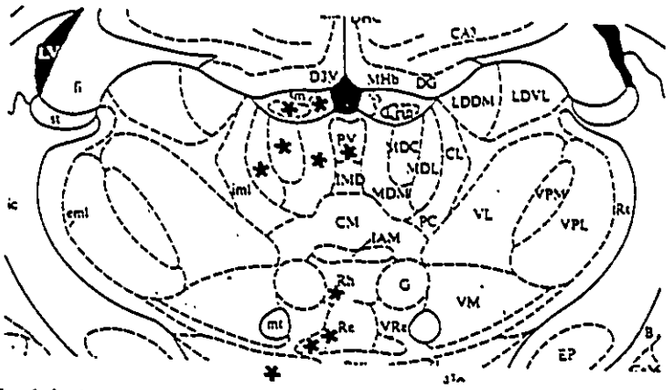
(For detail on abbreviations used in this figure, See Figure 26.)

Ibotenic MD

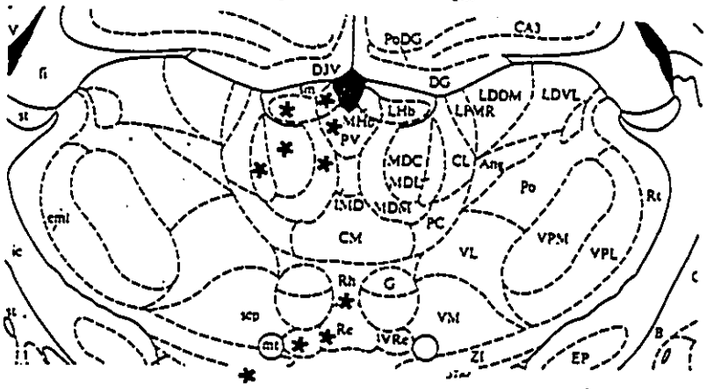
-1.8 mm



-2.3 mm



-2.8 mm



-3.8 mm

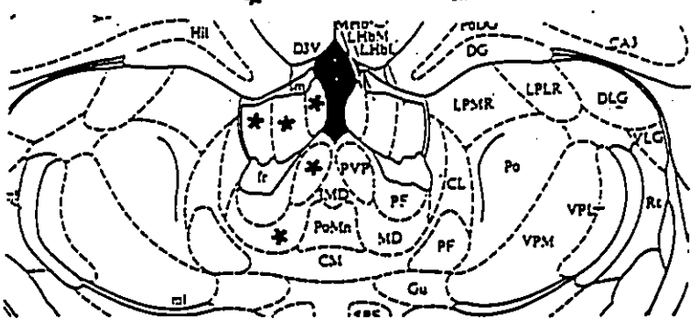
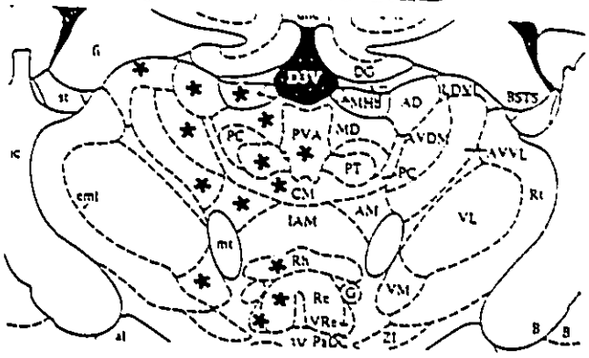


Figure 43. Reproductions of coronal sections through the thalamus of a rat. The sections are located 1.8, 2.3, 2.8 and 3.8 mm posterior to bregma (see Paxinos and Watson, 1985). Stars are placed on the nuclei whose damage ratings correlated significantly with behavior of the rats who received lesions of the MD via quinolinic acid infusions in this study. The nuclei whose damage ratings correlated with behavior of the quinolinic thalamic rats included: the stria medullaris, the ANT, the lateral dorsal thalamic nucleus, the MD, the paraventricular nucleus, the paratenial nucleus, the centromedial thalamic nucleus, the rhomboid thalamic nucleus, the reuniens thalamic nucleus, the ventral medial thalamic nucleus, the vental posterior thalamic nucleus, the lateral posterior thalamic nucleus and the posterior thalamic complex. In general, the more damage the MD rats had to these nuclei, the more impaired they were on the behavioral tasks in this study. Note that not all of these nuclei are located close to the MD. The quinolinic acid spread and produced extensive calcification throughout the thalamus.

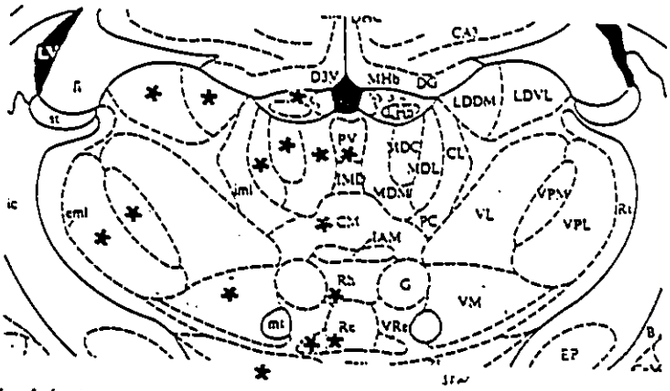
(For detail on abbreviations used in this figure, See Figure 26.)

Quinolinic MD

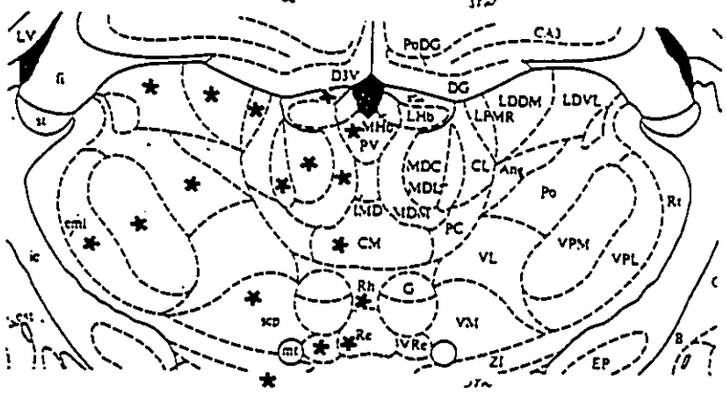
-1.8 mm



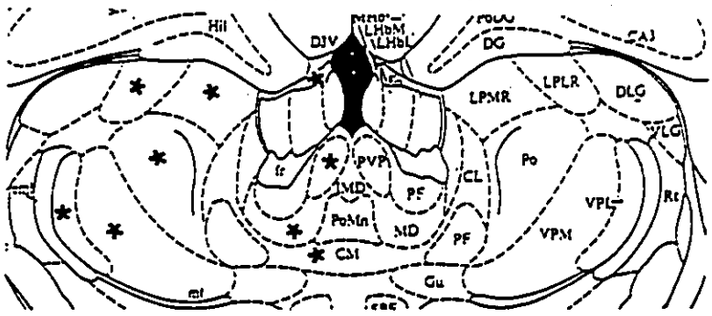
-2.3 mm



-2.8 mm



-3.8 mm



When comparing amphetamine-induced activity with thalamic nuclei damage, not many of the coefficients obtained were significant (see Table A-25). Of those that were, some were positive and some were negative. Thus, amphetamine-induced activity did not seem to correlate with amount of thalamic damage in any meaningful way.

Discussion

This experiment was performed with two questions in mind. First, could evidence be obtained that would suggest that the MD plays a role in acquiring either simple associations or configural associations? Second, could the results obtained on the changing platform water maze and activity tasks in Experiment I be replicated? Rats with MD lesions displayed no impairment on the simple associations and were only mildly impaired on the configural task. They were impaired on the changing platform task in much the same way found in Experiment I, but, unlike Experiment I, the quinolinic group locomoted more than the control group.

Though the thalamic rats were impaired on the configural task, they were not impaired on Stages 1 and 2. Stage 1 is a simple odor discrimation and Stage 2 is an odor discrimination reversal. Some researchers claim that rats with MD nucleus damage are impaired on olfactory discriminations and reversals (Eichenbaum, Shedlack and Eckmann, 1980; Staubli, Schottler and Nejat-Bina, 1987; Slotnick and Kaneko, 1981), so the results on Stages 1 and 2 might be considered surprising. Eichenbaum et al. (1980) point out that impairments are obtained only with similar odors. They also point out that on detection problems, which require rats to distinguish between a commercial odor and "clean air", MD thalamic damage does not impair performance. On Stages 1 and 2 of the configural string pulling task, rats had to distinguish between the smell of tape with almond

extract painted on it and the smell of tape with no odor painted on it. This is a detection problem in a sense, so it is not surprising that the rats were not impaired. The results clearly confirm that the MD is not necessary for the acquisition or retention of simple associative tasks.

On Stage 3 of the configural task, the thalamic rats had acquisition and retention deficits that were about the same as those of rats with hippocampal damage (Whishaw and Tomie, 1991), and were smaller than those of rats with prefrontal cortex damage (Whishaw et al., 1992). This result could equally support the idea that the MD plays a facilitatory role with learning or that the impairments are nonspecific or are due to damage to some adjacent structures. Clearly, this finding provides little support for the idea that the MD is any more essential for configural learning than it is for simple associative learning.

On the changing platform spatial task, the thalamic rats were impaired and, the larger their lesions, the more impaired they were. Behavior on the retention, one-trial learning and performance components of the changing platform task was analyzed as it was in Experiment I. The analyses indicated that the quinolinic group took longer to find the platform and made more errors than the control group on the one-trial learning and performance components, and that the ibotenic group did not differ from the control group or quinolinic group on any of the components. The analyses also indicated that lesion size and behavior on the one-trial learning and performance components was directly related. The fact that lesion size correlated with behavior on both the one-trial learning and performance components is not surprising given that only the quinolinic group was impaired on these components and, relative to the ibotenic group, the quinolinic group's lesions were large. Due to the extensive thalamic damage typical of the quinolinic rats,

nothing can be concluded about function of medial thalamic structures from their data. The ibotenic group did not differ from the control group or quinolinic group on any of the components of the changing platform task. This finding supports claims that deficits of rats with MD damage are probably not with learning and memory.

Curiously, the quinolinic group locomoted significantly more than the control group in the present experiment, whereas there was only a tendency in this direction in Experiment I. The source of this difference is unclear. As was found in Experiment I, the ibotenic group did not locomote significantly more than the control group. Thus, it seems safe to conclude that lesions confined to the MD and adjacent nuclei do not alter spontaneous and amphetamine-induced activity like lesions to the hippocampus and prefrontal cortex do (Whishaw and Mittleman, 1991).

GENERAL DISCUSSION

Contemporary views on the neuroanatomy of memory suggest that it is distributed across many brain areas, each of which makes a different contribution. There is abundant evidence for involvement of the hippocampus and the prefrontal cortex in learning and memory, and several lines of evidence suggest that medial thalamic structures, such as the ANT and MD, might also be involved. The ANT and MD have been hypothesized tc form a memory circuit with the hippocampus, amygdala, and prefrontal cortex (Mishkin and Appenzeller, 1987). This idea is supported with evidence from humans who have memory impairments and correlated MD damage (e.g., N.A., Korsakoff's patients), and from experimental studies of MD or ANT function in nonhumans (Markowitsch, 1982; Sutherland and Rodriguez, 1989).

The purpose of the research undertaken in this thesis was to test this theory by presenting rats with ANT or MD damage with tasks sensitive to hippocampal or prefrontal cortex damage. Rats received lesions of the ANT or MD electrolytically or via infusion of ibotenic acid or quinolinic acid. The ability to solve spatial tasks and a configural learning task was then examined, and spontaneous and amphetamine-induced activity was measured. These behavioral measures are sensitive to damage to the hippocampus and prefrontal cortex. If the hippocampus, prefrontal cortex and thalamus form a "memory circuit", it would be expected that these behavioral measures would also be sensitive to thalamic damage.

In the spatial task, rats swim through murky water to escape to a platform hidden just below the water's surface. It is thought that rats know where they are and navigate in this task using relational properties of room cues. Two versions of the task were used. In the

changing platform version, the platform was in a different location each day. In the same platform version, the platform was in the same location each day. The main findings from these tasks were that thalamic rats were impaired, that larger lesions produced greater impairments, and that damage to certain thalamic nuclei was more related to the impairments than damage to other nuclei.

Based on behavior that rats can be expected to display across each day's trials, the changing platform task can be theoretically divided into retention, one-trial learning and performance components. Analyses of behavior and of relations between lesion size and behavior on these components raised the possibility that the deficits shown by the rats were more than simple acquisition or retention deficits. Retention of previously learned spatial locations and acquisition of new locations did not correlate with lesion size whereas performance variables, such as latency and errors to reach the platform after its location was learned, did correlate with lesion size. Together, the pattern of behavior displayed by the rats and the results of analyses of the relation between task variables and performance provide only lukewarm support for the idea that either the ANT or MD is essential for spatial learning.

At asymptote, some of the thalamic groups were impaired on the spatial tasks. This could have been due to a sensory-motor impairment or to a navigational impairment, such as loss of directionality due to disruption of 'head direction cells' like those McNaughton, Barnes and O'Keefe (1983) claim fire when rats are located in a particular place and are moving in a particular direction in an environment. It might also be similar to the impairment seen in people Balint's Syndrome. When asked to reach for objects placed in front of them, and which they know are there, people with Balint's Syndrome often under or over-reach (Kolb and Whishaw, 1990). Whether the thalamic rats had a similar

navigational problem in the water maze tasks in this thesis could have been addressed by having the rats swim to a visible platform. It is unlikely that damage to the MD or ANT would produce navigational deficits on the water maze tasks, however. Rats with relatively confined lesions were not impaired on the place tasks and likely would not have been impaired on a cue task.

The idea that thalamic damage does not unambiguously produce learning deficits is consistent with other work. Sutherland and Rodriguez (1989) found that, relative to controls, rats with electrolytic ANT lesions were impaired on a same place water maze task. Performance of their ANT rats improved across trials, however, and by the last block of trials, their ANT rats were not significantly different from their controls. The platform was moved to a different location after completion of testing on the same place task, and the ANT rats found the platform in its new location as rapidly as controls. These findings support the findings in this thesis of the ANT not being essential for spatial learning and of damage to the ANT impairing other features of performance moreso than learning.

Kolb et al. (1982) found that rats with small electrolytic MD lesions were not impaired on a same place water maze task. Similarly, the small electrolytic MD group was not impaired on the water maze tasks in this thesis. On other spatial tasks, such as the radial arm maze and spatial alternation tasks, some people have found rats with MD lesions are impaired and some people have found they are not (see Table 2). Rats with MD lesions were not impaired on the radial arm maze tasks of Kolb et al. (1982) and Beracochea et al. (1989), for example, but were impaired on the radial arm maze tasks of M'Harzi et al. (1991), Stokes and Best (1988, 1990) and Kessler et al. (1982).

Of the researchers who found that MD rats were impaired on the radial arm maze, the

only ones to claim their MD rats have a memory deficit without at least acknowledging the fact that their rats could have an attentional or motor deficit that secondarily affects memory were M'Harzi et al (1991). Additionally, M'Harzi et al. apparently misrepresent the literature to support their claims; e.g., their claim that Kolb et al.'s (1982) results are similar to theirs. Stokes and Best (1990) do not claim that their MD damage-induced deficit is due to a memory impairment, and Kessler et al. (1982) suggest that their rats' memory deficits are "subtle" and that MD damage might also produce nonspecific deficits. Thus, as is suggested here, support for the MD being necessary for learning spatial tasks in the literature is not strong.

In the configural string task, rats are presented with two strings, one of which has food tied on its distal end. The rats are to pull up this string. The task consists of three stages. On Stage 1, the rats must select a string based on its odor. On Stage 2, the rats must reverse the response learned on Stage 1. On Stage 3, the rats have to use both tactile and olfactory information to identify the correct string.

The task is designed to measure the two major types of memory that characterize a number of contemporary theories (Sutherland and Rudy, 1989; Cohen and Squire, 1980). It would be expected that if the MD has anything to do with memory, damaging it would impair performance of animals on at least one of the three stages of the configural task. Furthermore, since acquisition of this task depends upon the function of the prefrontal cortex (Whishaw et al., 1992), if the MD shares mnemonic functions with prefrontal cortex then damage to the MD would be expected to impair performance of animals on this task. It was found that rats with lesions confined to the MD and adjacent medial nuclei were not impaired on the first two stages of the task, and had mild deficits on the third stage. These findings confirm the finding from the spatial tasks in showing that, following damage

to the MD, an absolute deficit does not occur. Rather, the result leaves open the question that the lesion-induced impairment of rats with MD damage has more to do with using information than with learning it.

Although nobody else has examined ability of rats with MD lesions to solve configural tasks of this kind, the ability of MD rats to solve other nonspatial learning tasks has been examined (see Table 2). Again, findings from these studies are not clearcut for some studies find deficits and some do not. On delayed non-matching-to-sample tasks, Neave et al. (1992) report that MD rats were not impaired whereas Mumby et al. (1993) and Hunt and Aggleton (1991) report that they were. Mumby et al. (1993) admit their rats' deficits could be the result of incidental damage to other thalamic structures. Similarly, Hunt and Aggleton (1991) note that the impairments exhibited by their rats might be due to ANT rather than MD damage. Again, support for the MD being critical for learning of nonspatial tasks is not strong.

Given that the spatial tasks presented to the rats in the present study are also configural, by definition, and given that results obtained in the spatial and string pulling tasks were quite similar, the present results along with other results do not provide convincing support for the notion that the MD is involved in configural learning.

Activity does not measure learning or memory but it can be thought of as a measure of unconditioned behavior and a normal prerequisite behavior for learning. Indeed, O'Keefe and Nadel (1978) support just this position when they state that hippocampal lesions that produce spatial deficits also produce abnormal exploratory behavior. It has been found that abnormal activity can be produced "on demand" by administering amphetamine and measuring locomotor activity. This "on demand" test is thought to provide a robust analogue to tests in which rats are placed in novel environments in which

exploratory behavior is measured. Indeed, rats with either hippocampal or frontal cortex lesions have been reported to show heightened locomotion on amphetamine tests and heightened locomotion on exploratory tests (Lynch et al., 1971; Whishaw and Mittleman, 1991).

Activity was assessed by placing rats in wire mesh cages and counting how often they crossed the cages. Of the 10 thalamic groups, five locomoted more than the control group after administration of amphetamine. These five groups had large lesions that destroyed fibers of passage or were full or calcification and destroyed far more than just the ANT or MD. The other five groups had lesions that were more confined to the ANT or MD. Thus, the heightened locomotion of some of the thalamic groups cannot be unequivocally attributed to damage to the ANT or MD. Furthermore, when comparing the locomotion levels with those reported by Whishaw and Mittleman (1991) after hippocampal or prefrontal cortex lesions have been made, the activity increases of the thalamic groups in this thesis were slight.

No previous study has looked at amphetamine-induced acitivity of rats with ANT or MD lesions, but spontaneous activity and exploratory behavior have been measured (see Table 2). The consensus from such studies is that relative to controls, rats with MD damage are slightly hyperactive, especially at night (Kolb, 1977; Beracochea, 1989; Means et al., 1974). Again, because the lesions of rats in these studies were not confined to the MD, the slight hyperactivity can not be unequivocally attributed to the MD.

Because there was inadvertent damage to nuclei surrounding the ANT and MD, the possibility that damage to nuclei other than the ANT and MD might have contributed to the behavioral deficits cannot be ruled out. As mentioned, in no study on MD function have lesions been confined to the MD. Thus, lesion specificity is a general problem

(Mumby et al., 1993; Hunt and Aggleton, 1991; Vanderwolf, 1969; Kessler and Markowitsch, 1981; Means et al., 1973b). It has been suggested that damage to structures other than the MD, such as the ANT (Hunt and Aggleton, 1991), the centromedial and parafascicular nuclei combined (Delacour, 1971), or the internal meduallary lamina (Mair and Lacourse, 1992) is responsible for deficits observed in rats with thalamic damage.

Since thalamic nuclei project to many cortical targets, it is possible that deficits reported following thalamic damage could be due to structural or metabolic changes in one or a number of these targets. Additionally, a number of fiber systems surround or pass through the MD. The MD is enclosed laterally by the internal medullary lamina, for example. The fascicularis retroflexus is in direct contact with neurons of the MD. The stria medullaris and fornix lie dorsal to the MD, and the mammillothalamic tract is located close to the anterior end of the MD. Markowitsch (1982) notes that it is possible that fiber systems such as these, rather than neurons of the MD, carry the main burden for memory functions, and that deficits of animals with MD damage on learning and memory tasks can be accounted for by damage to surrounding fibers of passage. Neurotoxins, that kill cells and spare fibers of passage, were used in the present study to control for this possibility. If deficits of animals with thalamic damage can be accounted for by damage to fibers of passage, one would not expect animals with thalamic damage induced by infusion of neurotoxins to be impaired on memory tasks. Some of the ibotenic acid and quinolinic acid rats were impaired on the tasks in this thesis, however, and some of the electrolytic rats were not. These findings support Hunt and Aggleton's (1991) claim that memory impairments of animals with thalamic damage cannot be accounted for by incidental damage to fibers passing through the thalamus.

When dealing with their rats' nonspecific lesions, Means et al. (1973b) state that the number of thalamic and extrathalamic structures damaged bilaterally correlated with behavioral deficits of their MD rats, but that no specific structure was uniquely associated with the deficits. The correlational analyses performed in this thesis support this claim. Damage to several thalamic nuclei correlated with impairments of the rats in this thesis, and no specific nucleus stood out as being any mo ' important than the other nuclei. It cannot be ruled out that damage to specific nuclei is necessary for deficits to surface, however, but additional research with more confined lesions would be neccesary to support such a claim.

Because damage to the ANT and MD was seldom complete, residual portions of the ANT or MD may have mediated spared behaviors. The correlational analyses can be interpreted as supporting this view since they indicated that the more extensive the damage to the ANT and MD, the more impaired the rats were. Several other papers have made a similar suggestion (Kessler et al., 1982; Means et al., 1975a; Means et al., 1975b; Eichenbaum et al., 1980). Stokes and Best (1990) are most specific in claiming that at least 80% of the MD needs to be damaged for behavioral impairments to occur. Still other studies claim that posterior (Waring and Means, 1976) or medial parts of the MD need to be damaged (Staubli et al., 1987; Slotnick and Kaneko, 1981). Medial portions of the MD were seldom spared in the rats in this thesis, but the anterior and posterior poles of the MD were often spared. It is difficult to precisely quantify the amount of damage, but most of the rats in this thesis had extensive MD damage with less than 20% of the MD spared. Thus, damaging central portions of the MD or at least 80% of the MD will not guarantee that severe behavioral impairments will surface. The claim about lesion location made by Waring and Means (1976) might be correct, however. Variability in behavior of MD rats

in this thesis and in other studies on MD function could be partly explainable by sparing of variable amounts of posterior MD. Additional work with more confined lesions would be needed to determine if this is the case.

A number of researchers who claim the MD is involved in learning and memory acknowledge that their data could be interpreted in terms of some nonspecific, nonmemory deficit. Others are more explicit and claim that the deficits induced by MD damage are not with mnemonic processes but are attentional deficits, emotional deficits, or motor deficits such as reduced ability to initiate proper and inhibit improper motor acts (Stokes and Best, 1990; Vanderwolf, 1969; Beracochea et al., 1989). On the basis of the findings in the present study, there is no evidence that would point to some non-mnemonic functions of the thalamus that would account for the present results. Therefore, in the following paragraphs, some representative non-mnemonic suggestions put forward by others will be presented.

Vanderwolf (1962, 1963, 1969) reports that medial thalamic nuclei are important for voluntary movements. Rats in his experiments were trained to move from one compartment of a box to another within a given length of time to avoid electric shock. Rats with electrolytic lesions of medial thalamic nuclei were impaired at avoiding shock, but were able to avoid it if given more time than control rats. Once rats initiated movement, their avoidance was as efficient as controls. Vanderwolf (1962) claimed that the impairment he observed was not a motor impairment or learning impairment, but was an impairment in ability of rats with medial dorsal thalamic damage to voluntarily initiate movement.

Stokes and Best (1990), because of the perseveration and patterned responding rats with MD lesions exhibited on their radial arm maze task, claim that the impairment of their

MD rats is a nonspecific, nonmemory dysfunction that could be attentional or motor in nature. Likewise, Kolb et al. (1982), seeing perseverative tendencies in their rats, claim that the MD might be an important modulator of behavioral flexibility. Other researchers make similar claims (Gross et al., 1965; Means et al., 1973a, 1973b; Sakurai and Sugimoto, 1985). Thus, the idea presented in this thesis that MD damage impairs performance moreso than learning and memory is consistent with reports by others.

If animals with thalamic damage do have motor deficits, based on observations made while testing rats for this thesis and based on claims by Vanderwolf (1962, 1969), the deficits are subtle. To detect them, behavior of the rats would need to be studied in more detail. In water maze tasks, for example, analyzing paths rats traverse enroute to the platform using more than just a binary right/wrong scale would be interesting and could shed light on performance deficits. Videotaping the rats while they are swimming and subsequently analyzing their head and paw movements could also help shed light on their deficits (Whishaw and Tomie, 1987).

There have been a number of studies on rat species typical behavior following MD lesions. Kolb (1977) found that electrolytic MD lesions decreased hoarding, increased social interactions, and increased shock-induced aggression. Schacter, Phelps, Brodbeck, Mogenson and Roberts (1991) found that the probability of rats carrying food to the center of a radial arm maze rather than eating it at the ends of the arms decreased after damaging the MD electrolytically. Beracochea et al. (1989) found that ibotenic acid MD lesions increase food and water intake. Means et al. (1973b) found that rats with electrolytic MD lesions were less responsive to tactile stimuli, and Vanderwolf (1962, 1963, 1969) found that rats with electrolytic MD lesions reared more and froze less than controls in an unfamiliar environment and were slow to initiate exploratory behavior.

The severity of these changes can be questioned, however. Whishaw (1993) has reexamined food carrying behavior of rats with electrolytic MD lesions. He found that although initially abolished, auditory stimulation from brief crinkling of a piece of tinfoil could restore food carrying. This result should caution that unless care is taken to control for extraneous variation arising from features of the environment, such as noise level and level of illumination, and unless qualitative aspects of behavior are studied along with quantitative aspects, impairments could be overestimated.

When discussing qualitative aspects of behavior of their MD rats, Stokes and Best (1988) note that for the first two to three weeks after surgery, the eating behavior of their rats was abnormal. Their rats gnawed at food pellets on the ground rather holding them in their paws while eating them. Kolb (1977) noticed this phenomenon in his MD rats, and, though it was not formally studied, it was a phenomenon that was also observed in this experiment. Throughout the string pulling experiment, the MD rats required more supplementary feeding than the control rats to maintain their body weight, in fact. This suggests that, though feeding behavior appears to recover after a few weeks in MD rats, it might not completely recover.

A qualitative change in behavior sometimes observed in rats with incomplete damage to the hippocampus is periodic occurrence of seizures (Whishaw, 1987). The thalamic rats in the current study did not seizure, and nor has anyone reported occurrence of seizures following damage to medial thalamic nuclei. Stokes and Best (1988) report that their MD rats froze when they were reintroduced to the radial arm maze after surgery, however, and Vanderwolf (1962, 1969) reports impairment of his MD rats at initiating voluntary behavior. It has not been reported that rats are seizuring at these times. To not be able to initiate voluntary behavior or to inhibit involuntary behavior is, in a

sense, seizuring. Perhaps the inflexibility in behavior that is sometimes exhibited by MD rats (Kolb et al., 1982) is due to projections from the hippocampus to the MD moreso than to cells of the MD, however. Further study is necessary to determine if this is the case.

When describing surgical procedures, Beracochea et al. (1989) note that in pilot studies they found that simultaneous bilateral lesions of the ANT induced a high rate of death among subjects, so they made their ANT lesions in two stages with unilateral lesions being separated by one week. When damaging the ANT in the current study, a high death rate among subjects was also noted so, rather than making lesions in two stages, ANT lesions were made slightly more posteriorly than Beracochea et al. (1989) made their lesions or than Sutherland and Rodriguez (1989) made theirs. Interestingly, Sutherland and Rodriguez used the electrolytic lesion technique and do not report having found a high death rate among their subjects. Beracochea et al. (1989) made their lesions with ibotenic acid, and it was during use of ibotenic acid that a high death rate was noticed in subjects in the current study. Why ibotenic acid is as potent as it seems to be when infused into the ANT would be an interesting question for future research to address.

The nonselective lesions typical of studies on thalamic function have their drawbacks in that it is impossible to attribute functions to specific nuclei if lesions are not confined to those nuclei. Thus, although the nonselective lesions may model the kinds of lesions reported in humans (e.g., N.A. and Korsakoff's patients), they are less useful for structure/function studies. Of the three lesion techniques used in this thesis, ibotenic acid infusion seemed to be the most promising for making selective lesions. The electrolytic lesions were large and damaged fibers of passage and cell bodies. The quinolinic acid spread extensively from the place of infusion and produced extensive calcification. The

ibotenic acid did not spread excessively, did not seem to damage fibers, and did not produce calcification. Thus, it could be used for making more selective lesions.

Jarrard (1989) describes a method for making selective hippocampal lesions, and this could be used for making selective thalamic lesions. To make selective bilateral lesions of the hippocampus, Jarrard infuses small amounts of ibotenic acid through a glass micropipette into 26 sites. One can make lesions of the hippocampus by infusing larger amounts of neurotoxins into fewer sites (Whishaw and Tomie, 1991; Sutherland and Rudy, 1989; Sutherland and McDonald, 1990; Sutherland, McDonald, Hill and Rudy, 1989), but a drawback is that the lesions are less selective (Tomie and Whishaw, 1993). Employing a technique similar to that of Jarrard (1989), it should be possible to make selective thalamic lesions.

Because of calcification and spread, quinolinic acid should not be used. Nevertheless, the calcium deposits it produces are interesting. Administration of the calcium channel antagonist, nimodipine, has been reported to reduce impacts of brain damage and aging on behavior of animals (Isaacson and Poplawsky, 1993; Finger, Green, Tarnoff, Mortman and Anderson, 1990; Schuurman, Klein, Beneke and Traber, 1987). Thus, the calcium deposits might have contributed to deficits observed in this thesis. Formation of calcium deposits after lesions of the brain has been found in other studies (Whishaw, Schallert and Kolb, 1981; Whishaw and Kolb, 1984), but why and how they form is not well understood. Given that quinolinic acid seems to produce extensive calcificiation, it could provide an excellent model for researchers interested in understanding calcium deposition.

In conclusion, it can not be ruled out that the MD and ANT are involved in learning and memory, but findings in this thesis and in literature in general do not lend strong support to claims that the ANT or MD play a central role with learning and memory. If

lesions are confined to these nuclei and behavior is carefully studied, perhaps role of the MD or ANT in learning and memory will become clear, but results here suggest this role would be minimal. The overall conclusion in this thesis is that damage to medial thalamic nuclei, such as the MD and ANT, results in nonspecific deficits on the tasks studied. These deficits could secondarily affect performance on learning tasks, but the primary role of medial thalamic nuclei may not be with learning and memory.

As mentioned at the outset of this thesis, contemporary theorists assume that learning and memory are distributed across several brain structures, including temporal lobe structures and prefrontal cortex. They also assume that, because of their central location and connections with temporal lobe structures and prefrontal cortex, and because people with amnesia often have damage to them, the MD, ANT, and other medial thalamic nuclei, should be involved in learning and memory (Mishkin and Appenzeller, 1987). Reports that animals with damage to the MD are not impaired on learning tasks often seem neglected.

According to Cohen (1990), W.S. Gosset ("Student") published the t-test a decade before World War I, but the test did not appear in statistics books until after World War II. Because of this, Cohen says "if you publish something that you think is really good, and a year or a decade or two go by and hardly anyone seems to have taken notice, remember the t-test, and take heart". According to Hebb (1980), it takes 50 to 100 years for scientific findings to become common sense and 100 years to change that common sense if it is wrong. If this is the case, it may take a few more years, and perhaps a paradigm shift, before the search begins for the non-mnemonic functions of thalamic nuclei.

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APPENDIX A: LIST OF TABLES

Table A-1. Follow-up test (t-tests) results for latency and errors on the changing place water maze task. The rats that received electrolytic ANT or MD lesions were compared with each other and with controls.

Average of Trials 1 to 8

	Latency					Errors				
	SMD	LMD	SAnt	LAnt	Cont	SMD	LMD	SAnt	LAnt	Cont
SMD	–	**	*	**	–	–	**	**	**	*
LMD		–	–	–	**		–	–	–	**
SAnt			–	–	**			–	–	**
LAnt				–	**				–	**

Trial 1 Only

	Latency					Errors				
	SMD	LMD	SAnt	LAnt	Cont	SMD	LMD	SAnt	LAnt	Cont
SMD	–	*	–	**	–	–	–	–	*	**
LMD		–	**	*	*		–	*	**	–
SAnt			–	–	**			–	–	**
LAnt				–	–				–	**

Trial 1 minus Trial 2

	Latency					Errors				
	SMD	LMD	SAnt	LAnt	Cont	SMD	LMD	SAnt	LAnt	Cont
SMD	–	–	**	**	–	–	*	–	*	–
LMD		–	–	–	–		–	–	–	**
SAnt			–	–	**			–	–	**
LAnt				–	**				–	**

Average of Trials 3 to 8

	Latency					Errors				
	SMD	LMD	SAnt	LAnt	Cont	SMD	LMD	SAnt	LAnt	Cont
SMD	–	**	**	**	**	–	**	**	**	**
LMD		–	–	–	**		–	–	–	**
SAnt			–	–	**			–	–	**
LAnt				–	**				–	**

SMD=small electrolytic MD rats, LMD=large electroytic MD rats, SAnt=small electrolytic ANT rats, LAnt=large electrolytic ANT rats, Cont=control rats

*=p<0.05
**=p<0.01

Table A-5. Results from analysis of variance comparing crosses made in the activity cages by the electroytic, ibotenic and quinolinic thalamic rats after administration of no drug or 1.25 or 2.5 mg/kg d-amphetamine with crosses made by controls.

Electrolytic versus Controls

No Drug	
Group	$F(4,36)=4.5$, $p<0.005$
Time Bin	$F(11,396)=149.46$, $p<0.001$
Group X Time Bin	$F(44,396)=1.86$, $p<0.001$
1.25 mg/kg d-Amphetamine	
Group	$F(4,36)=1.02$, $p=0.409$
Time Bin	$F(11,396)=28.84$, $p<0.001$
Group X Time Bin	$F(44,396)=1.48$, $p=0.028$
2.5 mg/kg d-Amphetamine	
Group	$F(4,36)=7.23$, $p<0.001$
Time Bin	$F(11,396)=47.10$, $p<0.001$
Group X Time Bin	$F(44,396)=3.93$, $p<0.001$

Ibotenic versus Controls

No Drug	
Group	$F(2,25)=4.29$, $p=0.025$
Time Bin	$F(11,275)=65.7$, $p<0.001$
Group X Time Bin	$F(22,275)=0.79$, $p=0.732$
1.25 mg/kg d-Amphetamine	
Group	$F(2,25)=0.46$, $p=0.6384$
Time Bin	$F(11,275)=13.5$, $p<0.001$
Group X Time Bin	$F(22,275)=1.19$, $p=0.255$
2.5 mg/kg d-Amphetamine	
Group	$F(2,25)=0.63$, $p=0.543$
Time Bin	$F(11,275)=30.24$, $p<0.001$
Group X Time Bin	$F(22,275)=1.21$, $p=0.235$

Quinolinic versus Controls

No Drug	
Group	$F(2,24)=4.24$, $p=0.026$
Time Bin	$F(11,264)=45.57$, $p<0.001$
Group X Time Bin	$F(22,264)=0.72$, $p=0.816$
1.25 mg/kg d-Amphetamine	
Group	$F(2,24)=0.02$, $p=0.984$
Time Bin	$F(11,264)=13.65$, $p<0.001$
Group X Time Bin	$F(22,264)=0.98$, $p=0.495$
2.5 mg/kg d-Amphetamine	
Group	$F(2,24)=1.75$, $p=0.196$
Time Bin	$F(11,264)=26.05$, $p<0.001$
Group X Time Bin	$F(22,264)=1.14$, $p=0.309$

Table A-6. Follow-up test (t-tests) results for total crosses made in the activity cages with no drug or after administration of 1.25 or 2.5 mg/kg d-amphetamine. Rats that received electrolytic, ibotenic or quinolinic acid lesions of the ANT or MD were compared with each other and with controls.

Electrolytic Rats

	d-Amphetamine													
	No Drug					1.25 mg/kg					2.5 mg/kg				
	SMD	LMD	SAnt	LAnt	Cont	SMD	LMD	SAnt	LAnt	Cont	SMD	LMD	SAnt	LAnt	Cont
SMD	-	-	*	**	**	-	-	-	-	-	-	-	-	-	**
LMD		-	*	*	-		-	-	-	-		-	-	-	**
SAnt			-	-	-			-	-	-			-	-	**
LAnt				-	-				-	-				-	**

Ibotenic Rats

	d-Amphetamine								
	No Drug			1.25 mg/kg			2.5 mg/kg		
	MD	Ant	Cont	MD	Ant	Cont	MD	Ant	Cont
MD	-	*	*	-	-	-	-	-	-
Ant		-	-	-	-	-	-	-	-

Quinolinic Rats

	d-Amphetamine								
	No Drug			1.25 mg/kg			2.5 mg/kg		
	MD	Ant	Cont	MD	Ant	Cont	MD	Ant	Cont
MD	-	-	-	-	-	-	-	-	-
Ant		-	*	-	-	-	-	-	-

SMD=small electrolytic MD rats, LMD=large electrolytic MD rats, SAnt=small ANT rats, LAnt=large ANT rats, MD=rats that received MD lesions, Ant=rats that received ANT lesions, Cont=control rats that had no lesions

*=$p<0.05$
**=$p<0.01$

Table A-7. Follow-up test (t-tests) results for crosses made in the activity cages during each of the 12 ten minute time bins after administration of no drug, 1.25 or 2.5 mg/kg d-amphetamine. The electrolytic, ibotenic and quinolinic thalamic rats were all compared with controls.

Electrolytic	Time Bin (10 Minutes)											
	1	2	3	4	5	6	7	8	9	10	11	12
No Drug												
SMD	-	-	*	*	*	**	*	*	*	*	-	-
LMD	-	-	-	-	**	*	-	*	*	*	-	-
SAnt	*	*	-	-	-	-	-	*	-	-	-	-
LAnt	**	-	*	-	-	-	-	-	-	-	-	-
1.25 mg/kg d-Amphetamine												
SMD	-	-	-	-	-	-	-	-	-	-	-	-
LMD	-	-	-	-	-	-	-	-	-	-	-	-
SAnt	-	-	-	-	-	-	-	-	-	-	-	-
LAnt	-	-	-	-	*	-	-	-	-	-	-	-
2.5 mg/kg d-Amphetamine												
SMD	-	-	**	**	**	**	**	**	*	-	-	-
LMD	**	**	**	**	**	**	**	**	**	**	**	**
SAnt	**	*	-	-	-	-	-	-	-	-	-	-
LAnt	*	**	**	**	**	**	*	-	-	-	-	*

Ibotenic	Time Bin (10 Minutes)											
	1	2	3	4	5	6	7	8	9	10	11	12
No Drug												
MD	-	-	-	-	*	*	-	-	-	-	-	-
Ant	-	*	-	-	-	-	-	-	-	-	-	-
1.25 mg/kg d-Amphetamine												
MD	-	-	-	-	-	-	-	-	-	-	-	-
Ant	**	-	-	-	-	-	*	-	-	-	-	-
2.5 mg/kg d-Amphetamine												
MD	-	-	-	-	-	-	-	-	-	-	**	*
Ant	-	-	-	-	-	-	-	-	-	-	-	-

Quinolinic	Time Bin (10 Minutes)											
	1	2	3	4	5	6	7	8	9	10	11	12
No Drug												
MD	-	-	-	-	-	-	-	-	-	-	-	-
Ant	-	*	-	-	-	-	-	*	-	-	-	-
1.25 mg/kg d-Amphetamine												
MD	-	-	-	-	-	-	-	-	-	-	-	-
Ant	-	*	-	-	-	-	-	-	-	-	-	-
2.5 mg/kg d-Amphetamine												
MD	-	-	-	*	*	-	-	-	-	-	-	-
Ant	-	-	-	-	-	-	-	-	-	-	-	*

SMD=small electrolytic MD rats, LMD=large electrolytic MD rats, SAnt=small electrolytic ANT rats, LAnt=large electrolytic ANT rats, MD=rats that received MD lesions, Ant=rats that received ANT lesions, Cont=control rats that had no lesions

*=$p<0.05$, **=$p<0.01$

Table A-8. Correlation coefficients obtained when comparing changing place water maze task latencies and errors for the electrolytic, ibotenic and quinolinic thalamic rats and for all thalamic rats combined with thalamic area at three different coronal planes and averaged across the planes.

Anterior Thalamic Rats

	Electrolytic		Ibotenic		Quinolinic		All	
	Latency	Errors	Latency	Errors	Latency	Errors	Latency	Errors
Plane 1	-0.2160*	-0.1619*	-0.7914**	-0.9043**	0.2328	-0.2622	-0.4555**	-0.4716**
Plane 2	-0.5435*	-0.6509**	-0.1243	-0.3331	-0.1136	-0.5566*	-0.2528	-0.4740**
Plane 3	0.1972	0.0235	0.0526	0.0249	-0.0143	-0.4750	0.1579	-0.0612
Average	-0.1228	-0.2977	-0.2752	-0.4271	-0.0080	-0.5137*	-0.2094	-0.4602*

Medial Dorsal Thalamic Rats

	Electrolytic		Ibotenic		Quinolinic		All	
	Latency	Errors	Latency	Errors	Latency	Errors	Latency	Errors
Plane 1	-0.0796	-0.2544	-0.1255	-0.3609	0.0004	0.3448*	-0.1282	-0.0887
Plane 2	-0.0581*	-0.2910*	-0.4182	-0.6658	-0.4405	-0.8616**	-0.1229**	-0.3413**
Plane 3	-0.5435*	-0.6088**	-0.2887	-0.5542	-0.7231	-0.7767**	-0.5104**	-0.6043**
Average	-0.3475	-0.5670**	-0.3174	-0.6171	-0.6528	-0.8023**	-0.3720	-0.5362**

Plane 1 = 1.4 mm posterior to bregma, Plane 2 = 2.3 mm posterior to bregma, Plane 3 = 3.8 mm posterior to bregma

*=p<0.05, **=p<0.01

Table A-9. Correlation coefficients obtained when comparing same place water maze task latencies and errors for the electrolytic, ibotenic and quinolinic thalamic rats and for all thalamic rats combined with thalamic area at three different coronal planes and averaged across the planes.

Anterior Thalamic Rats

	Electrolytic		Ibotenic		Quinolinic		All	
	Latency	Errors	Latency	Errors	Latency	Errors	Latency	Errors
Plane 1	-0.2881	-0.0833	-0.5706	-0.7448*	-0.1114	-0.3730	-0.4926**	-0.4308*
Plane 2	-0.3627	-0.6041*	-0.4689	-0.6128	-0.2599	-0.4802	-0.2955	-0.5500**
Plane 3	0.1488	0.0170	-0.1340	-0.1331	-0.2393	-0.5534	0.0794	-0.0967
Average	-0.1431	-0.2448	-0.4698	-0.5940	-0.2425	-0.5240	-0.2956	-0.5009**

Medial Dorsal Thalamic Rats

	Electrolytic		Ibotenic		Quinolinic		All	
	Latency	Errors	Latency	Errors	Latency	Errors	Latency	Errors
Plane 1	-0.2039	-0.4719	-0.4491	-0.4315	0.0793	0.5896	-0.1927	-0.0116
Plane 2	0.1137	-0.0974*	-0.3201	-0.2143	-0.6232	-0.7179	0.0544*	-0.1042*
Plane 3	-0.4708	-0.5577	-0.3926	-0.3430	-0.5140	-0.3116	-0.3914	-0.3992
Average	-0.2222	-0.4578	-0.4741	-0.4094	-0.6008	-0.3840	-0.2264	-0.2692

Plane 1 = 1.4 mm posterior to bregma, Plane 2 = 2.3 mm posterior to bregma, Plane 3 = 3.8 mm posterior to bregma

*=p<0.05, **=p<0.01

Table A-10. Correlation coefficients obtained when comparing total crosses in the activity cages after administration of either no drug or 1.25 or 2.5 mg/kg d-amphetamine for the electrolytic, ibotenic and quinolinic thalamic rats and for all thalamic rats combined with thalamic area at three different coronal planes and averaged across planes.

Anterior Thalamic Rats

	Electrolytic			Ibotenic			Quinolinic			All		
		d-Amphetamine (mg/kg)			d-Amphetamine (mg/kg)			d-Amphetamine (mg/kg)			d-Amphetamine (mg/kg)	
	No Drug	1.25	2.5	No Drug	1.25	2.5	No Drug	1.25	2.5	No Drug	1.25	2.5
Plane 1	0.3354	0.0774	0.4048	0.1384	0.6231	0.4322	-0.5758	-0.5485	0.3349	0.1464	-0.0387	0.1614
Plane 2	0.2543	-0.3957	-0.2678	0.0010	0.2596	0.0466	-0.5823	-0.6523	0.1221	-0.1342	-0.2447	-0.0571
Plane 3	0.0606	-0.3095	0.1845	0.4046	0.6300	0.3219	-0.0086	-0.0927	-0.4118	0.1084	-0.1235	0.1277
Average	0.3295	-0.3949	0.2983	0.2319	0.6131	0.3041	-0.4621	-0.5192	0.0228	0.0697	-0.2097	0.1243

Medial Dorsal Thalamic Rats

	Electrolytic			Ibotenic			Quinolinic			All		
		d-Amphetamine (mg/kg)			d-Amphetamine (mg/kg)			d-Amphetamine (mg/kg)			d-Amphetamine (mg/kg)	
	No Drug	1.25	2.5	No Drug	1.25	2.5	No Drug	..25	2.5	No Drug	1.25	2.5
Plane 1	-0.2432	0.3918	0.3606	-0.3015	0.5703	0.4754	0.2648	0.2007	0.1050	0.0885	0.3108	0.0016
Plane 2	0.4779	-0.2054	-0.3615	-0.2215	0.3192	0.2400	0.2896	-0.2831	-0.1813	0.2572	-0.1870	-0.2624
Plane 3	-0.2205	-0.3708	-0.0519	-0.2741	0.4975	0.2787	0.6114	-0.1035	-0.3161	0.0852	-0.1943	-0.1168
Average	0.1396	-0.2556	-0.1893	-0.3247	0.5708	0.4145	0.5853	-0.1491	-0.2495	0.2207	-0.1163	-0.2130

Plane 1 = 1.4 mm posterior to bregma, Plane 2 = 2.3 mm posterior to bregma, Plane 3 = 3.8 mm posterior to bregma

*=p<0.05, **=p<0.01

Table A-11. Correlation coefficients obtained when comparing changing place water maze task latencies and errors for the electrolytic, ibotenic and quinolinic ANT rats and for all ANT rats combined with ratings of the amount of damage to several thalamic nuclei.

	Electrolytic		Ibotenic		Quinolinic		All	
	Latency	Errors	Latency	Errors	Latency	Errors	Latency	Errors
AD	-0.5135	-0.3751	-0.7441 *	-0.8369 **	-0.0540	-0.3114	-0.5561 **	-0.5453 **
AV	-0.3202	-0.1897	-0.8454 **	-0.8492 **	-0.1765	-0.4176	-0.5541 **	-0.5593 **
AM	0.1111	0.2675	-0.7407 *	-0.9318 **	-0.6209	-0.6845 *	-0.0964	-0.4076 *
HAB	0.0859	0.1704	-0.9650 **	-0.8712 **	-0.4018	-0.8287 *	-0.1674	-0.2552
LD	-0.0994	-0.0266	-0.7845 *	-0.6004	-0.2612	-0.0191	-0.0876	-0.1921
LP	0.2476	0.1746	0.0000	0.0000	0.0471	0.0837	0.1602	-0.0197
MD	0.0717	0.1038	-0.8805 **	-0.7273 *	-0.6585	-0.5405	-0.0476	-0.3052
VAL	0.0797	0.1136	-0.8359 **	-0.6566	-0.4190	-0.3035	0.0094	-0.1623
VB	0.1438	0.0367	0.0000	0.0000	-0.4607 *	-0.1726	0.0511	-0.0675
SM	-0.0744	0.0968	-0.7276 *	-0.7388 **	-0.8256 *	-0.7438 *	-0.4440 *	-0.4232 **
PVT	-0.0969	-0.0443	-0.7396 *	-0.8971 *	-0.8270 *	-0.8060 *	-0.3689 *	-0.5611
PT	-0.2576	0.2503	-0.6982 **	-0.7944 *	-0.6342 *	-0.5893	-0.3905	-0.3407
CM	0.0926	0.1037	-0.8534 **	-0.7552 *	-0.7534 *	-0.7148 *	-0.0221	-0.3178
RH	0.1438	0.0367	-0.8535 **	-0.6586	-0.7353 *	-0.7874 *	0.0104	-0.3206
RE	0.1438	0.0367	-0.3438	-0.2704	-0.8381	-0.7526	0.0480	-0.2348
SMT	0.1438	0.0367	-0.3438	-0.2704	-0.6593	-0.6560	0.0798	-0.2182
VM	0.1439	0.0367	-0.3438	-0.2704	-0.6593	-0.6560	0.0798	-0.2182
PCCLR	0.2350	0.2002	-0.5553	-0.4365	-0.7209	-0.6043	0.0693	-0.2200

AD=anterior dorsal thalamic nucleus, AV=anterior ventral thalamic nucleus, AM=anterior medial thalamic nucleus, HAB=habenula, LD=lateral dorsal thalamic nucleus, LP=lateral posterior thalamic nucleus, MD=medial dorsal thalamic nucleus, VAL=ventral anterior lateral thalamic nucleus, VB=ventrobasal thalamic nuclei, SM=stria medullaris, PVT=paraventricular thalamic nucleus, PT=paratenial thalamic nucleus, CM=centromedial thalamic nucleus, RH=rhomboid thalamic nucleus, RE=reuniens thalamic nucleus, SMT=subthalamic nucleus, VM=ventral medial thalamic nucleus, PCCLR=paracentral thalamic nucleus and claustrum

*=p<0.05, **=p<0.01

Table A-12. Correlation coefficients obtained when comparing changing place water maze task latencies and errors for the electrolytic, ibotenic and quinolinic MD rats and for all MD rats combined with ratings of amount of damage to several thalamic nuclei.

	Electrolytic		Ibotenic		Quinolinic		All	
	Latency	Errors	Latency	Errors	Latency	Errors	Latency	Errors
AD	0.1111	-0.1657	-0.0200	-0.0783	-0.5509	-0.8258*	0.0577	-0.3036
AV	0.0346	-0.2407	-0.1624	-0.3324	-0.5818*	-0.8259*	-0.0042	-0.3610
AM	0.1837	-0.0174	-0.4064	-0.5499	-0.7630*	-0.7119	0.0059	-0.1853
HAB	-0.7819**	-0.8258**	0.5087*	0.3638	-0.3186	0.0669	-0.6321**	-0.4692*
LD	-0.5609*	-0.6713**	-0.8177*	-0.8409*	-0.8090*	-0.8883**	-0.3904	-0.5448*
LP	-0.3735	-0.4430	-0.6871	-0.8344*	-0.7834*	-0.4405	-0.3287	-0.3537
MD	-0.5664*	-0.7226**	-0.1822	-0.1453	-0.6707	-0.8255*	-0.4893*	-0.5798**
VAL	-0.3168	-0.4386	0.2499	0.2981	-0.3475	-0.6051	-0.1588	-0.1850
VB	-0.4951	-0.5515*	0.2473	0.3513	-0.4091	-0.5324	-0.1456	-0.1446
SM	-0.4130	-0.5909*	0.0766	-0.1136	-0.2312	0.0603	-0.3130	-0.4223*
PVT	-0.3738	-0.5270	-0.6907*	-0.7231*	-0.7569*	-0.4859	-0.2913	-0.5114*
PT	0.0188	-0.1761	-0.5977*	-0.7296*	-0.1585	-0.8545*	-0.0012	-0.3855**
CM	-0.4817	-0.6445*	-0.2368	-0.5056	-0.4701	-0.5888	-0.4438*	-0.5490*
RH	-0.4874**	-0.5635**	-0.4507	-0.6719*	-0.7161*	-0.4689	-0.4297**	-0.4133*
RE	-0.6970**	-0.7193**	-0.2589	-0.4292	-0.5091	-0.6308	-0.5014*	-0.4350
SMT	-0.6874*	-0.6703*	-0.0578	-0.1052	-0.7091	-0.4130	-0.4250	-0.2915
VM	-0.5503*	-0.6090*	-0.0411	-0.0279	-0.7230*	-0.4566	-0.2827**	-0.2277**
PCCLR	-0.5706*	-0.6414*	-0.3460	-0.4211	-0.7427*	-0.8278*	-0.5417*	-0.5744*

AD=anterior dorsal thalamic nucleus, AV=anterior ventral thalamic nucleus, AM=anterior medial thalamic nucleus, HAB=habenula, LD=lateral dorsal thalamic nucleus, LP=lateral posterior thalamic nucleus, MD=medial dorsal thalamic nucleus, VAL=ventral anterior lateral thalamic nucleus, VB=ventrobasal thalamic nuclei, SM=stria medullaris, PVT=paraventricular thalamic nucleus, PT=paratenial thalamic nucleus, CM=centromedial thalamic nucleus, RH=rhomboid thalamic nucleus, RE=reuniens thalamic nucleus, SMT=subthalamic nucleus, VM=ventral medial thalamic nucleus, PCCLR=paracentral thalamic nucleus and claustrum

*=p<0.05, **=p<0.01

Table A-13. Correlation coefficients obtained when comparing same place water maze task latencies and errors for the electrolytic, ibotenic and quinolinic ANT rats and for all ANT rats combined with ratings of the amount of damage to several thalamic nuclei.

	Electrolytic		Ibotenic		Quinolinic		All	
	Latency	Errors	Latency	Errors	Latency	Errors	Latency	Errors
AD	-0.1029	-0.6219*	-0.6184*	-0.8099**	-0.5247	-0.3153	-0.4728**	-0.6126**
AV	0.0641	-0.5055	-0.7687**	-0.8718**	-0.6254*	-0.4486*	-0.4921**	-0.6652**
AM	0.1238	-0.0353	-0.6074*	-0.8615**	-0.8003*	-0.7737*	-0.1033	-0.4227
HAB	-0.0490	-0.0735	-0.8165**	-0.8318**	-0.3333	-0.7160*	-0.2594	-0.3314
LD	-0.2695	-0.1862	-0.3825	-0.3521	-0.3250	-0.1557	-0.1271	-0.1853
LP	-0.0620	-0.0831	0.0000	0.0000	0.0005*	-0.0944	-0.0116	-0.1091
MD	-0.2029	-0.0752	-0.6497	-0.6538	-0.7813*	-0.6454	-0.1254	-0.2658
VAL	-0.1753	-0.1803	-0.4979	-0.4607	-0.7385*	-0.4116	-0.1333	-0.2186
VB	-0.1556	-0.1340	0.0000*	0.0000**	-0.8639*	-0.2968*	-0.1969**	-0.1582**
SM	-0.1610	-0.0904	-0.7939*	-0.8602**	-0.8225*	-0.7839**	-0.5553**	-0.5373**
PVT	-0.3150	-0.2503	-0.7168	-0.9142**	-0.8524*	-0.8681	-0.5208**	-0.6309*
PT	-0.0050	-0.0378	-0.6865**	-0.8647**	-0.8463**	-0.5913**	-0.3071	-0.4260
CM	-0.1431	-0.0556	-0.8375**	-0.8460**	-0.9017*	-0.8860**	-0.1527	-0.3557*
RH	-0.1556	-0.1340	-0.9685*	-0.8569	-0.8432**	-0.8776*	-0.1624	-0.3742
RE	-0.1556	-0.1340	-0.7688*	-0.6655	-0.8700**	-0.7988*	-0.1621	-0.3064
SMT	-0.1556	-0.1340	-0.7688*	-0.6655	-0.9052**	-0.8042*	-0.1199	-0.2915
VM	-0.1556	-0.1340	-0.7688**	-0.6655*	-0.9052**	-0.8042*	-0.1199	-0.2915
PCCLR	-0.0485	-0.0844	-0.8973	-0.7841	-0.9302	-0.8458	-0.1350	-0.3522

AD=anterior dorsal thalamic nucleus, AV=anterior ventral thalamic nucleus, AM=anterior medial thalamic nucleus, HAB=habenula, LD=lateral dorsal thalamic nucleus, LP=lateral posterior thalamic nucleus, MD=medial dorsal thalamic nucleus, VAL=ventral anterior lateral thalamic nucleus, VB=ventrobasal thalamic nuclei, SM=stria medullaris, PVT=paraventricular thalamic nucleus, PT=paratenial thalamic nucleus, CM=centromedial thalamic nucleus, RH=rhomboid thalamic nucleus, RE=reuniens thalamic nucleus, SMT=subthalamic nucleus, VM=ventral medial thalamic nucleus, PCCLR=paracentral thalamic nucleus and claustrum

*=p<0.05, **=p<0.01

Table A-14. Correlation coefficients obtained when comparing same place water maze task latencies and errors for the electrolytic, ibotenic and quinolinic MD rats and for all MD rats combined with ratings of amount of damage to several thalamic nuclei.

	Electrolytic		Ibotenic		Quinolinic		All	
	Latency	Errors	Latency	Errors	Latency	Errors	Latency	Errors
AD	0.1891	0.0091	-0.5628	-0.5797	-0.1540	-0.3981	0.1261	-0.3210
AV	0.1441	-0.0581	-0.6492	-0.6066	-0.3573	-0.6393	0.0929	-0.3661
AM	0.2295	0.0926	-0.5366	-0.4633	-0.6933	-0.6571	0.1195	-0.1323
HAB	-0.5520*	-0.5274	0.4230*	0.4293	0.0989	0.1600	-0.4707*	-0.0948
LD	-0.4483	-0.5116	-0.7896*	-0.7434	-0.7073**	-0.6712	-0.2383	-0.4518*
LP	-0.3153	-0.3129	-0.6109	-0.5115	-0.9005**	-0.5817	-0.2066	-0.2759
MD	-0.4267	-0.5066	0.1572	0.1829	-0.4515	-0.3582	-0.3118	-0.2372
VAL	-0.1379	-0.1081	-0.1055	-0.1728	-0.4522	-0.3271	-0.0607	-0.0200
VB	-0.2322	-0.1290	-0.0569	-0.0636	-0.6191	-0.4145	-0.0391	-0.0469
SM	-0.2300	-0.3366	0.0363	0.0520	0.3377	0.4509	-0.1869	-0.1658*
PVT	-0.2245	-0.3108	-0.7441*	-0.7100*	-0.5653	-0.4277	-0.1515	-0.4679
PT	0.1025	-0.0489	-0.8515*	-0.7934*	-0.1005	-0.4413	0.0664	-0.3150
CM	-0.2793	-0.3570	-0.3292	-0.2813	-0.5858	-0.5496	-0.2713	-0.2381
RH	-0.3693	-0.3547	-0.4845	-0.4213	-0.5975	-0.4092	-0.3054*	-0.1563
RE	-0.5197	-0.4102	-0.5296	-0.4873	-0.6041	-0.3762	-0.3829*	-0.1621
SMT	-0.4757	-0.2891	-0.4185	-0.5074	-0.6161	-0.3978	-0.2696	-0.0866
VM	-0.2876	-0.2426	-0.2377	-0.3429	-0.6006	-0.3787	-0.1105	-0.0914
PCCLR	-0.4151	-0.4247	-0.0220	0.0390	-0.6373	-0.5566	-0.3472	-0.2516

AD=anterior dorsal thalamic nucleus, AV=anterior ventral thalamic nucleus, AM=anterior medial thalamic nucleus, HAB=habenula, LD=lateral dorsal thalamic nucleus, LP=lateral posterior thalamic nucleus, MD=medial dorsal thalamic nucleus, VAL=ventral anterior lateral thalamic nucleus, VB=ventrobasal thalamic nuclei, SM=stria medullaris, PVT=paraventricular thalamic nucleus, PT=paratenial thalamic nucleus, CM=centromedial thalamic nucleus, RH=rhomboid thalamic nucleus, RE=reuniens thalamic nucleus, SMT=subthalamic nucleus, VM=ventral medial thalamic nucleus, PCCLR=paracentral thalamic nucleus and claustrum

*=p<0.05, **=p<0.01

Table A-15. Correlation coefficients obtained when comparing total crosses made in the activity cages with ratings of the amount of damage to several thalamic nuclei. Rats had either electrolytic, ibotenic acid or quinolinic acid lesions of the ANT and were administered either no drug or 1.25 or 2.5 mg/kg d-amphetamine.

	Electrolytic			Ibotenic			Quinolinic			All		
		d-Amphetamine (mg/kg)			d-Amphetamine (mg/kg)			d-Amphetamine (mg/kg)			d-Amphetamine (mg/kg)	
	No Drug	1.25	2.5	No Drug	1.25	2.5	No Drug	1.25	2.5	No Drug	1.25	2.5
AD	0.1979	-0.1629	-0.4858	0.2084	0.3797	0.3310	-0.7644*	-0.6965	0.3505	0.0119	-0.2290	-0.0946
AV	0.1883	-0.1562	-0.4552	0.2520	0.3287	0.3586	-0.7113	-0.5793	0.1874	0.0484	-0.2228	-0.1616
AM	0.5650	-0.0640	-0.0542	-0.1638	0.1306	0.2009	-0.3619	-0.0978	-0.3960	0.0479	0.0068	-0.0516
HAB	0.0510	-0.4010	-0.3042	0.1957	0.2693	0.2276	-0.3309	-0.3192	-0.3321	0.0489	-0.3487	-0.2572
LD	0.1705	-0.4758	-0.3429	0.3503	0.2099	0.2414	0.1858	0.1102	-0.3076	0.0846	-0.1642	-0.1824
LP	0.0949	-0.4028	-0.1844	0.0000	0.0000	0.0000	0.6884	0.5258	-0.6408	0.1745	-0.1277	-0.2348
MD	0.2796	-0.2918	-0.1653	0.5238	0.4752	0.2623	-0.2951	-0.0791	-0.3493	0.0868	-0.0027	0.0054
VAL	0.2174	-0.3182	-0.1580	0.2567	0.1809	0.1359	-0.4798*	-0.3597	0.0062	-0.0201	-0.1867	-0.0668
VB	0.0764	-0.2419	-0.1967	0.0000	0.0000	0.0000	-0.7568*	-0.3928	0.3123	-0.0587	-0.2328	-0.1210
SM	0.2619	-0.2713	-0.2574	0.1504	0.3280	0.4757	-0.4328	-0.1057	-0.3580	0.1538	-0.2410	-0.2592
PVT	0.4606	-0.4456	-0.0209	-0.0898	0.2587	0.3550	-0.5237	-0.0824	-0.3302	0.0627	-0.2795	-0.0627
PT	0.2067	-0.1398	-0.4987	0.0713	0.1528	0.0032	-0.5411	-0.2010	-0.1690	0.0035	-0.1245	-0.2842
CM	0.0844	-0.2183	-0.2218	0.4228	0.4674	0.2182	-0.5089	-0.0224	-0.3154	-0.1117	0.0262	-0.0335
RH	0.0764	-0.2419	-0.1967	0.4477	0.3789	0.2213	-0.5212	-0.0728	-0.3261	-0.1406	-0.0183	-0.0534
RE	0.0764	-0.2419	-0.1967	0.2303	0.2322	0.1610	-0.5264	-0.0544	-0.2989	-0.1680	-0.0835	-0.1271
SMT	0.0764	-0.2419	-0.1967	0.2303	0.2322	0.1610	-0.5423	-0.0904	-0.2478	-0.2042	-0.0514	-0.0861
VM	0.0764	-0.2419	-0.1967	0.2303	0.2322	0.1610	-0.5423	-0.0904	-0.2478	-0.2042	-0.0514	-0.0861
PCCLR	0.1255	-0.5037	-0.1712	0.2958	0.2706	0.1958	-0.5350	-0.0361	-0.2294	-0.1392	-0.1453	-0.0487

AD=anterior dorsal thalamic nucleus, AV=anterior ventral thalamic nucleus, AM=anterior medial thalamic nucleus, HAB=habenula, LD=lateral dorsal thalamic nucleus, LP=lateral posterior thalamic nucleus, MD=medial dorsal thalamic nucleus, VAL=ventral anterior lateral thalamic nucleus, VB=ventrobasal thalamic nuclei, SM=stria medullaris, PVT=paraventricular thalamic nucleus, PT=paratenial thalamic nucleus, CM=centromedial thalamic nucleus, RH=rhomboid thalamic nucleus, RE=reuniens thalamic nucleus, SMT=subthalamic nucleus, VM=ventral medial thalamic nucleus, PCCLR=paracentral thalamic nucleus and claustrum

*=p<0.05, **=p<0.01

Table A-16. Correlation coefficients obtained when comparing total crosses made in the activity cages with ratings of the amount of damage to several thalamic nuclei. Rats had either electrolytic, ibotenic acid or quinolinic acid lesions of the MD and were administered either no drug or 1.25 or 2.5 mg/kg d-amphetamine.

	Electrolytic			Ibotenic			Quinolinic			All		
		d-Amphetamine (mg/kg)			d-Amphetamine (mg/kg)			d-Amphetamine (mg/kg)			d-Amphetamine (mg/kg)	
	No Drug	1.25	2.5	No Drug	1.25	2.5	No Drug	1.25	2.5	No Drug	1.25	2.5
AD	0.3631	-0.2660	-0.0073	-0.6043	0.3445	0.2861	0.5182	0.1695	-0.1176	0.1342	0.0121	0.2318
AV	0.4019	-0.3032	-0.1532	-0.7833	0.2790	0.5774	0.3639	0.0296	-0.1285	0.0792	-0.0759	0.1733
AM	0.6842	-0.2126	-0.3221	-0.4182	0.0525	0.3505	0.3992	-0.1069	-0.2468	0.2403	-0.1428	-0.0800
HAB	-0.4753	-0.5816	-0.2524	0.2277	0.7491	0.3352	0.1280	0.2602	0.2029	-0.0151	-0.2266	-0.3704
LD	-0.1516	-0.2757	-0.3376	-0.2524	-0.1112	-0.3169	0.5395	-0.0506	-0.1499	-0.0591	-0.1542	-0.0535
LP	-0.1575	-0.0991	-0.2644	-0.2869	0.0335	0.0624	0.2812	-0.1827	-0.0434	-0.1343	-0.1164	-0.0442
MD	-0.0618	-0.6563	-0.1734	0.1724	-0.3795	-0.2345	0.6178	-0.0496	-0.3216	0.2305	-0.3677	-0.2815
VAL	0.2079	-0.4323	-0.5345	-0.0954	0.2700	0.0542	0.2391	-0.4954	-0.5986	-0.0340	-0.3054	-0.2951
VB	0.0409	-0.6664**	-0.6797	-0.4477	-0.2444	0.2636	0.2150	-0.4661*	-0.4750	-0.1828	-0.3264	-0.1443
SM	0.1365	-0.6954**	-0.4535	0.0932	0.7249	0.0925	0.4854	0.7512	0.5495	0.2227	-0.1436	-0.2263
PVT	0.2280	-0.5304	-0.3593	-0.3403	0.0351	-0.3351	0.1899	-0.3880	-0.5521	0.1117	-0.3550	-0.0972
PT	0.6081	-0.4097	-0.3424	-0.6726	0.1668	0.0684	0.4023	0.0347	-0.1302	0.3432	-0.1790	-0.0547
CM	0.1281	-0.5373	-0.2445	-0.2166	0.5662	0.2697	0.3898	0.0202	-0.0546	0.1711	-0.2112	-0.2133
RH	-0.0355	-0.5379	-0.3167	-0.3417	0.2156	0.2096	0.4018	-0.0285	-0.2165	-0.0517	-0.2578	-0.2404
RE	-0.1709	-0.4469	-0.3918	-0.6339	0.2523	0.2579	0.5485	-0.0027	-0.0838	-0.1395	-0.2085	-0.2466
SMT	-0.1488	-0.3615	-0.5020	-0.2401	0.1452	0.0485	0.2556	-0.2671	-0.4270	-0.1569	-0.2455	-0.2898
VM	0.0488	-0.5095	-0.5932	0.1460	0.0646	-0.0916	0.2984	-0.2610	-0.4408	-0.1014	-0.2788	-0.2226
PCCLR	-0.1461	-0.5202	-0.1688	0.1104	-0.0110	-0.2296	0.4804	-0.1986	-0.3500	0.0957	-0.3584	-0.2856

AD=anterior dorsal thalamic nucleus, AV=anterior ventral thalamic nucleus, AM=anterior medial thalamic nucleus, HAB=habenula, LD=lateral dorsal thalamic nucleus, LP=lateral posterior thalamic nucleus, MD=medial dorsal thalamic nucleus, VAL=ventral anterior lateral thalamic nucleus, VB=ventrobasal thalamic nuclei, SM=stria medullaris, PVT=paraventricular thalamic nucleus, PT=paratenial thalamic nucleus, CM=centromedial thalamic nucleus, RH=rhomboid thalamic nucleus, RE=reuniens thalamic nucleus, SMT=subthalamic nucleus, VM=ventral medial thalamic nucleus, PCCLR=paracentral thalamic nucleus and claustrum

*=p<0.05, **=p<0.01

Table A-17. Follow-up test (t-tests) results obtained when comparing latencies and errors of the anterior and medial dorsal thalamic rats with latencies and errors of controls on the retention, one-trial learning and performance components of the changing place water maze task.

	Retention		One-Trial Learning		Performance	
	Latency	Errors	Latency	Errors	Latency	Errors
Anterior	*	**	*	**	**	**
Medial Dorsal	-	**	*	**	**	**

* = significantly different from controls, p=0.05
** = significantly different from controls, p=0.01

Table A-18. Correlation coefficients obtained when comparing latencies and errors on the retention, one-trial learning and performance components of the changing place water maze task with area of the thalamus at three different coronal planes and averaged across the three planes. The rats had either electrolytic, ibotenic acid or quinolinic acid lesions of the ANT.

Retention

	Electrolytic		Ibotenic		Quinolinic		All	
	Latency	Errors	Latency	Errors	Latency	Errors	Latency	Errors
Plane 1	-0.2969	-0.1106	0.2086	0.5887*	0.4967	-0.1055	0.1253	0.2413
Plane 2	-0.3203	0.0321	0.8244*	0.7263*	0.3192	-0.5742	0.3186	0.0992
Plane 3	0.1657	0.2570	0.1738	0.3985	0.5495	-0.3656	0.1468	0.1697
Average	-0.1166	0.1969	0.5587	0.7287*	0.4663	-0.4505	0.2959	0.2580

One-Trial Learning

	Electrolytic		Ibotenic		Quinolinic		All	
	Latency	Errors	Latency	Errors	Latency	Errors	Latency	Errors
Plane 1	-0.1942	-0.2820	-0.7056*	-0.7092*	0.4882	-0.2152	-0.2624	-0.2557
Plane 2	-0.6719**	-0.4735	-0.0877	-0.3260	0.0169	-0.5254	-0.2773	-0.3351
Plane 3	0.2305	-0.0040	0.1540	0.1576	-0.0454	-0.4646	0.1809	-0.0019
Average	-0.1253	-0.3253	-0.1835	-0.3027	0.1168	-0.4818	-0.1239	-0.2656

Performance

	Electrolytic		Ibotenic		Quinolinic		All	
	Latency	Errors	Latency	Errors	Latency	Errors	Latency	Errors
Plane 1	-0.1870	-0.0282	-0.8234*	-0.8901**	-0.1186	-0.2488	-0.4891**	-0.4554*
Plane 2	-0.4935	-0.4869	-0.3268	-0.3615	-0.2927	-0.4594	-0.2908	-0.4222
Plane 3	0.1751	-0.0329	-0.0121	-0.0273	-0.2666	-0.4098	0.1255	-0.0847
Average	-0.1104	-0.2208	-0.4170	-0.4616	-0.2705	-0.4376	-0.2622	-0.4443*

Plane 1 = 1.4 mm posterior to bregma, Plane 2 = 2.3 mm posterior to bregma, Plane 3 = 3.8 mm posterior to bregma

*=p<0.05, **=p<0.01

Table A-19. Correlation coefficients obtained when comparing latencies and errors on the retention, one-trial learning and performance components of the changing place water maze task with area of the thalamus at three different coronal planes and averaged across the three planes. The rats had either electrolytic, ibotenic acid or quinolinic acid lesions of the MD.

Retention

	Electrolytic		Ibotenic		Quinolinic		All	
	Latency	Errors	Latency	Errors	Latency	Errors	Latency	Errors
Plane 1	0.1702	0.0585	0.2613	-0.5121*	-0.4585*	0.2675	-0.0353	-0.0731
Plane 2	-0.1792	-0.2581	-0.2671	-0.7820*	0.8062*	0.0618	-0.1544	-0.3114
Plane 3	-0.2955	-0.3080	-0.2131	-0.7392*	0.3213	0.3996	-0.1901	-0.1035
Average	-0.2416	-0.3212	-0.0535	-0.7998*	0.4726	0.3440	-0.1984	-0.2572

One-Trial Learning

	Electrolytic		Ibotenic		Quinolinic		All	
	Latency	Errors	Latency	Errors	Latency	Errors	Latency	Errors
Plane 1	-0.0079	0.0296	0.4772	0.0366	-0.0922	0.5150	0.0086	0.2073
Plane 2	-0.1531	-0.2768	-0.2132	-0.5762	-0.3384	-0.6460	-0.1907*	-0.3539*
Plane 3	-0.4851	-0.4519	-0.0394	-0.7092	-0.7360	-0.4800	-0.4687*	-0.4292*
Average	-0.3627	-0.4168	0.1332	-0.4581	-0.6345	-0.4678	-0.3494	-0.3654

Performance

	Electrolytic		Ibotenic		Quinolinic		All	
	Latency	Errors	Latency	Errors	Latency	Errors	Latency	Errors
Plane 1	-0.1218	-0.2939	-0.2913	-0.4106	0.0796	0.2933*	-0.1554	-0.1218
Plane 2	-0.0257*	-0.2833*	-0.4256	-0.5932	-0.5572	-0.8692**	-0.1012**	-0.3070**
Plane 3	-0.5682*	-0.6197*	-0.3076	-0.4225	-0.7448	-0.8313**	-0.5359*	-0.6059**
Average	-0.3483	-0.5757*	-0.4050	-0.5643	-0.7029	-0.8531**	-0.3804*	-0.5269**

Plane 1 = 1.4 mm posterior to bregma, Plane 2 = 2.3 mm posterior to bregma, Plane 3 = 3.8 mm posterior to bregma

*=p<0.05, **=p<0.01

Table A-20. Correlation coefficients obtained when comparing trials and errors accumulated by the ibotenic and quinolinic MD rats during acquisition and retention of stage three of the configural string pulling task with area of the thalamus at three different coronal planes and averaged across the three planes.

	Ibotenic				Quinolinic				Both Groups			
	Acquisition		Retention		Acquisition		Retention		Acquisition		Retention	
	Trials	Errors	Trials	Errors	Trials	Errors	Trials	Errors	Trials	Errors	Trials	Errors
Plane1	0.6513	0.7567*	0.4168	0.4602	-0.5535	-0.4682	-0.7182*	-0.7104*	0.0729	0.1393	-0.3209	-0.3096
Plane2	-0.8886**	-0.9197**	-0.0300	0.0544	-0.3550	-0.3299	-0.8844**	-0.8813**	-0.6131*	-0.6009*	-0.8592**	-0.8698**
Plane3	-0.9793**	-0.9393**	-0.4598	-0.3653	-0.7256*	-0.7522*	-0.6927*	-0.7072*	-0.8206**	-0.8094**	-0.7488**	-0.7582**
Average	-0.8936**	-0.8467*	-0.1292	0.0119	-0.6104	-0.5908	-0.9533**	-0.9542**	-0.7319**	-0.6999**	-0.9023**	-0.9099**

Plane1=1.4 mm posterior to bregma, Plane2=2.3 mm posterior to bregma, Plane3=3.8 mm posterior to bregma

*=p<0.05, **=p<0.01

Table A-21. Correlation coefficients obtained when comparing latencies and errors of the ibotenic and quinolinic MD rats on the changing place water maze task with area of the thalamus at three different coronal planes and averaged across the three planes.

	Ibotenic		Quinolinic		Both Groups	
	Latency	Errors	Latency	Errors	Latency	Errors
Plane1	0.1566	-0.0734	-0.3773	-0.3110	-0.1593	-0.1598
Plane2	0.2029	0.3921	-0.6411*	-0.5242	-0.4896**	-0.1921
Plane3	0.0040	0.2428	-0.3939	-0.3621	-0.3798*	-0.1719
Average	0.1705	0.3318	-0.5646*	-0.4800	-0.4830**	-0.2256

Plane1=1.4 mm posterior to bregma, Plane2=2.3 mm posterior to bregma, Plane3=3.8 mm posterior to bregma

*=p<0.05, **=p<0.01

Table A-22. Correlation coefficients obtained when comparing total crosses made by the ibotenic or quinolinic MD rats in the activity cages after administration of either no drug or 1.25 or 2.5 mg/kg d-amphetamine with area of the thalamus at three different coronal planes and averaged across the three planes.

	Ibotenic			Quinolinic			Both Groups		
	No Drug Baseline	d-Amphetamine 1.25 mg/kg	d-Amphetamine 2.5 mg/kg	No Drug Baseline	d-Amphetamine 1.25 mg/kg	d-Amphetamine 2.5 mg/kg	No Drug Baseline	d-Amphetamine 1.25 mg/kg	d-Amphetamine 2.5 mg/kg
Plane1	-0.0004	0.2826	-0.0562	-0.1987	-0.0826	0.0418	-0.1045	0.1534	0.0455
Plane2	-0.4866	-0.1277	0.4309	-0.3334	-0.3368	0.0026	-0.3592	-0.2210	-0.0304
Plane3	-0.3694	0.2683	0.5133	-0.0283	-0.0699	-0.4035	-0.1739	0.0740	-0.1378
Average	-0.4782	0.1625	0.5045	-0.2166	-0.2060	-0.1654	-0.3012	-0.0426	-0.0701

Plane1=1.4 mm posterior to bregma, Plane2=2.3 mm posterior to bregma, Plane3=3.8 mm posterior to bregma

*=p<0.05, **=p<0.01

Table A-23. Correlation coefficients obtained when comparing trials and errors accumulated by the ibotenic and quinolinic MD rats during acquisition and retention of stage three of the configural string pulling task with ratings of the amount of damage to several thalamic nuclei.

	Ibotenic				Quinolinic				Both Groups			
	Acquisition		Retention		Acquisition		Retention		Acquisition		Retention	
	Trials	Errors	Trials	Errors	Trials	Errors	Trials	Errors	Trials	Errors	Trials	Errors
AD	-0.4476	-0.5566*	-0.4441	-0.4004	0.0050	-0.0678	-0.1742	-0.3071*	-0.1902*	-0.2587*	-0.2029*	-0.2414*
AV	-0.6616	-0.7609*	-0.4991*	-0.4482	-0.4447	-0.5007	-0.7137*	-0.8258*	-0.5355*	-0.5895*	-0.5711*	-0.6035*
AM	-0.5745	-0.6580*	-0.7080*	-0.6196*	-0.4242	-0.4606	-0.4511	-0.5110	-0.5235*	-0.5630*	-0.4737	-0.4657
HAB	0.4817	0.3537	0.2048	0.2201	-0.2042	-0.1879	0.5458*	0.4791	-0.1499	-0.1786	0.3134*	0.2912*
LD	0.5994*	0.5898*	0.8485**	0.8148**	-0.4804	-0.5720*	-0.2381	-0.2175	-0.3227	-0.3632	-0.6136*	-0.6395*
LP	0.7518**	0.7956**	0.1080	0.0905	-0.2602	-0.2541	-0.0354	-0.0214	-0.2087	-0.2062	-0.5558*	-0.5771*
MD	-0.1525	-0.3724	-0.8281**	-0.8194**	-0.3401*	-0.2716*	0.0603	0.1262	-0.3467*	-0.3804*	-0.5654*	-0.5629*
VAL	0.0000	0.0000	0.1468	0.3581	-0.7632**	-0.8104**	0.1271	0.0889	-0.5843*	-0.6172*	-0.4714	-0.5037*
VB	-0.0999	-0.2648	0.2163	0.2340	-0.5999*	-0.6966**	0.2633	0.3228	-0.4699	-0.5213*	-0.5015*	-0.5170*
SM	0.2063	0.1641	0.5137	0.5616*	-0.6564*	-0.7495**	0.2054	0.2908	-0.1536	-0.2215*	0.1084	0.1390
PVT	-0.5806*	-0.5794*	-0.3685	-0.2647	-0.4449*	-0.5062*	-0.2190	-0.2976	-0.4962*	-0.5406*	-0.1263	-0.1468
PT	-0.0533	-0.3025	-0.4158	-0.3136	-0.7533**	-0.7416**	-0.2836	-0.2663	-0.4736*	-0.5565*	-0.3547*	-0.3347*
CM	-0.0646	-0.1758*	-0.5875*	-0.4478	-0.4278	-0.5063*	-0.2368	-0.1807	-0.2920*	-0.3833*	-0.5635*	-0.5513*
RH	-0.8392**	-0.7755**	-0.4593	-0.2759	-0.4494	-0.4308	0.1782	0.1862	-0.6046*	-0.5723*	-0.3842*	-0.3711*
RE	-0.8920**	-0.7571**	-0.5431*	-0.4068	-0.2693	-0.2822	-0.1244	-0.1269	-0.4829*	-0.4578*	-0.5424*	-0.5430*
SMT	0.0012	0.0293	-0.3578	-0.2351	-0.4283	-0.5385*	-0.3461	-0.3458	-0.3785	-0.4383*	-0.5726**	-0.5817**
VM	0.1562	0.2605	-0.3578	-0.2351	-0.3428	-0.4568*	-0.4323	-0.4401	-0.3057*	-0.3476*	-0.6444**	-0.6594**
PCCLR	-0.4848*	-0.3925	-0.2670	-0.2592	-0.5448*	-0.6361**	-0.2210	-0.2379	-0.5337*	-0.5601*	-0.5917**	-0.6147**

AD=anterior dorsal thalamic nucleus, AV=anterior ventral thalamic nucleus, AM=anterior medial thalamic nucleus, HAB=habenula, LD=lateral dorsal thalamic nucleus, LP=lateral posterior thalamic nucleus, MD=medial dorsal thalamic nucleus, VAL=ventral anterior lateral thalamic nucleus, VB=ventrobasal thalamic nuclei, SM=stria medullaris, PVT=paraventricular thalamic nucleus, PT=paratenial thalamic nucleus, CM=centromedial thalamic nucleus, RH=rhomboid thalamic nucleus, RE=reuniens thalamic nucleus, SMT=subthalamic nucleus, VM=ventral medial thalamic nucleus, PCCLR=paracentral thalamic nucleus and claustrum

*=$p<0.05$, **=$p<0.01$

Table A-24. Correlation coefficients obtained when comparing latencies and errors of the ibotenic and quinolinic thalamic rats in the changing place water maze task with ratings of the amount of damage to several thalamic nuclei.

	Ibotenic		Quinolinic		Both Groups	
	Latency	Errors	Latency	Errors	Latency	Errors
AD	-0.8112**	-0.7229**	-0.4373*	-0.5761**	-0.4794**	-0.6601**
AV	-0.8103**	-0.6982**	-0.6452**	-0.7376**	-0.6443**	-0.7323**
AM	-0.7495**	-0.5707*	-0.5053	-0.6868**	-0.5273**	-0.6324**
HAB	-0.2166	-0.3669	0.4635*	0.2471	-0.0366*	-0.2175
LD	0.2825	0.3059	-0.5904**	-0.7444**	-0.5435**	-0.4275*
LP	0.3638	0.3692	-0.5295*	-0.6420**	-0.5366**	-0.4156*
MD	-0.2064	-0.2304	-0.2566	-0.1547	-0.3341	-0.2766
VAL	-0.0125	-0.1729	-0.1912	-0.3463*	-0.3576*	-0.3513
VB	0.2428	0.2143	-0.3458	-0.6244**	-0.4307**	-0.4037**
SM	0.0428	-0.1490	-0.1222	-0.2374	-0.0538	-0.1781
PVT	-0.7402**	-0.5826**	-0.3098*	-0.5493**	-0.3451**	-0.5513**
PT	-0.7696**	-0.6911**	-0.6067**	-0.6880**	-0.5685**	-0.6916**
CM	-0.1972	-0.2269	-0.5008**	-0.6897**	-0.4902**	-0.5332**
RH	-0.2677	-0.1852	-0.4469*	-0.6963**	-0.4447**	-0.4876**
RE	-0.1763	0.0007	-0.5384**	-0.7549**	-0.5229*	-0.4727**
SMT	0.1379	0.1868	-0.4159*	-0.5636**	-0.4037**	-0.2970*
VM	0.2050	0.2370	-0.5778**	-0.6956**	-0.5076**	-0.3743**
PCCLR	-0.0169	-0.0133	-0.1907	-0.2421	-0.2982*	-0.2339

AD=anterior dorsal thalamic nucleus, AV=anterior ventral thalamic nucleus, AM=anterior medial thalamic nucleus, HAB=habenula, LD=lateral dorsal thalamic nucleus, LP=lateral posterior thalamic nucleus, MD=medial dorsal thalamic nucleus, VAL=ventral anterior lateral thalamic nucleus, VB=ventrobasal thalamic nuclei, SM=stria medullaris, PVT=paraventricular thalamic nucleus, PT=paratonial thalamic nucleus, CM=centromedial thalamic nucleus, RH=rhomboid thalamic nucleus, RE=reuniens thalamic nucleus, SMT=subthalamic nucleus, VM=ventral medial thalamic nucleus, PCCLR=paracentral thalamic nucleus and claustrum

*=p<0.05, **=p<0.01

Table A-25. Correlation coefficients obtained when comparing total crosses made by the ibotenic and quinolinic MD rats in the activity cages after administration of either no drug or 1.25 or 2.5 mg/kg d-amphetamine with ratings of the amount of damage to several thalamic nuclei.

	Ibotenic			Quinolinic			Both Groups		
	No Drug	d-Amphetamine		No Drug	d-Amphetamine		No Drug	d-Amphetamine	
	Baseline	1.25 mg/kg	2.5 mg/kg	Baseline	1.25 mg/kg	2.5 mg/kg	Baseline	1.25 mg/kg	2.5 mg/kg
AD	0.1363	0.6911**	0.3635	-0.4241	-0.4444	0.0907	-0.1725	0.2702	0.1379
AV	0.0515	0.6929**	0.4206*	-0.4097	-0.3621	0.2064	-0.2179	0.2355	0.1402
AM	-0.1270*	0.6326*	0.5404*	-0.0890	-0.4163	-0.2657	-0.1160	0.2442*	0.0140
HAB	0.5417	0.5679	-0.1853	-0.3865	0.2503	0.2394	0.0880	0.3810	-0.1987*
LD	0.0152	0.3602	0.0346	0.0003	-0.3401	-0.3755	-0.0446	-0.1077	-0.4288*
LP	0.0675	0.1943	0.0310	0.0967**	-0.2823	-0.4390	0.0195*	-0.1303	-0.4539
MD	0.4773	0.5427**	0.2389	0.6808	-0.0244	-0.2188	0.4379	0.2548	-0.1650
VAL	-0.2818	0.6826	0.3489	0.1419	0.0112	-0.2647	-0.0147	0.0890	-0.3191*
VB	0.1315	0.2213	0.2050	0.1245	-0.3236	-0.5065	0.0298	-0.1302	-0.4538
SM	0.2469	0.2467	-0.3232	0.2075	0.0174	-0.2920	0.2135	0.1769	-0.2821
PVT	-0.0960	0.7879**	0.2107	0.0214	-0.1824	-0.2106	-0.0219	0.3445	-0.0327
PT	0.0101	0.6355*	0.3023	-0.0703	-0.4476*	-0.2585	-0.0457	0.2547	-0.0694
CM	-0.1290	-0.0649	0.2684	-0.0375	-0.5692*	-0.1721	-0.0876	-0.2819	-0.1354
RH	-0.3443	0.4462	0.4263	0.0121	-0.5629**	-0.3184	-0.1496	0.0254	-0.1201
RE	-0.2398	0.4083	0.3761*	-0.2116	-0.6948	-0.3249	-0.2137	-0.0987	-0.2200
SMT	-0.3269	0.1053	0.5224	-0.0081	-0.4581	-0.4240	-0.1404	-0.1400	-0.2260
VM	-0.2677	0.2212	0.4710	-0.0147	-0.4508	-0.3657	-0.1104	-0.1225	-0.2859
PCCLR	0.2553	0.4849	0.1704	0.0577	-0.2520	-0.5010	0.0788	0.1145	-0.3376

AD=anterior dorsal thalamic nucleus, AV=anterior ventral thalamic nucleus, AM=anterior medial thalamic nucleus, HAB=habenula, LD=lateral dorsal thalamic nucleus, LP=lateral posterior thalamic nucleus, MD=medial dorsal thalamic nucleus, VAL=ventral anterior lateral thalamic nucleus, VB=ventrobasal thalamic nuclei, SM=stria medullaris, PVT=paraventricular thalamic nucleus, PT=paratenial thalamic nucleus, CM=centromedial thalamic nucleus, RH=rhomboid thalamic nucleus, RE=reuniens thalamic nucleus, SMT=subthalamic nucleus, VM=ventral medial thalamic nucleus, PCCLR=paracentral thalamic nucleus and claustrum

*=p<0.05, **=p<0.01