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NIGROSTRIATAL ASYMMETRY AND ASSOCIATIVE FUNCTIONS OF THE STRIATUM

by

BETTY ZIMMERBERG

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Oct 30, 1975
date

J. Goldfarb
Chairman of Examining Committee
Dr. J. Goldfarb

October 30, 1975
date

Terry AmKulich
Executive Officer
Dr. T. Kaulwich

Dr. S.D. Glick

Dr. M.D. Hamburg

Dr. J.E. Shriver

Dr. S. Wilk

Supervisory Committee

The City University of New York

Abstract

NIGROSTRIATAL ASYMMETRY AND ASSOCIATIVE FUNCTIONS OF THE STRIATUM

by

Betty Zimmerberg

Advisor: Associate Professor Stanley D. Glick

Animals will turn in circles, or rotate, after unilateral stimulation or ablation of the nigrostriatal system contralateral to the side with greater dopaminergic activity. Rotation has recently been found to occur in normal (e.g. nonlesioned and nonstimulated) rats after administration of amphetamine; this rotation was contralateral to the striatum with higher dopamine levels. Spontaneous rotation was interpreted as evidence for an intrinsic asymmetry in the left and right nigrostriatal systems. This thesis further examined the asymmetry of this system, and explored its role in side preference, learning and memory, and activity.

Normal rats were found to have spontaneous and stable left or right side preferences in a T maze. There was a 12% difference in dopamine levels in the two striata, and the direction of side preference was contralateral to the striatum with higher dopamine levels. Amphetamine potentiated the spontaneous side preferences, and unilateral caudate lesions resulted in ipsilateral side preferences regardless of pre-operative preferences. Rats were found to rotate following d-amphetamine administration in the same direction as their non-drug preference in the T maze. Unilateral caudate stimulation elicited contralateral side preferences in a two-lever operant task. These results suggested that

side preference reflects a normal asymmetry in nigrostriatal function.

Side preference, as a correlate of nigrostriatal asymmetry, was used to investigate the relationship of this asymmetry to associative behaviors previously shown to be related to striatal function. Rats took more trials to learn a left-right discrimination in the T maze when the correct side was contralateral to their spontaneous preferences than when it was ipsilateral. The strength of side preferences was shown to be inversely related to the rate of learning of an active avoidance response. In mice, which also exhibited spontaneous side preferences in a T maze, strength of side preference was positively correlated with the retention of a passive avoidance response. There was also a positive correlation between strength of side preference and spontaneous locomotor activity in mice. Animals with no side preferences were found to have the greatest activity and were poor learners of either avoidance task. The results of these experiments indicated that there may be an important role of the nigrostriatal asymmetry in the learning of both spatial and nonspatial tasks.

Side preference was found to be primarily affected by drugs stimulating (apomorphine) or blocking (haloperidol) dopamine receptors while passive avoidance learning was impaired more by alterations in cholinergic activity (scopolamine or pilocarpine). The results of drug interactions on both tasks were inconclusive, although there was some support for dopamine-acetylcholine reciprocity in the striatum.

The results of this investigation suggested that an intrinsic asymmetry of the nigrostriatal system functions in spatial behavior, and as such, influences the performance of other behaviors. Interpretations of the

results were discussed in terms of the evolution of asymmetric function and the relationship of this work to studies on spatial orientation and sensory neglect in animals and man.

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INTRODUCTION

"The royal road of the sensations of the body to the soul is through the corpora striata, and all determinations of the will also descend by that road."

Swedenborg, 1740 (from Wilson, 1914)

The striatum¹ attracted the attention of early anatomists and physiologists because of its prominent position in the telencephalon. Vesalius' seventh book of the *Fabrica* shows a diagram of the corpus striatum which distinguishes between the caudate nucleus, putamen, globus pallidus and internal capsule (McHenry, 1969). The basal ganglia were named by Willis in 1667, who described the corpus striatum as "internodes by which the cerebrum coheres with the medulla oblongata" (Wilson, 1914). By the mid-nineteenth century, all major investigators agreed that the striatum had direct control of voluntary movement. This conclusion was based on anatomical studies by Burdach in 1819 (Wilson, 1914) showing that the pyramidal tracts originated in the striatum. According to a neurologist in 1881, "the distribution of the fibers of the crus cerebri certainly points strongly to the corpus striatum as a motor ganglion" (Ranney, 1881). The hemispheres were still considered to be the "organ of will" which gave orders to the motor centers in the striatum (Young, 1970). The striatum was subsidiary to the cortex above, but controlled movement through the pyramidal tracts. Even the early physiological investigations of the role of the striatum supported this view. Magendie in 1839 demonstrated that a lesion of the striatum of a

¹ Although early anatomists referred to the caudate nucleus and putamen as corpus striatum, modern definitions include the globus pallidus in that term. The term striatum refers to only the caudate nucleus and putamen, which are fused in the rat brain.

rabbit caused it to leap forward, and concluded that the striatum was the center for backward movements (Laursen, 1963). In 1876 Ferrier reported that stimulation of the striatum produced convulsive movements, and that lesions caused hemiplegia (Ferrier, 1876). In the same year Broadbent referred to the corpus striatum as "the motor ganglion for the entire opposite half of the body. It translates volitions into actions, or puts in execution the commands of the intellect" (Young, 1970).

By the end of the nineteenth century, the true anatomical nature of the pyramidal tracts began to be described. In 1874 Betz showed that the pyramidal tracts originated in the cortex (Young, 1970). In 1878 Frank and Piters found that no movements followed stimulation of the striatum in decorticate dogs but that movements did follow stimulation of the internal capsule (Wilson, 1914). And although Ferrier had indicated that the striatum was a motor organ, he clarified his findings in light of the new anatomical evidence:

The various physiological and pathological data which have been advanced to show that the destruction of the corpus striatum causes paralysis of voluntary motion . . . do not, however, suffice to determine the special function of these ganglia as distinct from the cortical centres. For we have also seen that paralysis of voluntary motion may also result from lesions of the cortex . . . apart from injury to the basal ganglia, and, as lesions of these ganglia necessarily interrupt the projection system between the cortex and the periphery, therefore the hemispheres can no longer exercise their functions . . . as regards the transmission of motor impulses outward . . . (Ferrier, 1876)

Ferrier suggested that the striatum acts as the "centres of automatic or subvoluntary integration" of volitional movements originating in the cortex, but becoming automatic through repetition. However, with the new interest in the cortex as the center of voluntary movement (by 1890 standard textbooks had the corticospinal tracts passing through

the striatum), investigation of the role of the striatum slowed, and it was assigned an unknown function.

The next major theory of the role of the striatum stemmed from observations by neurologists. Anton, in 1896, described the first case of a striatal syndrome: a boy with involuntary movements of all parts of his body who was shown to have bilateral lesions in the putamen (Laursen, 1963). In 1912 Wilson advanced the new theory of the role of "progressive lenticular degeneration", a striatal syndrome consisting of:

bilateral involuntary movements, practically always of the tremor variety; weakness, spasticity or hypertonicity (sometimes spasmodic contractions) and eventually contracture of the skeletal musculature; dysarthria or anarthria and dysphagia, and a degree of emotionalism; but without any sensory disturbance, without any true paralysis, and without any alteration in the cutaneous reflexes. (Wilson, 1912).

Wilson noted the similarity between progressive lenticular degeneration and paralysis agitans, which had been described in 1817 by Parkinson as "involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards and to pass from a walking to a running pace; the senses and intellects being uninjured" (Parkinson, 1817). Due to the clinical appearance of the corpus striatal syndrome, Wilson concluded that in the intact system the corpus striatum "exercises a steadying effect on the corticospinal system", via a lenticular-rubro-spinal system (Wilson, 1912). A deficit in this steadying influence thus affects the pyramidal function and results in hypertonicity or rigidity and tremor during voluntary movement. In 1914 Wilson continued his investigations in an experimental study with monkeys. Stimulation of the striatum produced no motor phenomena unless the

placements were adjacent to the internal capsule. Small unilateral electrolytic lesions caused an interesting phenomenon, a preference for the ipsilateral limb with a slight awkwardness of the contralateral limbs: "some of the monkeys . . . showed a preference, in the taking of nuts or bananas, for the homolateral limb" (Wilson, 1914). Wilson likened the awkwardness to the tremor seen clinically after pathological lesions of the striatum, thus supporting his view that the striatum acts to steady the pyramidal innervation.

Herrick, in 1926, agreed with Wilson's view that the chief function of the striatum was control of the tone, steadiness and co-ordinated action of muscles, but added the control of innate and instinctive behavior as well (Herrick, 1926). Some of the "dynamogenic" functions included various visceral activities and locomotor and facial reflexes involved in feeding. Support for the role of the striatum in "instinctive" movements came primarily from phylogenetic studies. Rogers, in 1922, studied the homologue of the striatum in birds, and concluded that it was essential for mating (Gybel et al., 1967). Several studies by Jacob in the 1920's had labelled the caudate and putamen as the centers of emotional expression, fear and flight, orientation and attention, automatic adjustment of posture and position, and automatic associative movements (Laursen, 1963). These observations were valid for submammalian forms, where the cortex is poorly developed and the striatum is very important in the "instinctual" movements of locomotion, defense, feeding and courting. Commenting on the changing role of the striatum as one moves up the phylogenetic scale, Wilson stated:

from the strictly motor point of view the corpus striatum seems to have been progressively shorn of its possessions; its proportionate size in man is less than in any of the lower animals, and it may be that the superman of the future will have no corpus striatum at all. (Wilson, 1914)

The theory that the striatum was involved in vegetative functions continued to have support as recently as the 1950s (Buchwald and Ervin, 1957). However, Laursen showed that their reported effects of stimulation (lipsmacking, salivation, gagging and sexual responses) were due to spread of current to the septum (Laursen, 1962a).

Wilson's role of the striatum in "steadyding" movements via a separate descending pathway was challenged in 1938 by the demonstration that a functional relationship existed between the cortex and the striatum. Dusser de Barenne and McCulloch (1938) recorded electrical activity in monkeys after lesions or local application of strychnine to various areas of the brain. Their findings indicated that two areas of the sensorimotor cortex (L4-S and A-4S) excited the caudate nucleus, and that the caudate nucleus in turn inhibited or "braked" the thalamus opticus (the evidence of the "braking" function was that caudate lesions activated the thalamus and stimulation with strychnine suppressed activity in the thalamus). The thalamus, in turn, influenced the activity of two motor areas in the cortex (L4 and A4). This "one-way" system provided a basis for the new theory of the role of the striatum advanced by Mettler the following year, known as the "Suppressor Circuit". According to Mettler, the primary role of the striatum was the "conditioning", or inhibition, of motor manifestations which originated in the cortex. Stimulation experiments in anesthetized monkeys and cats demonstrated that when the caudate nucleus was stimulated, there were no effects.

However, when the caudate nucleus was stimulated during stimulation of motor cortex, the ongoing movements were blocked (Mettler et al, 1939). In the next few years, Mettler published additional evidence for the "inhibitory" theory. In 1941 he showed that stimulation of the caudate nucleus in anesthetized cats inhibited not only stimulation-elicited movements, but spontaneous movements as well (Mettler and Mettler, 1941). The following year he reported that striatal injury caused hyperkinesis, thus supporting his view that the striatum acts as an important inhibitory mechanism subject to cortical control via the "suppressor circuit" (Mettler and Mettler, 1942).

In agreement with Mettler and Mettler, Hunter and Jasper (1949) described an "arrest reaction" of spontaneous movements after brief and strong stimulation of the caudate nucleus. However, Forman and Ward (1957) reported the simultaneous stimulation of motor cortex and caudate nucleus in unanesthetized cats did not inhibit the motor effects of cortical origin. Caudate spindles (long latency trains of high amplitude synchronous waves, recorded after low frequency stimulation of the caudate nucleus) in the frontal poles of cats could be interpreted as evidence of striatal inhibition of the cortex (Buchwald et al. 1961). However, they also found that high frequency stimulation of the caudate nucleus produced no caudate spindles. In a follow-up study using lever-pressing during stimulation as a behavioral index, they showed that although the low frequency stimulation (1 pulse per 5 sec to 5 pulses per sec.) did decrease the rate of responding, high frequency stimulation (300 pulses per sec.), or a combination of low and high frequency stimulation, did not affect the rate of responding. "Arrest" was reported after intermediate frequency stimulation (20 to 30 pulses per sec.) "Arrest" here did

not mean cessation of all activity; the cats did not barpress, but they had a slow, tonic turn of the neck and head to one side. The most convincing refutation of Mettler's inhibitory theory were the stimulation experiments of Laursen (1962b). Cats were stimulated during the performance of an escape or avoidance jump. Stimulation of the internal capsule "froze" the cat in any phase of performance. Arrest of movement after caudate stimulation was seen only with high intensities, and the threshold for arrest increased with increasing distance from the internal capsule. These results were interpreted to indicate that arrest of movement phenomena were due to current spread to the internal capsule, and that the caudate did not subserve inhibition of cortically evoked movements.

Discarding the "inhibitory" theory, which gave a purely motor function to the striatum, Laursen advanced a new role for the striatum: a sensory-motor-integrative center (Laursen, 1963). His theory was based primarily on two kinds of studies; first, those concerned with circling and second, those concerned with learning. Contraversive head turning and circling after unilateral stimulation, or ipsilateral circling after unilateral damage to the striatum had been reported for over one hundred years. Nothnagel in 1873 found that injections of chromic acid into the striatum caused a bending of the trunk to the side of the lesion two to ten minutes afterwards (Wilson, 1914). Ferrier (1876) stated that "irritation of the corpus striatum causes general muscular contraction on the opposite side of the body. The head and body are strongly flexed to the opposite side, so that the head and tail become approximated" (Ferrier, 1876). These results were seen in monkeys, cats, dogs, jackals and rabbits (Ferrier, 1876). In 1921 Lashley described the rotation

syndrome after combined unilateral destruction of the caudate nucleus and the motor cortex above it; furthermore, he found that these lesions did not impair visual discrimination in a problem box, but did change the ability of the rats to make contralateral turns (they would turn 270° to solve the problem) (Lashley, 1921). "Circus" movements after "partial and unsymmetrical injuries to the striatum" were reported by Herrick (1926). Laursen cites a French thesis by Delmas-Marsalet in 1925 as experimental evidence for contraversive circling after stimulation of the caudate (Laursen, 1962a). Unilateral striatal lesions in dogs were reputed to cause circus movements and a forced posture toward the side of the lesion, in a study by Mettler and Mettler in 1942. Several investigators in the 1950s demonstrated that contraversive circling followed striatal stimulation, but Laursen's study in cats gave specificity to the phenomena (Laursen, 1962). He stated that the only motor response of caudate origin was circling, because it was eliminated by lesions in the caudate, but unaffected by degeneration of the internal capsule. Flexion of the contralateral extremities, also reported after stimulation, was still elicited after caudate lesions, but not after degeneration of the internal capsule. This specific effect of caudate stimulation or damage, circling, seemed to Laursen to indicate something more than a mere motor pattern:

"The functional significance of contraversive circling is unknown. The cats look as if they were searching for something . . . the circling response is a complex behavioral manifestation rather than a stereotyped movement, suggesting that the function of the caudate is at a high level of integration." (Laursen, 1962a)

The second area adding credence to Laursen's theory of the striatum as integrative center was the emerging picture of its role in

learning and memory. Rosvold and Delgado demonstrated in 1956 that the deficits in delayed alternation could be caused by damage to the caudate nucleus as well as to the frontal lobes, a finding first described by Jacobsen in 1936. Impairment in delayed alternation and delayed response tasks can be interpreted as a specific deficit in recent memory when unaccompanied by visual discrimination problems. Dean and Davis (1959) reported that monkeys had chance performance on a delayed response task with no impairment in color discrimination after bilateral caudate lesions. Small doses of phenidylacetate (.25-.5 mg/kg) restored performance to pre-operative levels. The lesioned monkeys were described as indifferent or less responsive to stimuli (Dean and Davis, 1959). In 1960 Battig et al. compared the effects of caudate and anterior frontal damage on delayed alternation, delayed response, and visual discrimination tests in monkeys. He found that although both groups were impaired on the first two tasks with no change on the third, the caudate-lesion group made fewer errors than the frontal-lesion group and the caudate-lesion group were less impaired on delayed response than on the delayed alternation (Battig et al., 1960). Hyperactivity was also observed after caudate lesions in monkeys (Rosvold and Delgado, 1956, Dean and Davis, 1959) and in rats (Whittier and Orr, 1962; but not by Beach, 1941). Self-stimulation was also reported to be elicited from implantation sites in the striatum in cats by Brady et al. (1957). Thompson and Mettler (1963) found that cats showed no conditioned avoidance retention after bilateral lesions of the caudate nucleus and the lateral gyri

above it. Their interpretation of the role of the striatum was similar to Laursen's: the caudate nucleus as an area of convergence of inputs from conditioned and unconditioned stimuli, outputs to response systems, and feedback from response systems (Thompson and Mattler, 1963).

Laursen's view of the striatum as an integrative center for motor, sensory and associative functions has been supported by investigators, Krauthamer and Albe-Fessard (1965) studied the effect of striatal stimulation on multisensory potentials evoked in association cortex. They observed selective inhibition of nonspecific peripherally-evoked sensory potentials after dorsolateral caudate stimulation. An investigation of the effects of caudate nucleus lesions in cats by Gybels et al (1967) also lent support to Laursen's theory. There were no primary sensory impairments, but there were deficits in sensori-motor integration (e.g. poor proprioceptive-motor seen by abnormal postures when sitting or standing, poor vestibular-motor evidenced by problems in landing and righting, and poor visual-motor observed by lack of visual placing, and bumping into obstacles and corners when walking). They also noted a disturbance unique to unilateral caudate nucleus lesions; a disturbance in the contralateral visual field that was not blindness. These cats had difficulty finding a food dish placed in the contralateral field while a similar dish placed in the ipsilateral field was discovered immediately. Similarly, when two mice or two bottles of milk were placed simultaneously in the two fields (left and right) the animals always chose the ipsilateral goal. In addition, the eyes would only follow in the ipsilateral field. This phenomena was interpreted by the authors as an "inattention" for the

contralateral visual field (Gybels et al., 1967). More recent evidence of this contralateral "inattention" will be discussed later. The net result of these experiments with both unilateral and bilateral lesions was the conclusion by the authors that the caudate nucleus may be involved in the initiating and steering functions of sensory (proprioceptive and visual) systems on the motor aspects of behavior: "the most striking feature observed in cats with a caudate nucleus lesion is the peculiar discrepancy between the integrity of the elementary motor and sensory functions and the appearance of severe motor and sensory disturbances as soon as the animal finds itself in a behavioral situation" (Gybels, 1967).

Structural and Functional Connections of the Striatum

There are several major afferent systems to the striatum. Corticostriate fibers originate from all areas of the cortex. Emmolaeva and Ermolenka (1972) reported direct typographical connections between the cat somatosensory cortex (SI and S II) and the caudate nucleus. Unmyelinated collaterals descending in the internal capsule from primary motor and somatosensory areas were revealed with the silver impregnation technique in monkeys (Glees, 1944). Silver-staining methods by Nauta (1964) indicated the presence of a specific frontal cortex-caudate nucleus pathway in monkeys; this finding confirmed earlier suggestions of a specific frontal-striatal connection from lesion studies (Harman et al., 1954). Firing of caudate neurons has been reported in response to stimulation of the frontal

cortex in cats (Liles, 1974). In rats, the presence of this specific connection has been confirmed by Nauta et al. (1974) using horse-radish peroxidase staining. In addition to cortical afferents, fibers from the thalamus project to the striatum from the centro-median nucleus, the parafascicular nucleus, the small intralaminar nuclei, and the dorsomedial nucleus. Potegal and coworkers (1971) noted the presence of an indirect bilateral vestibular input to the caudate nucleus, probably via the medial geniculate body, using evoked potential recordings. Another afferent system appears to originate in the dorsal nuclei of the midbrain raphe in rats (Nauta et al., 1974).

The afferent projection of primary interest to this investigation is the nigrostriatal fiber system. The presence of a nigrostriatal tract has now been confirmed by reports of striatal degeneration after nigral lesions using the Wittenen technique (Carpenter and Peter, 1972), and retrograde cell changes in the nigra following striatal lesions, first demonstrated in 1901 by Holmes. Histochemical techniques have confirmed that the nigrostriatal fibers originate in cell bodies in the zona compacta of the substantia nigra and run rostromedially to enter the lateral hypothalamus. There they ascend in a dense bundle lateral to the medial forebrain bundle. The fibers enter the internal capsule and then fan out in the globus pallidus and terminate in the striatum (Ungerstedt, 1971a).

The striatum has few direct efferent connections; only 3% of the neurons are long-axoned and leave the structure (Mensah and Deadwyler, 1974). Most of the efferents course medially through the lateral

medullary lamina or ventrally through the internal capsule to the lateral globus pallidus. A second efferent pathway, the strionigral system, terminates in the zona reticularis of the substantia nigra. There may also be efferent system to the raphe nucleus (Usunoff et al., 1974). Recently functional and structural evidence of an interconnection between the left and right caudate nuclei has been reported. Levine and co-workers (1974) found that unilateral caudate nucleus lesions in cats inhibited unit firing in the contralateral caudate nucleus. In addition, Mensah and Deadwyler (1974) have reported the presence of an intercaudate pathway in the ventral corpus collosum in rats.

The globus pallidus relays the majority of efferent information from the corpus striatum. Pallidofugal fibers form the lenticular fasciculus and the ansa lenticularis, which join in the pre-rubral area as the thalamic fasciculus. At this juncture, some fibers leave the thalamic fasciculus and enter the pallido-hypothalamic system, which ends in the ventromedial nucleus of the tuberal region. Fibers continuing in the thalamic fasciculus terminate in the ventral anterior (VAN) and ventral lateral nuclei (VLN) of the thalamus. The VAN projects to the frontal cortex and the VLN, which also receives the input from the cerebellum, projects to the motor cortex. Other efferents from the globus pallidus terminate in the subthalamus or descend for a short distance into the midbrain tegmentum (Carpenter, 1975). Thus the complex interconnections of the striatum to sensory and motor subcortical relays, and to all parts of the cortex, lend support to the view of the role of the striatum as a primary sensory-motor integrative center.

Cajal (1911) provided the original descriptions of the fine cell structure of the striatum. The caudate nucleus has been called a "huge gray mass" (Mensah and Deadwyler, 1974). A recent examination of the ultrastructure of the rat caudate nucleus by Mensah and Deadwyler (1974) revealed six cell types. Three categories were defined: small (diameters 5 to 9 μm), medium (diameters 10 to 20 μm) and large cells (diameters 22 to 33 μm). About 90% of the total cell population were medium-sized stellate cells. They had four to six dendrites which branched and had large numbers of spines starting at about 20 μm from the soma. The axon was thin and appeared to turn back towards the soma after a short distance. Due to these characteristics, this cell was thought to be intrinsic, as Cajal (1911) had also concluded. A second type of medium-sized cell (3% of the population) was concluded to be an efferent cell because it was characterized by thicker, slightly spined, dendrites and an axon with no decrease in size. Two other medium-sized types were found, both intrinsic to the caudate. One type, 2% of the population, had four or five thin, branched non-spiny dendrites and an axon which originated in the soma or the basal dendrite and terminated within the radius of the dendritic tree. The other type, 1% of the population, had short varicose dendrites and a dense beaded axon which terminated in branches close to the soma. The remainder of the cell population (4%) were either small or large cells. The small

cells had varicose, spineless dendrites and a long axon originating from the main stem dendrite which may have been an efferent.

The ultrastructure of the synaptic connections in the striatum has also been investigated. Tennyson and Marco (1973) found the most common connection to be a small to medium diameter axospinous terminal with round and ovoid vesicles and asymmetrical junctions. Many axonal boutons had large granular vesicles. They also reported the presence of some axodendritic synapses with small round vesicles and asymmetrical junctions and some with mixed round and ovoid vesicles and symmetrical junctions. Also present were "en passant" terminals, axons with vesicles along their length, and terminals with interrupted synaptic thickenings. When they isolated the caudate nucleus surgically, there was a notable decrease (about 1/3) in synaptic terminals. The viable synapses, found in small groups, were the small axospinous junctions, the "en passant" terminals, and the synapses with interrupted junctions. Since there was a complete absence of catecholamine fluorescence in the isolated caudate nucleus, none of these terminals could be interpreted as containing dopamine, including the large granular vesicles in axonal boutons which were also present after isolation. A different approach to the question of the synaptic termination of the nigrostriatal tract was conducted by Hattori et al. (1973) with the injection of ^3H -leucine into the zona compacta of the substantia nigra, followed by autoradiography. He found two types of terminals: 75% asymmetrical with moderately pleomorphic vesicles and 25% symmetrical with highly pleomorphic vesicles. Both types of terminals had nonmyelinated axons of 100-200

nm diameter. Injection of 6-hydroxydopamine intraventricularly degenerated only the asymmetrical synapses. The question of the origin of the remaining symmetrical synapses is still in doubt; however, the substantia nigra could not be ruled out. This anatomical study is interesting in light of conflicting results obtained in electrophysiological recording experiments after stimulation of the substantia nigra.

Studies which involved stimulation of the substantia nigra with unit cell recording in the caudate nucleus have reported excitation, inhibition, or biphasic responses. The percentage of spontaneously firing cells which were inhibited by nigral stimulation was reported to be 61% by Feltz and Albe-Fessard (1972), 44% by York (1970) and 45% by Connor (1970). Similar proportions of cells fired by glutamate (Feltz and de Champlain, 1972b) or di-homocysteic acid (Connor, 1968) were also inhibited by nigral stimulation. Cells inhibited by substantia nigra stimulation were also found to be inhibited by iontophoretic application of dopamine; both inhibitions were antagonized by alphanemethyldopamine (Connor, 1970). Excitation of caudate neurons after substantia nigra stimulation was first reported in 1967 by McLennan and York, and by Frigyesi and Purpura, and confirmed in later studies (Connor, 1968, 1970; York, 1970; Feltz and de Champlain, 1972a, 1972b; Feltz and Albe-Fessard, 1972). Cells facilitated by nigral stimulation were found to be either not excited by dopamine (Feltz and de Champlain, 1972b), excited by

dopamine (York, 1970) or depressed by dopamine (McLennan and York, 1967). Lateral ventricular injection of 6-hydroxydopamine did not abolish the excitation after nigral stimulation, and may have enhanced it (Feltz and de Champlain, 1972a). Biphasic responses were also reported: excitation followed by inhibition (Feltz and McKenzie, 1969; Feltz and Albe-Fessard, 1972; Buchwald et al., 1973), and inhibition followed by excitation (York, 1970). Similar proportions of cells studied had their firing rates either facilitated by iontophoretic application of dopamine (Bloom et al., 1965; McLennan and York, 1967; York, 1970) or depressed (Bloom et al., 1965; McLennan and York, 1967; Frigyesi and Purpura, 1967).

Although there is no firm evidence as yet, it appears from both the anatomical and electrophysiological studies that there may be two nigrostriatal fiber systems, one inhibitory and one excitatory.

Neurotransmitters in the Striatum

Dopamine

The demonstration that the distribution of dopamine in the central nervous system differed from that of norepinephrine (Bertler & Rosengren, 1959) triggered the search for dopamine's functional role. In 1957 Blaschko had proposed that dopamine might function in the periphery as a neurotransmitter as well as functioning as the precursor of norepinephrine; the evidence for a peripheral and central role of dopamine as a transmitter has been discussed fully in a review by Hornykiewicz (1966). The highest concentration of dopamine in mammalian brain is found in the striatum (Bertler and Rosengren,

1959; Carlsson, 1959). The globus pallidus, nucleus accumbens, tuberculum olfactorium, and substantia nigra are also high in dopamine (Hornykiewicz, 1966). Dopa decarboxylase, the enzyme responsible for conversion of dopa (dihydroxyphenylalanine) to dopamine, has also been reported to be found in high levels in the striatum (Bogdanski et al., 1957; Kuntzman et al., 1961). The enzyme that inactivates dopamine via deamination, monoamine oxidase (Goldstein et al., 1959), is also present in high activity in the caudate nucleus (Bogdanski et al., 1957; Weiner, 1960). In 1962, Falck and co-workers developed a histochemical fluorescent technique for determining the cellular localization of monoamines; using this technique, dopamine was localized in cell bodies in the substantia nigra and in fibers and terminals in the striatum (Carlsson et al., 1962; Falck et al., 1962). A complete histochemical mapping of dopaminergic pathways in the rat brain (nigrostriatal, mesolimbic, and tubero-infundibular) was reported by Ungerstedt (1971a).

The histochemical findings implied that the presence of a dopaminergic nigrostriatal pathway was responsible for the high concentration of dopamine in the striatum. The existence of this dopaminergic pathway was suggested by the observation that the brains of Parkinson patients at autopsy had concurrent loss of dopamine in the striatum and the substantia nigra (Hornykiewicz, 1966). There has been increasingly more evidence to support this theory. Dopamine has been collected from the putamen through irrigation of implanted cannulae, and this output was increased after stimulation of the substantia nigra (McLennan, 1965). Perfusion of the anterior horn of the lateral ventricle, which is situated over the caudate nucleus, resulted in increased

collection of homovanillic acid, a major dopamine metabolite, after stimulation of the substantia nigra (Portig and Vogt, 1969a).

Lesions of the nigrostriatal pathway (electrolytic or 6-hydroxydopamine) have been shown by several investigators to cause degeneration of the dopaminergic terminals and a decrease in the striatal levels of dopamine (Poirier and Sourkes, 1965; Sharman et al., 1967; Parent and Poirier, 1969; Hokfelt and Ungerstedt, 1969; Heller, 1972).

There is a transient increase in striatal dopamine levels immediately after lesions of the substantia nigra (Faull and Lavery, 1969), 6-hydroxydopamine intraventricular injections (Bell et al., 1970) or lesions of the nigrostriatal bundle (Anden et al., 1972; Nyback, 1972; Heller, 1972). This increase in dopamine concentration in the striatum is present within 18 minutes of lesioning the nigrostriatal pathway, is maximum at 30 min., and starts to drop at 20 hours. At 48 hours post-lesion, there is only 55% of the control levels of dopamine, and at 12 days dopamine is virtually absent from the striatum (Walters et al., 1973). According to Walters et al., (1973), the initial increase is dependent on new synthesis of dopamine, because the increase is blocked by prior administration of alpha-methyl-p-tyrosine, an inhibitor of tyrosine hydroxylase; activation of dopamine synthesis after interruption of neural impulses is proposed to be due to a reduced influx of calcium into the terminals. A comparison of the effects of electrolytic lesions and 6-hydroxydopamine injections in the substantia nigra on this early increase in dopamine by Agid et al. (1974) revealed no significant differences in the two treatments, and the increase in levels was found to be accompanied by an increased accumulation of newly synthesized ^3H -dopamine and an increased rate of tyrosine hydroxylation.

Acetylcholine

In 1941 MacIntosh demonstrated that acetylcholine was present in high concentrations in the caudate nucleus and putamen (MacIntosh, 1941). The enzymes necessary for synthesis (cholineacetyltransferase) and degradation (acetyl-cholinesterase) of this purported transmitter are also found in the striatum (Feldberg and Vogt, 1948; Habb and Silver, 1956; Burgen and Chipman, 1951; Fahn and Cote, 1968a). Stimulation of the caudate nucleus in cats caused an increase in acetylcholine in the caudate nucleus (Traczyk and Sadowski, 1962) and in the perfusate of the caudate nucleus using a push-pull cannula (Gadd m, 1961; Mitchell and Szerb, 1962). Electrophoretic application of acetylcholine to single caudate nucleus cells caused an atropine-sensitive excitation (McLennan and York, 1966). Connor et al. (1966a, 1966b), observed that tremor induced by microinjection of cholinergic agents into the caudate nucleus was antagonized by muscarinic blocking agents and not by nicotinic blocking agents. These results suggest that there are muscarinic cholinergic receptors in the caudate nucleus.

The acetylcholine in the striatum is probably present mainly in interneurons. Butcher and Butcher (1974) found that after several types of lesions in rats designed to isolate the striatum (CuSO₄ injections into the substantia nigra or ventral thalamus, hemisections to sever connections to the brainstem, or suction ablation of the frontal cortex) only the hemisection changed acetylcholine levels, and this change was attributed to nonspecific damage. McGeer et al., (1971) also demonstrated that isolation of the striatum by lesions in the globus pallidus or known afferent systems produced no change in choline

acetyltransferase or acetylcholinesterase activity. Studies using cholinesterase staining procedures have indicated that there may be a cholinergic strio-nigral pathway (Olivier et al., 1970; Shute and Lewis, 1963, 1967). However, other investigators have contended that the staining procedure may be non-specific for all membranes, and that there is evidence for GABA as the transmitter in the strionigral pathway (see p. 22). After lesions in the putamen, caudate nucleus, globus pallidus or nucleus entopeduncularis (site of passage of strio system) there was no change in either acetylcholinesterase or choline-acetyl-transferase activity in the substantia nigra in cats (Fonnum et al., 1974). Hemitransection of the strionigral pathway in baboons was found to have little effect on either of the enzyme activities or on acetylcholine levels in the substantia nigra (Kataoka et al., 1974). Acetylcholine has also been suggested as the transmitter of a thalamo-striatal pathway. Electrical stimulation of the ventral anterior nucleus of the thalamus causes excitation of caudate cells (McLennan and York, 1966) and acetylcholine collection from the caudate nucleus increases after this type of stimulation (McLennan, 1964). However, the more recent isolation studies appear to argue against these earlier results.

Serotonin (5-hydroxytryptamine)

A third purported neurotransmitter, serotonin, is also found in the striatum (Bogdanski et al., 1957), and although the concentration is lower than in limbic system structures and hypothalamus, it is higher than in other structures such as cerebellum and cerebral cortex (Laursen, 1963). Relatively less attention has been paid to the role of serotonin in the striatum than to acetylcholine and dopamine. Microelectrophoretic application of serotonin on caudate nucleus cells has a

predominantly inhibitory action (Herz and Zieglansberger, 1968). Histochemical studies of the globus pallidus and substantia nigra reveal the presence of nerve terminals containing serotonin (Fuxe, 1964; Fuxe et al., 1968). These nerve fibers appear to originate in the raphe nucleus (Dahlstrom and Fuxe, 1964).

Only a few lesion studies have been undertaken in respect to the origin or function of serotonin in the striatum. Poirier and co-workers (1966) found that dorso-medial cerebral peduncle lesions reduced the concentration of serotonin in the striatum. Lesions of the raphe nucleus also reduces serotonin concentration (60-75%) without affecting dopamine concentration (Marsden et al., 1972; Marsden and Guldberg, 1973).

GABA (γ -aminobutyric acid)

GABA is found in highest concentration in the substantia nigra and the globus pallidus, and in medium concentration in the caudate nucleus and putamen (Fahn and Cote, 1968b). The distribution of glutamic acid decarboxylase (GAD), the enzyme responsible for the intraneuronal synthesis of GABA, parallels that of GABA. In the substantia nigra, GAD is found in highest concentration in the medial pars reticularis, and the concentration decreases as one moves medio-laterally to the medial pars compacta (Fonnum et al., 1974).

Lesions experiments have been useful in determining the role of GABA in the striatum. Fonnum and co-workers (1974) reported a loss of GAD activity in the putamen, caudate nucleus, globus pallidus and nucleus entopeduncularis after substantia nigra lesions in the cat. Transection of the strio-nigral system in baboons also reduced (by 70%) the GAD activity in the ipsilateral substantia nigra, and slightly decreased GABA-transaminase (degradative enzyme) activity (Katsoka et al., 1974).

Levels of GABA in the substantia nigra, but not in the striatum, also are reduced after lesions of the strionigral system in rats (Kim et al., 1971). In the rat, intraventricular injections of 6-hydroxydopamine had no effect on levels of GABA, GAD or GABA-transaminase, implying that there is not a one-to-one connection between the dopaminergic nigrostriatal system and the theorized GABA-minergic strionigral system (Kim, 1973).

Other evidence for the role of GABA as neurotransmitter for the strio-nigral system comes from electrophysiological studies. Stimulation of the striatum was reported to cause monosynaptic inhibition in the cat substantia nigra, and this inhibition was picrotoxin sensitive (Precht and Yoshida, 1968). Feltz (1971) demonstrated that microiontophoretic application of GABA depressed the firing rate of cells in the substantia nigra. In addition, Okado and Hassler (1973) reported that stimulation of nigral slices increased the uptake and release of GABA-¹⁴C. Although there are still some investigators who believe that acetylcholine is the transmitter in the strionigral system, based on histochemical studies of acetylcholinesterase staining, the mounting evidence, as presented above, does seem to indicate GABA in this role.

Norepinephrine

The concentration of norepinephrine in the striatum is low (0.25 μ /g of norepinephrine compared to 7.50 μ g/g of dopamine in the rat) (Iversen, 1967). There is at present no proposed functional role for this neurochemical in the striatum.

Neurochemical Interactions and Feedback Mechanisms

Control of dopaminergic function in the striatum has been studied with respect to possible sites of feedback mechanisms and interactions with other neurotransmitter systems. There appears to be an interaction between activity of the dopamine receptor and dopamine metabolism and/or release. Haloperidol, which blocks dopamine receptors (Rossum, 1966), was found to increase homovanillic acid in the striatum (Anden et al., 1964; Lavery and Sharman, 1965; Anden, 1970; Goldstein et al., 1973), increase the rate of disappearance of dopamine after treatment with alpha-methyl-p-tyrosine, the tyrosine hydroxylase inhibitor (Anden and Bedard, 1971), and increase the synthesis of labelled dopamine in striatal slices (Goldstein et al., 1973). Conversely, apomorphine, which stimulates dopamine receptors (Anden et al., 1967; Ernst, 1967), produces a decrease in levels of homovanillic acid (Roos, 1969), reduces the rate of disappearance of dopamine after alpha-methyl-p-tyrosine (Anden and Bedard, 1971), and inhibits the synthesis of labelled dopamine in striatal slices (Goldstein et al., 1970). These results were interpreted as evidence for a feedback system in which dopamine receptor activation slows turnover of dopamine, and receptor inactivation increases dopamine turnover. This feedback mechanism could be located at the dopaminergic synapse. Apomorphine can still cause a decrease in dopamine turnover, which is blocked by haloperidol, after lesion of the nigrostriatal tract (Kehr et al., 1972). Also, the inhibition of dopamine synthesis after dopaminergic stimulants is present in isolated striatal slices (Goldstein et al., 1973).

Other investigators have argued for a neuronal feedback mechanism involving acetylcholine. Clinical observations of the ameliorative effects of anticholinergics on Parkinsonism and Parkinson-like tardive dyskinesias after long-term neuroleptic treatment suggested that there may be reciprocal interaction ("balance" or functional equilibrium) between dopamine and acetylcholine. Behavioral studies supported the "balance" theory. Anticholinergic agents potentiated the effects of amphetamine (which releases dopamine, Glowinski and Axelrod, 1965; Carlsson et al., 1966) on stereotypy, locomotor activity, avoidance learning, and resistance to extinction of bar-pressing (Carlton, 1961; Carlton and Didamo, 1961; Fibiger et al., 1970). In contrast, pilocarpine inhibits the hyperactivity induced by d-amphetamine (Fibiger et al., 1970). The catalepsy induced by dopaminergic blocking agents (e.g. haloperidol or spiroperidol) was found to be reversed by an anticholinergic drug, scopolamine (Corrodi et al., 1972; Anden and Bedard, 1971). Neurochemical studies also added to the accumulating evidence for a dopamine-acetylcholine reciprocity. Anticholinergic agents (scopolamine, atropine, trihexyphenidyl) antagonized the haloperidol-induced increased disappearance of dopamine fluorescence (Corrodi et al., 1972), antagonized the haloperidol-induced increase in homovanillic acid (Bartholini and Fletscher, 1971; Anden, 1972), and antagonized the haloperidol-induced increase in disappearance of dopamine after alpha-methyl-p-tyrosine (Anden and Bedard, 1971). Agents which increase cholinergic activity (oxotremorine, physostigmine) cause an increase in homovanillic acid which is blocked by muscarinic blocking agents

(atropine, trihexyphenidyl) (Anden, 1974; Nose and Takemoto, 1974).

Agents which reduce cholinergic function (atropine, scopolamine) lower homovanillic acid levels and reduce dopamine turnover (Anden and Bedard, 1971).

One proposed site of feedback regulation of dopaminergic function by cholinergic neurons may be in the substantia nigra. Corrodi and co-workers (1972) proposed that the interaction was subserved by a descending cholinergic strionigral system. However, Bedard and Larochelle (1973) found that sectioning the strionigral system had no effect on the increase in homovanillic acid seen after haloperidol administration. After recent evidence pointed to GABA, and not acetylcholine, as the neurotransmitter in the strionigral system, Javoy and co-workers (1973, 1974) hypothesized that the feedback system was in small cholinergic neurons in the substantia nigra. They found that infusions of carbachol (cholinergic agonist) directly into the substantia nigra increased dopamine levels in the striatum without affecting dopamine synthesis, thus decreasing dopamine utilization. Infusions of atropine into the substantia nigra had no effect on dopamine levels in the striatum, but increased dopamine synthesis and increased the rate of disappearance after decarboxylase inhibition, thus activating dopamine utilization. Since these effects were apparent very shortly after the nigral infusions, they felt that the cholinergic influence was probably at the level of the substantia nigra.

Another site where one might expect dopamine-acetylcholine interactions to occur is in the striatum. Cholinergic activity in the striatum can be altered by drugs which interact with the dopamine receptor. Piribedil, a dopaminergic agonist, increases acetylcholine levels in the striatum, but not in the mesencephalon, cerebellum or cerebral hemispheres (Ladinsky et al., 1974). This increase in acetylcholine is not accompanied by changes in either cholineacetyltransferase or cholinesterase activity, or choline levels, implying an effect on release. Furthermore, the effect was blocked by pimozide, a dopamine receptor blocking agent, but not by inhibition of tyrosine hydroxylase, indicating the involvement of a dopamine receptor in the mechanism of release inhibition. Other investigators have reported similar results after L-dopa, apomorphine, d-amphetamine, or trivastal (Sethy and Van Woert, 1973, 1974a, 1974b; Consolo et al., 1974). The effect on release is opposite after treatment with dopamine antagonists (chlorpromazine, haloperidol, pimozide or clozapine); these drugs decrease acetylcholine concentration in the striatum (Sethy and Van Woert, 1974a, 1974b) and they increase the acetylcholine collected in push-pull cannulae in the caudate nucleus with no change in cholinergic enzyme activity (Stadler et al., 1973). Again, the increased release appears to be specific to the striatum; the effects are not seen in subcortex, hippocampus or posterior cortex (Sethy and Van Woert, 1974b) or in the limbic system or cortex (Bartholini et al., 1973). Apomorphine reversed the effect of chlorpromazine, and by itself decreased release of acetylcholine into the cannulas (Bartholini et al., 1973), supporting the theory that dopaminergic

influence on cholinergic neurons involves a direct inhibitory receptor effect on these neurons, (McLennan and York, 1967; Wooley, 1970). The above results are more consistent with the dopamine neuron ending on a cholinergic interneuron than with two antagonistic systems converging on a target neuron (Stadler et al., 1973), and place a possible site of cholinergic-dopaminergic balance within the striatum (Sethy and Van Woert, 1974b). However, one group of investigators believe that there is no direct dopaminergic action on cholinergic neurons. Jones and coworkers (1973) reported that administration of amphetamine, L-dopa, alpha-methyl-p-tyrosine, or dopamine had no effect on the release of ACh into cups placed on the ventricular surface of the caudate nucleus in cats. There are probably several sites of dopamine and acetylcholine interaction which cannot all be explained by any one model as yet.

Associative Behaviors Involving Striatal Function

Studies in 1959-1963, as described earlier, demonstrated that the striatum is involved in recent memory because striatal lesions caused deficits in delayed alternation and delayed response. Interest in the role of the striatum in learning and memory has continued, especially in the last several years. This interest has been heightened by reports of impaired learning and memory in Parkinson patients, with an increased prevalence of dementia (Warburton, 1967; Ceesia and Wanamaker, 1972; Loranger et al., 1972b). In 1882 Ball had commented that "a slight degree of intellectual disturbance is almost the rule in this disease" although Parkinson had reported that "the senses and intellects were uninjured" (Parkinson, 1817). The mental deterioration of Parkinson

patients has been best correlated with the akinetic component of the disease, and this component is best correlated with deficits in dopamine (Barbeau, 1974) implying a crucial role of the nigro-striatal system. Animal experiments designed to measure the influence of striatal function on associative behaviors can use lesion or stimulation techniques and will be discussed in that order.

Any consideration of lesion experiments must recognize that recovery from the acute effects of the lesion is possible, and may be time-or use-dependent, or both. In addition, the intra-caudate location of the lesion is an important factor in these studies, because lesions in ventral sites will probably affect proportionately more of the fibers as they enter the caudate nucleus. Furthermore, since neuroanatomically the striatum in rodents differs from that of higher animals in that the putamen and caudate nucleus are fused, only those studies involving rats or mice may be considered directly applicable to the present project. Many of the lesion studies to be considered involve the use of avoidance or escape conditioning. In both cases the animal's response can affect the number or duration of negative reinforcements received (usually footshock). In escape conditioning, the subject can learn to terminate the shock by responding appropriately. In avoidance conditioning the animal can learn to avoid the punishment by emitting the correct response to a signal (conditioned stimulus) before the onset of the shock. Common responses the animal must learn to emit are jumping (onto either a ledge or a pole) or "shuttling" from one compartment to another in a box divided

by a hurdle (shuttle box). Some shuttle boxes require the animal to go back and forth during the test automatically (two-way shuttle boxes) while in other paradigms the experiment starts the animal in each trial (one-way shuttle). Since these procedures require the performance of a response to avoid the shock, they are termed "active avoidance." In some avoidance conditioning experiments the animal is required to inhibit a previously learned response in order to avoid the shock. For example, the animal may have to remain in one compartment of a two compartment box, or may have to refrain from eating or drinking. This procedure is called "passive avoidance".

Avoidance conditioning was one of the first procedures employed to investigate the effects of striatal lesions on learning. Thompson (1959) found that combined lesions in the caudate nucleus and the frontal cortex in cats caused temporary deficits in avoidance learning, which he interpreted as a sign of disturbances in behavioral feedback control. He later reported that lesions of the caudate nucleus and lateral gyri also produced avoidance retention deficits (Thompson and Mettler, 1963). Fox and co-workers (1964) reported conflicting results. Cats with bilateral lesions of the caudate nucleus were tested for active avoidance learning in a two-way shuttle box, but there was no impairment seen. General agreement with the results of the Thompson group was reported by a third group, Green and colleagues (1967). Here rats with bilateral electrolytic lesions of the caudate nucleus were impaired on avoidance performance in a two-way shuttle box. However, rats with similar lesions in another experiment (Albert and Bignami, 1968) were no different from controls. Winocur and Mills

(1969) advanced an explanation of the contradictory findings after they also demonstrated normal learning of a one-way shuttle box active avoidance paradigm in rats with bilateral electrolytic caudate lesions. According to these authors, the factors distinguishing those studies showing impairments from those showing no change were the locus and extent of the lesion. Their histological findings, and those of Albert and Bignami (1968) and Fox et al., (1964) reported major damage to the more anterodorsal regions of the caudate nucleus, while the Thompson (1959) and Green et al., (1967) lesions were larger and in a more postero-ventral position. To support their theory of "functional dissociation" within the caudate nucleus, a second study (Winocur, 1974) demonstrated that rats with posteroventral lesions had greater difficulty learning avoidance problem than those with anterodorsal lesions, although the later group also had significant learning deficits. An alternative explanation is that the avoidance deficits are due to specific damage to nigrostriatal system rather than to functional localization in the caudate nucleus. Thus, those lesions which disrupted a greater proportion of the nigrostriatal fibers as they entered the caudate, from a ventral and posterior position, would produce greater deficits than those lesions in anterior and dorsal regions, which would damage relatively fewer fibers as they were distributed homogeneously throughout the caudate. Consistent with this explanation is the finding that small bilateral substantia nigra lesions in rats cause active avoidance deficits greater than those produced by anteroventral caudate lesions (Mitcham and Thomas, 1972). Bilateral injections of

6-hydroxydopamine into the substantia nigra in rats also blocked learning of a one-way active avoidance task (Fibiger et al., 1974). Intracisternal (Cooper et al., 1973) or intrastriatal (Neill et al., 1974a) injections of 6-hydroxydopamine also impaired active avoidance behavior, and in both cases the impairment was correlated with dopamine depletion in the striatum. Alternatively, Kirkby and Polgar (1974) recently demonstrated no difference in active avoidance learning between anterodorsal lesioned groups and posteroventral lesioned groups, both of whom were impaired on the task under different conditions of shock levels and food deprivation, and suggest that differing results in other studies are probably due to differing testing conditions (illumination, spatial cues, presence of barrier). The effect of striatal lesions on passive avoidance behavior has also been studied. Cats trained to approach a feeding compartment learned at the same rate whether or not they had previously sustained lesions of the caudate nucleus (Fox et al., 1964). When a shock was paired with the food dish, however, the lesion group re-entered the feeding compartment significantly sooner than did the control group. Since these same animals were not impaired on an active avoidance task, or on the initial instrumental learning, the authors interpreted their results as a selective block of response inhibition normally mediated by the caudate nucleus, in accord with the Mettler theory of the inhibitory role of the striatum. Passive avoidance deficits after bilateral electrolytic lesions of the caudate nucleus have also been reported in rats (Winocur, 1974; Winocur and Mills, 1969; Mitcham and Thomas, 1972) and in mice (Glick and Greenstein, 1973; Glick et al.,

1974b). Lesions induced by 6-OHDA intracisternal injections, however, did not impair passive avoidance learning (Cooper et al., 1973).

The early studies on caudate lesions and spatial behavior in monkeys had demonstrated a relationship between this region and delayed alternation, as discussed earlier (Rosvold and Delgado, 1956; Battig et al., 1960). Delayed alteration has also been studied in the rodent, with particular focus on the role of spatial behavior in this task. Chorover and Gross (1963) reported that caudate lesions in rats impaired performance on a simple two-bar alternation task where subjects were rewarded with each alternated bar press. In a more complex alternation task, where only single left presses followed by single right presses were rewarded, caudate-lesioned rats were again impaired (Gross et al., 1965). In both studies, performance in the Hebb-Williams maze was not altered by caudate lesions, which indicates specific effect of the lesion on a spatial task (the alternation test) as opposed to a primarily visual task (the Hebb-Williams maze) and argues against a generalized deterioration in behavior.

Spatial alternation and position learning in a different apparatus, a T maze, was studied by Mikulas (1966). In the alternation task, the rats were required to enter the left arm of the T maze on odd-numbered trials, and the right arm on even numbered trials, for a total of ten trials. The the subjects were trained to go only to one side of the maze (position learning). In both tests, water reward was available at the end of the "correct" arm.

Rats who had received bilateral radio-frequency lesions of the caudate nucleus two weeks prior to training were significantly impaired in learning the spatial alternation habit but not the position habit. The impairment was somewhat ameliorated by a light cue over the "correct" arm, implying that the deficit was spatial and not visual. The authors interpreted the lack of impairment on position learning as a lesion-induced increased perseveration which was adaptive to the performance of that task. Alternatively, since the position task was learned only after successful learning of the spatial alternation task (and only three out of eight lesioned rats reached criterion), the time after surgery and the experience of the subject were greater when tested on the position test. Thus recovery of function may be a possible explanation (mice with caudate lesions recovered from passive avoidance deficits by one month after surgery, Glick et al., 1974b). Contradictory results on spatial tasks were reported by Schwartzbaum and Donovik (1968). Four days after surgery (bilateral caudate lesions) rats were trained to barpress on either the right or the left lever in a two-lever shuttle box (spatial discrimination). A second experiment required the subject to discriminate which lever had the brightest illumination on a display unit above each lever (brightness discrimination). Caudate-lesioned animals were not impaired on the spatial discrimination test, although they were impaired on the brightness discrimination. A third experiment examined the effect of the lesion on spatial alternation in the two-lever shuttle box. The caudate-lesioned animals were no different from controls in median number of sessions to criterion, but did show significantly more errors in the first few days of testing.

A more elaborate test of spatial behavior was devised by Potegal (1969) using a radial maze with twelve arms, 30° apart. He found that caudate-lesioned rats were impaired on several spatial tasks using this apparatus, and found that these subjects tended to repeat 150° or 120° turns in the same direction at choice points. This is reminiscent of the observation by Lashley (1921) that rats with unilateral caudate lesions would always turn in the same direction (contralateral to the side of the lesion) to solve a maze problem even if this meant a 270° turn. Potegal's results may be indicative of asymmetrical size of the lesion on either side, or a more posterior localization of the lesion on one side vs. the other side. The histology in this study showed a correlation between the degree of impairment and the more posterior location of the lesions, similar to that found in the avoidance studies. Again, this might be interpreted as implying a crucial role of the nigrostriatal system, or, as Potegal suggests, a functional locus within the caudate nucleus. An interesting complement to these experiments in spatial behavior in animals is the report by Bowen and colleagues (1972) that Parkinson patients performed significantly below control levels on an established test of spatial orientation, route-walking guided by a visual map.

Another important aspect of striatal function is its relationship to behavioral parameters of arousal. Physiological arousal refers to activity in the ascending reticular activating system, classically monitored by the degree of desynchronization in the EEG. Behavioral arousal refers to those measures of behavior which have been shown to correlate with physiological arousal, e.g. locomotor activity, defecation,

startle response, and performance levels on more complex behavioral tasks. A relationship between arousal and behavior was proposed by Hebb in 1955. He distinguished two different effects of a sensory event, its "cue function" and its "arousal or vigilance function". The effectiveness of the cue function as a guide to behavior increases monotonically with increases in arousal up to an optimal point, and then decreases non-monotonically with further increases in arousal. An optimal level of arousal is therefore postulated to be necessary for an optimum level of performance. Thus any examination of the associative effects of damage to a particular site in the brain must also consider the effects on arousal as well, since the two are interrelated. Hyperactivity has been observed after caudate lesions in monkeys (Rosvold and Delgado, 1956; Dean and Davis, 1959) and in rats (Whittier and Orr, 1962; Kirkby, 1967, 1973). Rats also defecated more and groomed less after bilateral caudate lesions but only in stressful testing situations (Kirkby, 1973). Intracisternal injections of 6-hydroxydopamine also increased locomotor activity in rats (Cooper et al., 1973). However, hypoactivity has also been reported after caudate lesions (Neill et al., 1974b). No change in locomotor activity after ventral lesions was seen when activity was measured by open field or stabilometer (Neill et al., 1974b). Bilateral 6-hydroxydopamine lesions of the nigrostriatal system also produced hypokinesia (Ungerstedt, 1974). Thus it is difficult to interpret the relationship between arousal (activity) and striatal functioning in other behaviors (learning and spatial). However, these conflicting results do argue against any theory of striatal function based solely on release of inhibition of cortical processes.

A second approach to the study of the relationship of striatal function to associative behaviors has been through the use of local electrical stimulation of the caudate nucleus or the nigrostriatal system. This procedure presents difficulties in comparing studies. The exact location of the stimulating electrode, the spread of the current to adjacent structures, and the frequency and amplitude of stimulation are important variables which may affect the results of seemingly similar studies. Stimulation of an area should not be always seen as the reverse of lesioning the same area; rather, the disruption of ongoing processes is as likely as an enhancement of physiological functioning.

The striatal related behavior that has been studied most extensively by use of electrical stimulation is passive avoidance learning. Wyers and his co-workers (1968) found that post-trial bilateral stimulation of the caudate nucleus impaired learning of two passive avoidance tasks. In the first task, rats trained to press a lever to obtain water were administered footshock through the lever, and received a single pulse stimulation at 0.1 to 30 seconds after the footshock. Stimulation at the time intervals tested were effective in blocking retention of the experience. The effect of post-trial caudate stimulation was also tested on a second type of passive avoidance task to see whether the effect was general, and the results were the same. Control placements in the internal capsule, corpus collosum, and subcortex did not produce amnesia, implying the effect was not due to current spread. In a series of further studies by this group, these results were extended (Wyers and Deadwyler, 1971, Wyers et al., 1973). Post-trial stimulation was found to be effective at five minutes after the footshock, but not at 15 minutes, indicating a retrograde amnesia

gradient similar to that produced by ECS (Wyers and Deadwyler, 1971). Pre-trial stimulation was found not to impair passive avoidance learning. The post-trial deficit was still present when the animals were retested four days later, implying that long-term as well as short-term memory for passive avoidance was disrupted (Wyers et al., 1973). These results have been confirmed by Gold and King (1972) and Haycock et al., (1973). Post-trial stimulation of the pars compacta of the substantia nigra but not surrounding structures also disrupts passive avoidance retention (Routtenberg and Holzman, 1973), which tends to implicate disruption of the nigrostriatal system as mediating the dysfunction in passive avoidance learning.

Two studies of spatial behavior have involved the use of electrical stimulation techniques. Donovan and Schwartzbaum (1966) reported that bilateral caudate stimulation impaired the reversal of a spatial discrimination, but not a brightness discrimination. Complex maze learning was also impaired by bilateral caudate stimulation when applied after each choice point in a Lashley III maze (Peake and Herz, 1971). Instrumental learning has also been studied for the effects of striatal stimulation, starting with the report of "arrest" by Buchwald et al. (1961) as discussed earlier. A parametric study of the effect of stimulation on bar-pressing (Deadwyler et al., 1974) found that response inhibition was relative to the intensity, frequency, and duration of stimulation. Although the decrease in response rate is interpreted as supporting an inhibitory role of the striatum, the results of another study imply that an alternative explanation is possible.

Herz and Peeke (1971) also studied the effect of caudate stimulation on bar-pressing, but administered the stimulation during a five minute period when the responses were not rewarded (extinction). They hypothesized that if the effect of the stimulation was inhibitory, then responding during this period would decrease. If, however, the effect of the stimulation was the disruption of memory formation, then responding during this period would not decrease, since extinction consists of learning not to respond to previously reinforcing stimuli. Stimulation during extinction did not decrease responding, and higher rates were seen with increased frequency of stimulation indicating that the effect was not inhibitory. Thus the interpretation of the effects of the stimulation on bar-pressing is still unclear. Another study has examined the effects of caudate stimulation on habituation (Deadwyler and Wyers, 1972). Habituation was defined as the rate of decrease in response rate with time. An animal with a high level of arousal may habituate to a novel stimulus slower than an animal with a lower level of arousal. Deadwyler and Wyers (1972) found that habituation to a light flash was impaired by caudate stimulation. They concluded that the striatum functions as an important link between sensory processing and motor effector mechanisms.

Unilateral Disturbances in Striatal Function

The preceding experiments have examined the effects of bilateral disturbance (ablation or stimulation) of striatal function on associative behaviors. Recently, a reinterest in the phenomena of circling, or rotation, after unilateral striatal dysfunction

(originally described over a hundred years ago) has focused on the neuroanatomical localization of this behavior and its use as a model of drug action. Anden and co-workers (1966) reported that unilateral electrolytic lesions of the crus cerebri, in the path of the ascending dopaminergic nigrostriatal system, also caused turning towards the side of the lesion in rats. This asymmetry, as well as an identical asymmetry after suction lesions of the striatum, lasted two to three days after surgery, and was correlated with a 60% loss of dopamine in the striatum of the lesioned side. Further evidence for the localization of the turning behavior in the nigrostriatal system was the demonstration that unilateral 6-hydroxy-dopamine injections into the substantia nigra in rats caused ipsilateral rotation and concurrent selective loss of dopamine fluorescence in the caudate nucleus (Ungerstedt, 1969). Lesions involving the substantia nigra produced rotation while lesions of areas in the mid-brain dorsal to the substantia nigra did not (Crow, 1971). Electrical stimulation experiments also added evidence for the localization of rotation: contralateral rotation occurred during stimulation of the nigrostriatal bundle at the level of the lateral hypothalamus in rats (Arbuthnott and Ungerstedt, 1969), the substantia nigra and structures just medial to it in the path of the nigrostriatal tract in rats (Arbuthnott and Crow, 1971), and the substantia nigra in cats (York, 1973). The interpretation of these results was that the striatum with the greater release of dopamine from the nigrostriatal system (stimulated vs. unstimulated, intact vs. lesioned) caused turning towards the opposite side of the body.

Although the rotation found after lesions of the nigrostriatal system was transient, it was observed that administration of certain drugs could re-elicite turning behavior long after surgery (Anden et al., 1966). The actions of these drugs supported the theory that rotation was directed away from the side of increased dopaminergic activity. After unilateral lesions of the substantia nigra or the striatum in rats and mice, amphetamines cause rotation towards the side of the lesion, presumably by increasing release of dopamine more on the intact than on the lesioned side (Ungerstedt, 1971b; Christie and Crow, 1971; Von Voigtlander and Moore, 1973). The action of apomorphine, however, differs with the site of the lesion; this dopaminergic stimulant also produces ipsilateral rotation after striatal lesions (Anden, 1970; Jerussi and Glick, 1975), but after lesions of the nigro-striatal system below the striatum it causes contralateral rotation (Ungerstedt, 1971c; Thornberg and Moore, 1974). The contralateral rotation may be due to a supersensitivity of the postsynaptic dopamine receptors on the lesioned side, making that side more active. Lesions of the striatum, however, would eliminate the receptors themselves, and thus ipsilateral rotation ensues. L-dopa administration also causes contralateral rotation after unilateral substantia nigra lesions (Ungerstedt, 1971c). This result, as with apomorphine, has been attributed to denervation supersensitivity, and suggest that there is enough dopa-decarboxylase still present in the lesioned supersensitive side to produce the contralateral rotation. The site of decarboxylation may be in serotonergic terminals where L-dopa is released as transmitter

(Ng et al., 1970; Ng et al., 1971). Rotation after amphetamine but not apomorphine was blocked by administration of alpha-methyl-p-tyrosine, the tyrosine hydroxylase inhibitor (Ungerstedt, 1971c; Christie and Crow, 1971; Von Voightlander and Moore, 1973), but haloperidol blocked the rotation after both drugs (Ungerstedt, 1971b, 1971c; Kehr et al., 1972). Haloperidol alone causes contralateral rotation after 6-hydroxydopamine lesions of the nigrostriatal system (Anden et al., 1966), apparently because the blocking agent is less effective on the supersensitive side.

Neurochemical specificity of rotation has been shown by several investigators. Norepinephrine appears to have little functional activity in rotation: inhibition of dopamine- β -hydroxylase, stimulation of norepinephrine receptors by clonidine, or block of norepinephrine receptors by phenoxybenzamine or propranolol all have no effect on rotation either before or after amphetamine (Anden et al., 1966; Christie and Crow, 1971; Ungerstedt, 1971b; Anden et al., 1973). The role of serotonin is also negligible, since administration of 5-hydroxytryptophan, which is converted in the brain to serotonin, does not cause rotation (Anden et al., 1966) and unilateral lesions of the raphe nucleus, the proposed origin of serotonergic terminals in the striatum, also do not produce rotation (Marsden and Guldberg, 1973). However, norepinephrine, in addition to dopamine, apomorphine, dexamphetamine, haloperidol and chlorpromazine, did cause rotation after unilateral intrastriatal infusions (McKensie et al., 1972). The effect of norepinephrine in this procedure may be due to a nonphysiological effect, since it is contradicted by other results cited

above. Injection of norepinephrine or serotonin into the striatum was shown by another investigator to have no rotatory effect (Cools, 1973).

Cholinergic influences on dopaminergic function have also been studied using the rotation model. Intrastriatal injection of atropine, the cholinergic blocking agent, causes ipsilateral rotation (Costall et al., 1972). Systemic administration of atropine or scopolamine also causes ipsilateral rotation in 6-hydroxydopamine lesioned animals (Ungerstedt, 1974) and scopolamine reverses haloperidol-induced turning (Anden and Bedard, 1971). Since the effect of the anticholinergic drugs is blocked by inhibition of tyrosine hydroxylase (Ungerstedt, 1974), the cholinergic activity appears to be modulatory of the dopaminergic system rather than primary. The direction of rotation produced by these drugs, as compared to that after dopaminergic drugs, also supports the theory of a reciprocal balance between the two neurotransmitters discussed previously.

Intrinsic Asymmetry of the Nigrostriatal System

The preceding experiments with the rotation model used animals with unilateral damage to the nigrostriatal system. Unilateral lesions were placed randomly on the left or right side of the brain with the implicit assumption that the two sides were identical. The observation by this laboratory (Jerussi and Glick, 1974) that non-lesioned, normal rats will also rotate after administration of d-amphetamine brought this assumption into question and was the direct precedent for the experiments in this thesis.

The results of a pharmacological and neurochemical investigation of rotation in normal rats (Jerussi, 1974; Jerussi and Glick, 1974; Glick et al., 1974a) indicated that there may be an intrinsic asymmetry of the left and right nigrostriatal systems. Amphetamine-induced rotation can be explained by the same mechanism as lesion-elicited rotation; release of dopamine from one striatum as compared to the other might be greater if one striatum intrinsically contained more dopamine or its content of the monoamine were more labile to the releasing action of the drug. Agents which increased dopaminergic activity all had an asymmetric effect and therefore induced rotation contralateral to the more active side. The rotation induced by amphetamine (Jerussi and Glick, 1974) or apomorphine (Jerussi and Glick, 1975) was found to be stable and consistent. Haloperidol blocked the rotation induced by these agents (Jerussi, 1974). Alpha-methyl-p-tyrosine, an inhibitor of tyrosine hydroxylase, but not diethyldithiocarbamate, an inhibitor of dopamine-beta-hydroxylase, also blocked rotation after d-amphetamine, indicating that dopamine rather than norepinephrine is primarily involved (Jerussi, 1974).

Neurochemical studies (Glick et al., 1974a) supported the postulate from the above pharmacological studies that there is a normal dopaminergic asymmetry in the striatum. The dopamine contents of left and right striata were found to differ significantly by 10-15%. This normal imbalance was potentiated by the administration of d-amphetamine (20 mg/kg) to a difference of 25%. The direction of rotation was shown to be contralateral to the side containing the higher level of dopamine. There was no intrinsic imbalance in acetylcholine in the

striatum or norepinephrine in the tel-diencephalon, nor was there any relationship to rotation with these two neurotransmitters.

Organization of Experiments

The observation that there was an intrinsic asymmetry of the dopaminergic nigrostriatal system correlated with rotation led this investigator to question the more general functional significance of this asymmetry, and to study the influence of this asymmetry on other behaviors in which the striatum is thought to play an important role, as presented in this introduction. The importance of this intrinsic asymmetry of the nigrostriatal system to the functioning of the striatum in associative behaviors is thus the hypothetical focus of this thesis.

There are two main sections in the present investigation. The first set of experiments involves the use of electrical stimulation of the brain and the second set involves the use of a T maze; both methods were chosen to analyze nigrostriatal asymmetry and compare effects of various treatments on motor, spatial, and cognitive functions.

GENERAL METHODS

Subjects

Two species were used in these experiments, rats and mice.

Rats were female Sprague-Dawley albinos, weighing 250-275 g. Mice were female CFI albinos, weighing 20 g. Rats were housed two to a cage; mice were housed six to a cage. Food and water were provided ad libitum unless otherwise specified.

Surgical Procedures

Implantation of electrodes: Rats were anesthetized with sodium methohexital i.p. The skull was inclined 5 mm and coordinates chosen according to the atlas of Pellegrino and Cushman (1967), using a Kopf stereotaxic head-holder. Electrodes used in implantation were stainless steel Formvar-coated bipolar twists, 0.02 inch diameter. With the exception of the mapping experiment, when coordinates were varied, implantation in the caudate nucleus was at 2.0 mm anterior to bregma, 3.0 mm lateral to the bregma, and 5.5 mm below the base of the skull. Electrodes were secured for chronic testing by the application of dental cement around the electrodes. After closing the scalp skin with wound clips, penicillin was administered i.m. Animals were returned to their home cages for a one week recovery period.

Lesions: Two procedures were used for lesioning rats. If the rats was already implanted with stimulation electrodes, the lesion was made using these electrodes. The subject was re-anesthetized with sodium methohexital, and a 2 mA direct current was passed for 15 sec. between the two poles of the bipolar implanted electrode,

using a grass DC constant current source. The subject's scalp was then re-closed, and it was returned to its home cage.

If there was no previous implanted electrode, the animal was anesthetized with sodium methohexital, and placed in the Kopf stereotaxic head holder, skull inclined 5 mm. A Formvar-coated unipolar stainless steel electrode was lowered into the brain; coordinates in the caudate nucleus were 2.0 mm anterior to bregma, 3.0 mm lateral to bregma, and 5.5 mm below the base of the skull. Lesions were made with a 2 mA anodal direct current for 15 sec. After an i.m. penicillin injection, animals were returned to their home cages.

Histology

At the completion of each experiment involving implantation or lesions, subjects received an i.p. injection of pentobarbital and were rapidly perfused with 10% formalin via an intra-cardiac infusion. The brain was removed from the skull, and immersed in formalin for several days. The brain was then sliced with a Yomato Koki microtome and the sections (40 μ m) were mounted on slides and stained with Luxol blue and cresyl violet. Histological verification of the site of implantation or lesion was conducted by magnifying the slide with a photographic enlarger and mapping the site in the rat brain atlas (Pellegrini and Cushman, 1967).

Drug Administration

When the experimental design specified drug administration, the following general procedures were followed. Drugs were dissolved in saline (0.9%) with the exception of apomorphine, which was dissolved in distilled, de-ionized water. The volume of injection was 0.05 cc

to 0.2 cc for both rats and mice.

Pharmacological agents used were: d-amphetamine sulphate, apomorphine hydrochloride, haloperidol, pilocarpine nitrate, scopolamine hydrobromide, and methylscopolamine hydrobromide.

Behavioral Testing

Electrical Stimulation: Rotation Test. Rats were placed in a 12 inch high by 12 inch diameter cylindrical Plexiglas chamber situated on a stainless steel grid. The implanted electrodes were connected to a lead cable attached to a mercury commutator that allowed free movement by the animal within the enclosure. Stimulation was delivered from a Grass S48 stimulator through a Grass stimulus isolation unit (constant current output) to the mercury commutator. Pulses were administered in single trains of 2 sec. duration, 5 msec. wide at 100 Hz. Pulse amplitude was varied from 10 to 300 μ A. These parameters were chosen to agree with prior studies in stimulation-induced rotation (Arbuthnott and Crow, 1971). Stimulation could be delivered unilaterally or bilaterally dependent on the experimental design.

The animal was observed for its movements within the testing chamber. The subject was first allowed a 5 min. habituation period to explore the stimulation chamber. Then, at varying current amplitudes in 10 μ A increments, the subject received three trial stimuli, 15 sec. apart, for each amplitude, with three minutes rest between amplitude changes. Rotation threshold was defined as that stimulus which was then presented on each occasion caused a 180° turn of the subject's head and body. Total turns and pre-threshold

head-turning were also recorded at stimuli above and below threshold, in addition to any other behaviors elicited by the stimulation.

T Maze Testing: The second series of experiments involved the testing of both rats and mice in T mazes. The T mazes were constructed from black Plexiglas and mounted on grid floors. The T maze for rats had a stem 30 cm long and 15 cm wide, and in two arms, each 15 cm long and 15 cm wide. The height of the walls was 30 cm. Continuous AC 0.6 mA scrambled shock could be delivered to the grid floor from a Lafayette A615C shock source. The floor was a grid of 0.4 cm stainless steel rods, spaced 1.3 cm apart.

The T maze for mice had a stem 30 cm long and 7.5 cm wide, and two arms 15 cm long and 7.5 cm wide, and two arms 15 cm long and 7.5 cm wide, and was 20 cm high. The floor was a grid of 0.2 cm stainless steel rods spaced 0.4 cm apart. Footshock could be administered from a BRS shock-generator-scrambler, SGS-003.

The subject was placed in the stem of the T maze facing away from the choice point, with the shock on. The shock was terminated when the subject entered the left or right arm of the maze; entry was defined as the presence of the total body of the subject within an arm. The subject was then removed from the maze, and the trial was then complete. Ten such trials in succession, with 5-15 sec between trials, was defined as a "test". Left and right choices were recorded; percent preference was computed as that percent of the trials towards the preferred side.

Active Avoidance Testing: The subjects used in this procedure were rats. The apparatus used to measure active avoidance learning was the two-way shuttle box (Lehigh Valley). The testing box was divided into two equal sized chambers (6 inches by 6 inches by 9 inches high) separated by a 3 inch high fence. The box was situated on a scrambled shock grid floor, counter balanced to indicate on which side the animal is standing. On the far wall of each chamber was a light bulb and a speaker attached to a tone generator. Foot-shock (0.1 mA, AC) was administered via a Lehigh Valley solid state shocker-scrambler, 113-33.

In each trial, a conditioned stimulus (light plus tone) was presented for 10 sec. in the chamber in which the subject was located. During this presentation, if the subject crossed the fence to the opposite chamber, the conditioned stimulus was extinguished and no shock was delivered. If, however, the subject did not cross the fence within the 10 sec. conditioned stimulus presentation, foot-shock was administered and the animal could then terminate the shock by crossing the fence. There was a 30-60 sec. intertrial "time out", and 100 trials were given to each subject. Avoidance responses were defined as fence-crossings during the conditioned stimulus (no shock received in that trial), and escape responses were defined as fence-crossings after the shock was turned on (shock only terminated, not avoided). Learning was measured by the number of correct avoidance responses in 100 trials.

Passive Avoidance Testing: The subjects used in passive avoidance testing were all mice. Testing for passive avoidance

learning was conducted in a step-through box (Jarvik and Kopp, 1967). The trough-shaped Plexiglas box consisted of two chambers: a light front chamber (11 cm by 11 cm) and a dark rear chamber (11 cm by 23 cm long) connected by a small opening (2.7 cm by 3.2 cm). Two parallel steel plates formed the floor of the box, so that when a mouse stood in the apparatus, it always bridged a pair of plates. Both compartments were covered by Plexiglas lids. Foot-shock could be administered through the plates in the dark chamber via a 0-500 volt Ac mA shock source. Solid-state logic and timing circuits were connected so that the latency for a subject to enter the dark chamber and thereby break a photocell beam was recorded. When the subject entered the dark chamber, footshock commenced, and was terminated when the subject re-entered the lit chamber.

Passive avoidance testing followed a two-day paradigm. On day 1, the subject was placed in the lit chamber, and the latency to enter the dark chamber recorded. After the animal escaped the shock by re-entering the lit chamber, it was removed and placed in its home cage. On day 2, the subject was again placed in the lit chamber. The latency to enter the dark chamber was recorded. No shock was administered on day 2. If the subject remained in the lit chamber for more than 600 sec., it was removed and given a latency score of 600+. The passive avoidance retention was defined as the day 2 latency to enter the dark chamber.

Activity Testing: The apparatus used to measure spontaneous motor activity was a photocell activity box (Lehigh Valley). This was a metal cylinder, 24 inches in diameter and 15 inches high. Six photocell beams

crossed the cylinder in regular array, 8 inches apart and 1 inch above the grid floor. When the subject crossed a photocell beam it registered on digital counters. The number of photocell crossings were thus defined as activity counts, and were printed out for each five minutes of the activity test.

Subjects used for activity testing were mice. The mice were placed in the box for 30 minutes.

Neurochemical Methods

Subjects for neurochemical assays of dopamine and norepinephrine were all rats. Each subject was killed by decapitation; the brain was removed immediately and dissected into four samples: left striatum, right striatum, the rest of the left tel-diencephalon, and the rest of the right tel-diencephalon. The samples were weighted and immediately homogenized in 5 ml of 0.4N perchloric acid (HClO_4) and 1.0 ml of 10% EDTA for the striatal samples, and double the volumes for the tel-diencephalon samples. Centrifugation at 27,000 G for 20 minutes followed, and the pellet was discarded. The samples were then adjusted to pH 8.4 with NaOH. The column separation procedure (Weil-Malherbe, 1968) employed alumina suspended in 10 ml 0.1 M ammonium acetate (pH 8) plus 0.3 ml 0.5 N NaOH. The sample was passed through the column and eluted in 5 ml of 0.2 M acetic acid. The samples to be assayed for dopamine (striatal samples) were then adjusted to pH 6.75 and the norepinephrine samples (tel-diencephalon rests) adjusted to pH 6.2, both with 1M K_2HPO_4 , dibasic potassium phosphate. Concentration of dopamine in each half striatum and norepinephrine in each half tel-diencephalon, were assayed by the spectrofluorometric method (Lavery and Taylor, 1968), in which the catecholamine was first oxidized with iodine-potassium

iodide to rearrange to form a fluorophore, then the fluorophore was stabilized and the reaction stopped with alkaline sulfite, and fluorescence maximized by the addition of acetic acid. Dopamine samples were heated for 40 minutes (100°C) before reading.

The particular experimental designs and additional apparatus and procedures will be discussed separately in Specific Methods and Results for better clarity.

SPECIFIC METHODS AND RESULTS

I. ELECTRICAL STIMULATION EXPERIMENTS

Experiment 1. Neuroanatomical basis of contralateral rotation

Part A. Map of stimulation-elicited contralateral rotation

Before attempting to correlate the effects of unilateral electrical stimulation on associative behaviors, a pilot study of the effects of such stimulation, including a histological map, was undertaken. Animals were implanted and tested, and brain sections analyzed, as described in the General Methods.

Contralateral circling, or rotation, was observed from implantation sites in the substantia nigra, the globus pallidus, and ventro-medial caudate nucleus-putamen (CD). Sites along the nigrostriatal bundle (Ungerstedt, 1971a) in the lateral hypothalamus and medial internal capsule also produced rotation. Two sites tested in the frontal cortex also elicited contralateral rotation. These sites are shown in Figure 1, marked Δ on the right side of the brain sections.

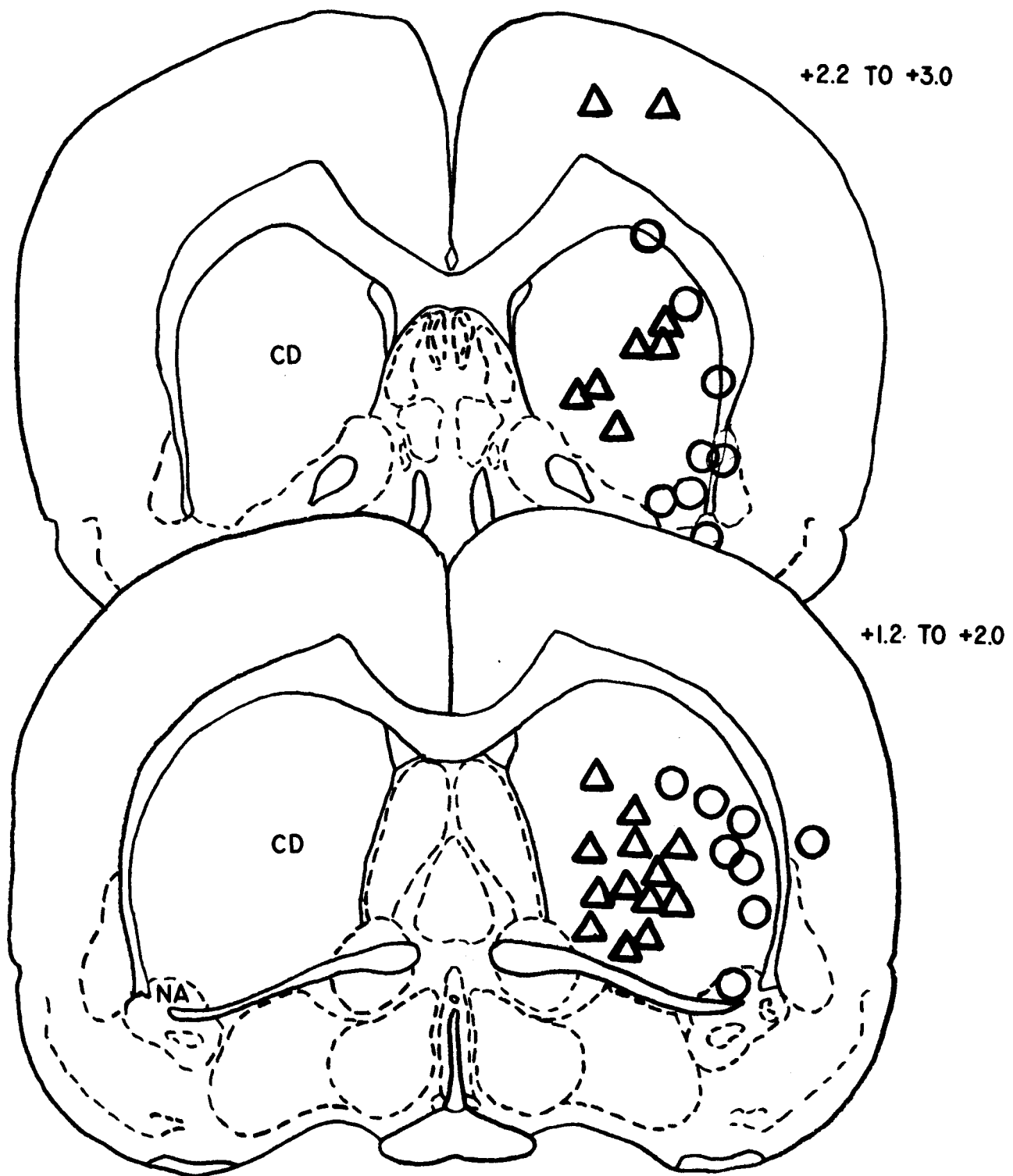
Implantation sites which did not result in rotation when stimulated under these conditions were the hippocampus, the nucleus accumbens, the zona incerta, the posterior nucleus of the thalamus, the reticular formation, and the medial forebrain bundle. Sites in the dorso-lateral CD also did not produce rotation. Posterior or temporal cortex stimulation did not cause rotation. Negative sites are shown in Figure 1, marked 0 on the right side of the brain sections.

Other behaviors in addition to rotation were observed. As the intensity of stimulation increased, the behavior of the animal tested appeared to progress through distinct phases, although the rate of change

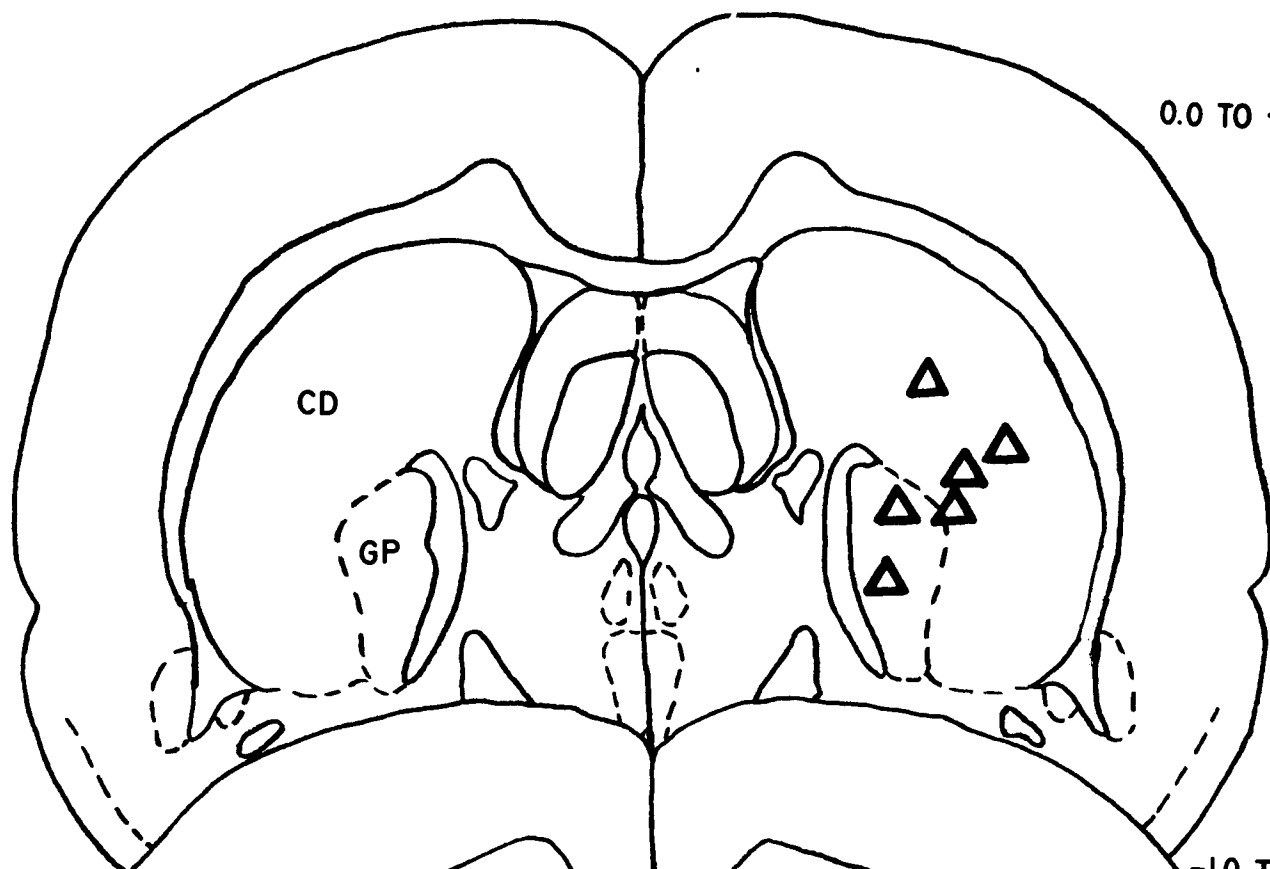
FIGURE 1

Map of electrode implantation sites: triangles (Δ) represent sites where stimulation elicited contralateral rotation; circles ($\bigcirc$) represent sites where stimulation did not elicit rotation. Coordinates are from Pellegrino and Cushman, 1967. Areas of the brain in which sites are located are:

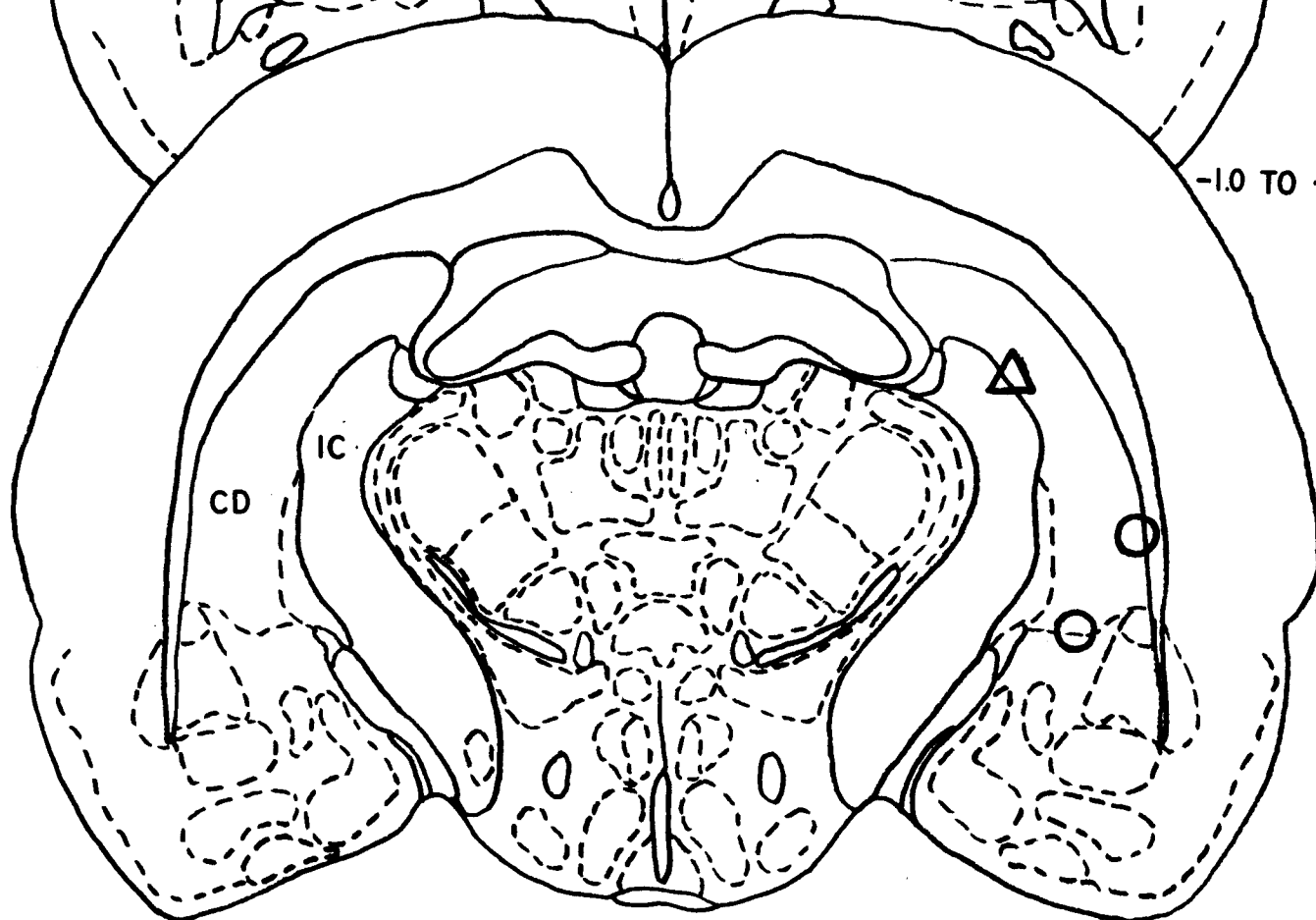
CD	caudate nucleus-putamen
GP	globus pallidus
HPC	hippocampus
IC	internal capsule
LH	lateral hypothalamus
MFB	medial forebrain bundle
NA	nucleus accumbens
PNT	posterior nucleus of thalamus
RF	reticular formation
SN	substantia nigra
ZI	zona incerta

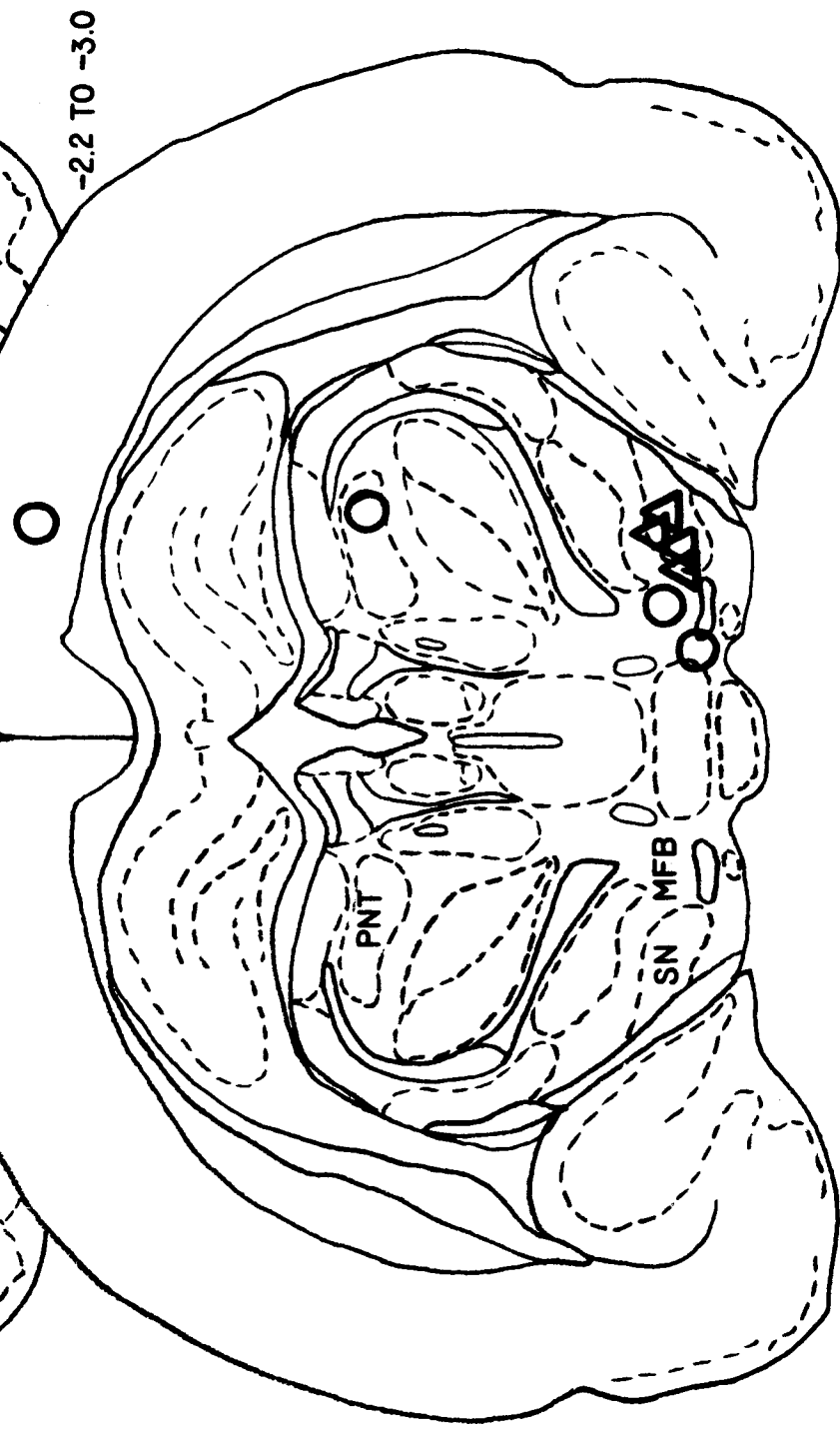
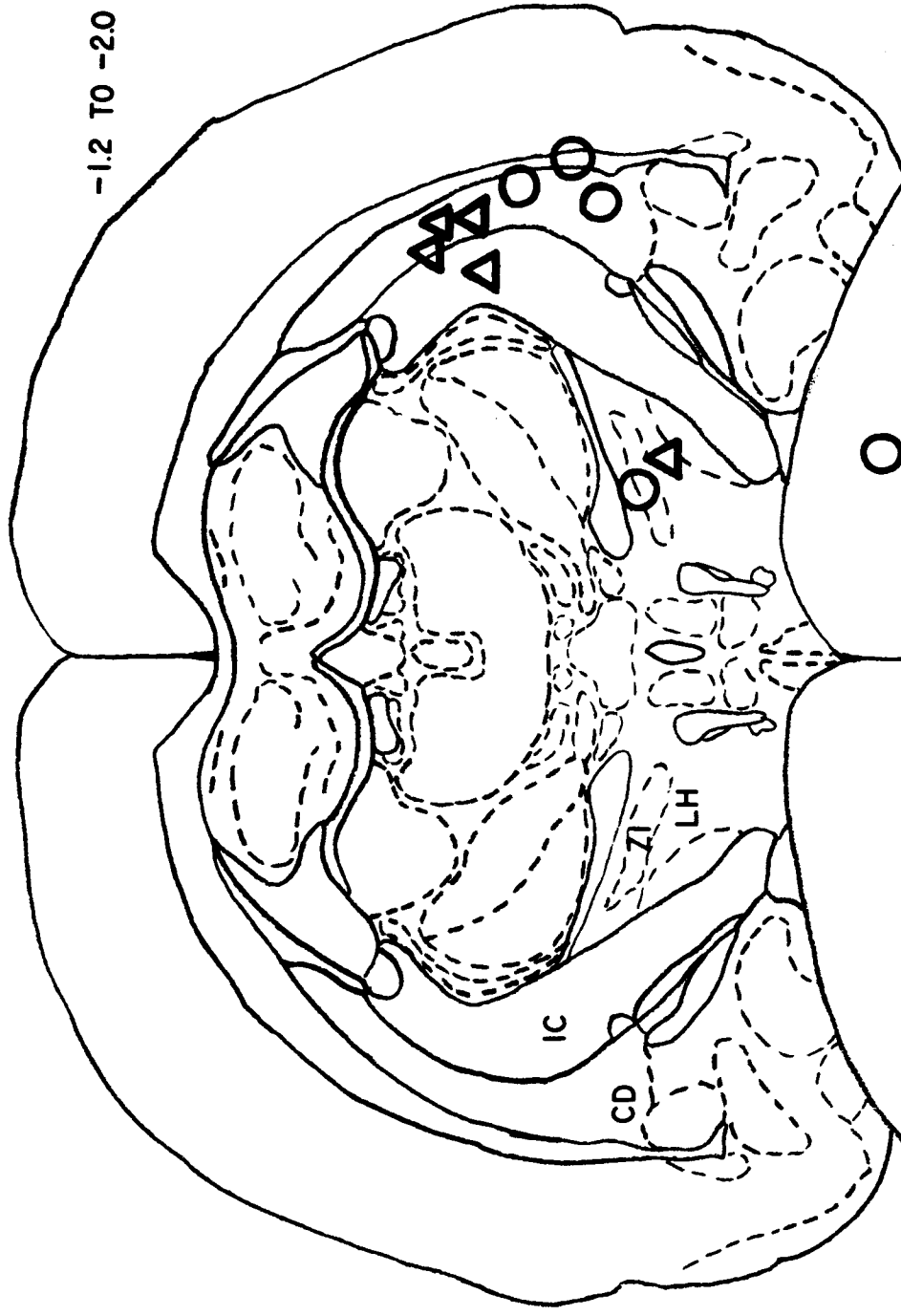


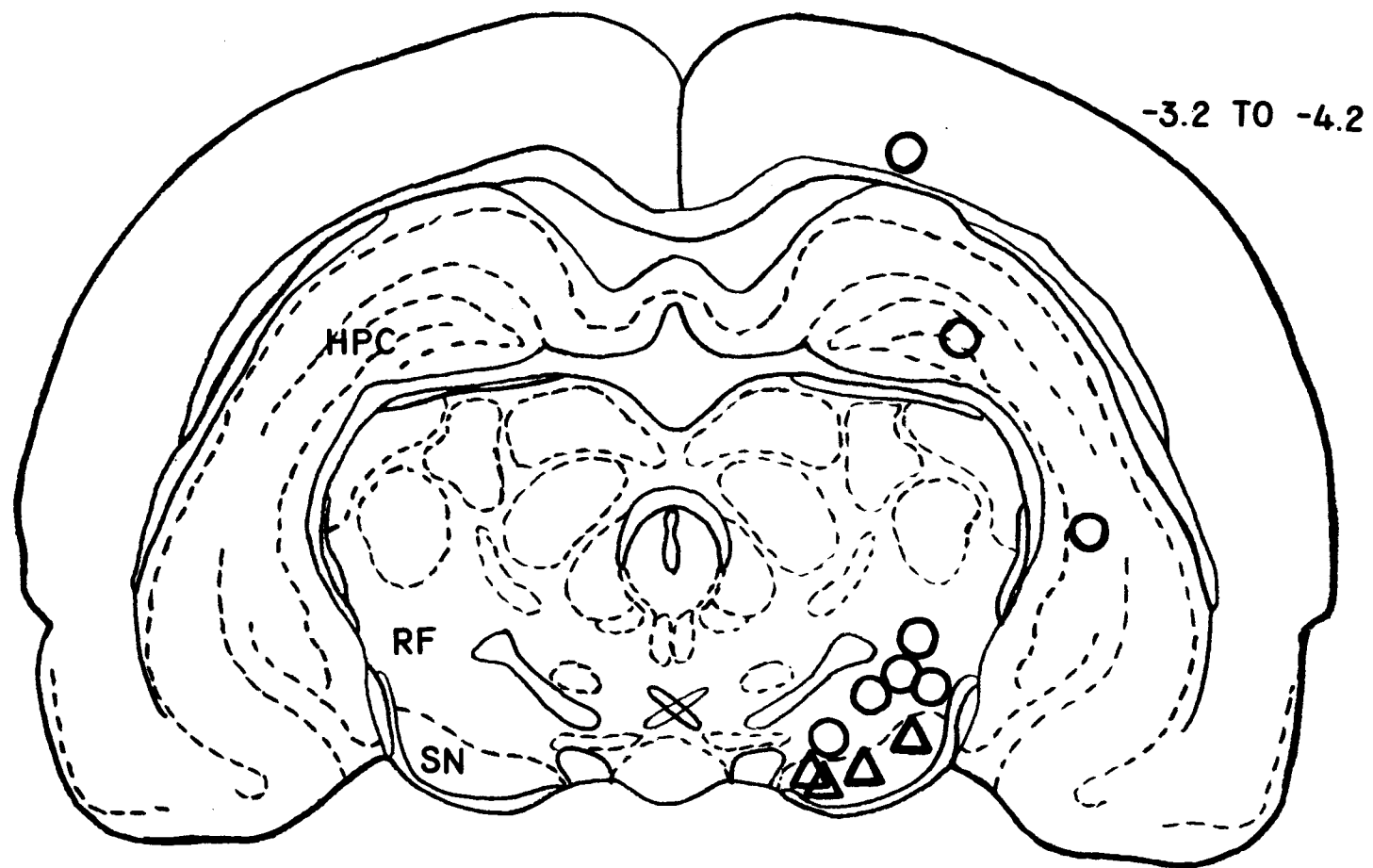
0.0 TO +1.0



-1.0 TO -0.2







was not consistent from animal to animal (i.e., one animal would exhibit a certain behavioral repertoire over a range of $100\mu\text{A}$, while a second animal would only exhibit that same pattern for $10\mu\text{A}$). The first sign of a stimulation effect was usually the lifting of the contralateral front paw. Then, at higher intensities, the paw lift would be accompanied by a raise and slight turn of the head, with an upturned contralateral lip, away from the side of the implant. Increasing stimulation produced a greater turn of the head and front paw, until a definite "quarter turn" was distinguishable. Generally the next 10 or $20\mu\text{A}$ increment produced a half-turn, defined here as rotation threshold. With greater intensity of stimulation, the animal would turn in a full circle, then two, three, or four total circles. This circling, as with the other behaviors, would terminate at the same time as termination of the stimulus, and could therefore be deemed "stimulus-bound" behavior. Even higher stimulation generally caused the animal to roll over on its back, and infrequently caused clonic seizures at very high intensities ($600\mu\text{A}$). The behavior observed at pre-threshold and threshold stimuli, in addition, did seem to look as though the animal was orienting towards that side in a purposeful sense, "as though it were looking for something", as had been reported of cats during unilateral caudate stimulation (Ursin et al., 1969).

Part B. Effect of nigral lesions on caudate nucleus stimulation-elicited rotation

The results of Part A of this experiment were intriguing in that there appeared to be a localization of function with the CD for rotation, although this nucleus is thought to have a homogenous structure. The other sites eliciting rotation followed the course of the nigro-striatal pathway, as

visualized histofluorescently (Ungerstedt, 1971a). The pattern of positive sites within the CD seemed to parallel the distribution of the nigrostriatal fibers; with sites close to its entrance into the CD or where a substantial portion of fibers would be present (caudal, ventral and medial) eliciting rotation, but those sites with only few nigrostriatal fibers or terminations ineffective in producing rotation. This possibility also suggested that the stimulation might be acting presynaptically. To test this hypothesis, the following experiment was conducted.

Rats were implanted unilaterally in both the CD and the substantia nigra (SN) of the same side, according to the General Methods. SN coordinates were 3.0 mm posterior to bregma, 2.3 mm lateral to bregma and 8.0 mm below the base of the skull. After a one week recovery period, both implanted electrodes were tested separately for rotation threshold. The data for each subject appears in Table 1. Five of the subjects had rotatory placements in the SN and three were not in the SN and were non-rotatory. All CD placements caused rotation; animals with non-SN electrodes were considered a control lesion group and treated identically to the SN group. The non-SN placements were: medial forebrain bundle (#4); zona incerta (#5) and reticular formation (#6). The subjects were then anesthetized with methohexital, and a 2 ma direct current was passed between the two poles of the bipolar SN electrode for 15 sec. The animals were awake within 30 min., and spontaneously rotated ipsilateral to the SN lesion. At four hours, one day, one week and one month post-operatively, the rats were retested for rotation. The results of these tests are shown in Table 1. Two of the five SN subjects still rotated in response to stimulation at four hours after the SN lesion. All animals showed a lack of stimulation-induced rotation from one day after the lesion and recovery

TABLE 1

EFFECT OF LESION OF THE SUBSTANTIA NIGRA ON ROTATION THRESHOLD (IN μ A)
 DURING UNILATERAL STIMULATION OF THE CAUDATE NUCLEUS OR SUBSTANTIA NIGRA

<u>Subject</u>		<u>Pre-op</u>	<u>Post-op</u>			
			<u>4 hr</u>	<u>1 day</u>	<u>1 week</u>	<u>1 month</u>
1	CD:	160	--	--	70	170
	SN:	100	--	--	300	130
2	CD:	80	60	--	100	80
	SN:	50	--	--	600	360
3	CD:	100	--	--	--	110
	SN:	70	--	--	--	80
7	CD:	120	60	--	--	--
	SN:	100	--	--	--	--
8	CD:	220	--	--	--	--
	SN:	100	--	--	--	--
4	CD:	120	140	120	160	120
	MFB:	--	--	--	--	--
5	CD:	70	70	120	160	170
	ZI:	--	--	--	--	--
6	CD:	60	60	60	50	50
	RF:	--	--	--	--	--

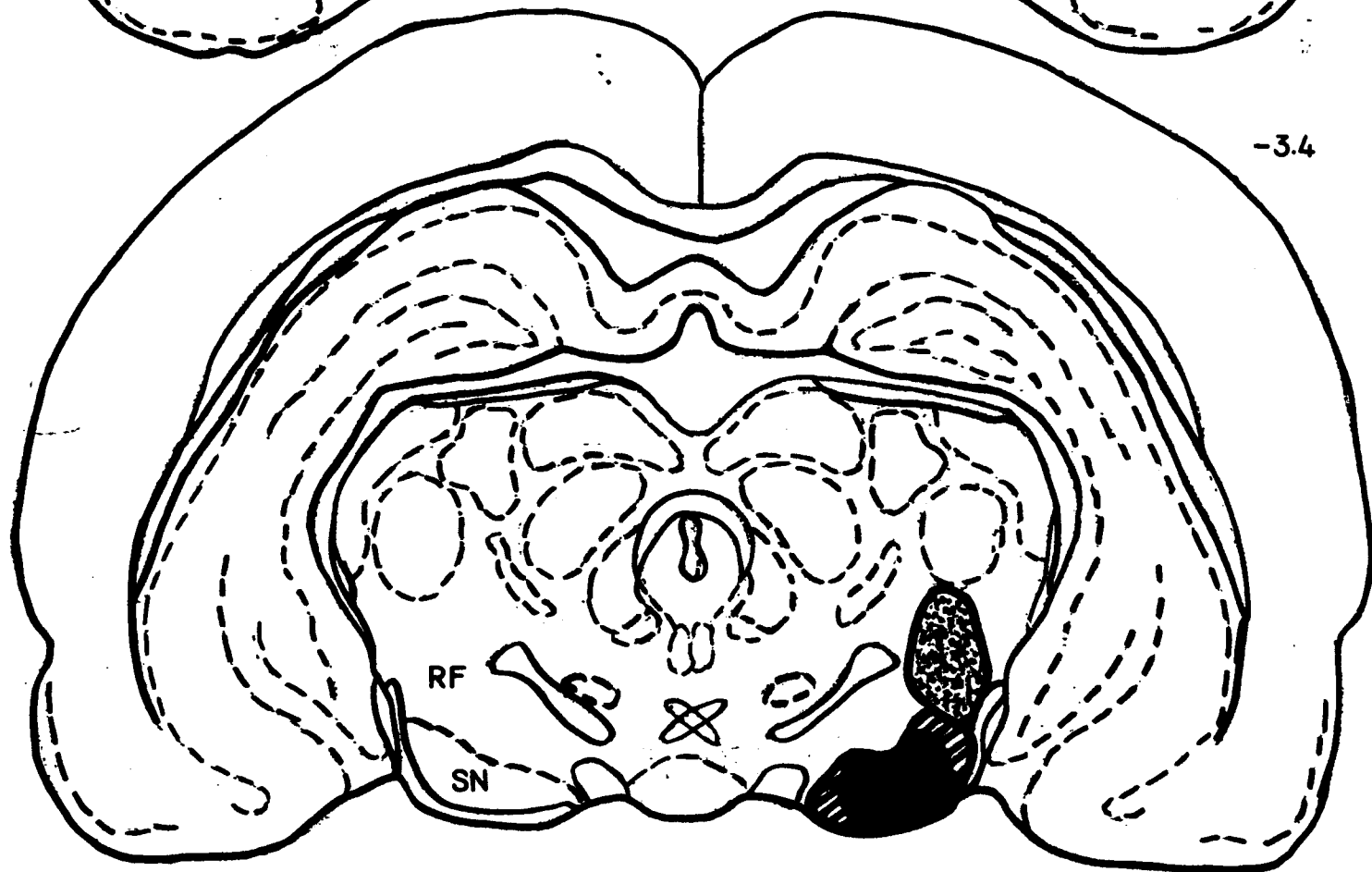
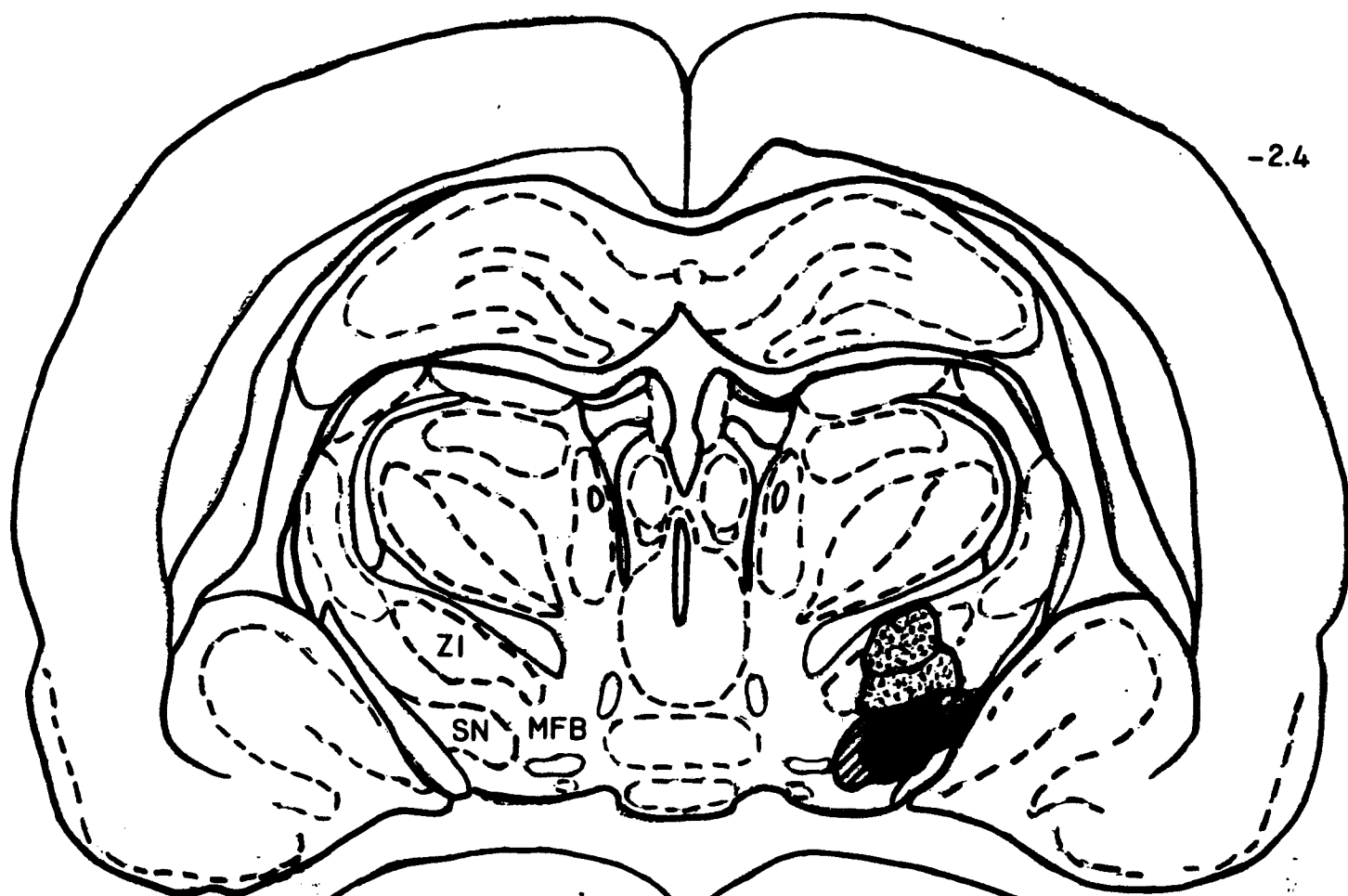
appeared in three animals thereafter at different rates. However, in no case was rotation re-elicited from the CD electrode without simultaneous recovery from the SN electrode. The results of the control lesion group are also shown in Table 1. These animals rotated contralaterally both prior to and after the lesion, with no loss of rotation from the CD electrode. This control group eliminates the possibility that there was a nonspecific change in the CD electrode from the SN lesion procedure. Histological mapping of the sites of the lesions showing minimal and maximal damage are seen in Figure 2.

Part C. Relationship of unilateral stimulation to bilateral stimulation

As part of the pilot study of the neuroanatomical basis of rotation, as supported by the results of Part A, the map, and Part B, the lesion study, a third experiment was undertaken to compare the effects of unilateral stimulation of the nigrostriatal system to bilateral stimulation. Amphetamine and apomorphine will cause rotation in non-lesioned animals (Jerussi and Glick, 1974, 1975) and these two drugs also produce a set of behavioral responses known as "stereotypy" - repetitive licking, gnawing, sniffing and rearing (Scheel-Kruger and Randrup, 1967; Randrup and Munkvad, 1967). However, there is some debate over whether the two behaviors, rotation and stereotypy, are the result of activation of a common mechanism (Anzelark et al., 1971; Ungerstedt, 1971b) or are served by different mechanisms (Costall et al., 1972). This experiment proposed to test the hypothesis that rotation and stereotypy were subserved by a common mechanism with stereotypy being bilateral activation of the rotatory system.

FIGURE 2

Unilateral electrolytic lesions (15 sec.) of the substantianigra (SN) in rats: dark areas represent the minimal extent of lesion; striped area the maximal extent. Stippled areas represent negative lesions in the zona incerta (ZI), medial forebrain bundle (MFB) and the reticular formation (RF). Coordinates (-2.4 top section; -3.4 bottom section) are from Pellegrino and Cushman, 1967.



Subjects and methods of implantation were identical to those described in the General Methods, except that in this case electrodes were implanted bilaterally in the CD. Ten rats were found to rotate contralaterally following unilateral stimulation of each electrode, using the same parameters of stimulation discussed previously. These animals were then tested for the effect of simultaneous stimulation of both electrodes at varying intensities of stimulation. Animals were then killed, electrode placements histologically verified.

Unilateral stimulation of each CD resulted in contralateral rotation, but when both CD were stimulated simultaneously at rotation threshold, no rotation was observed. Instead, the subjects were observed to rear, sniff, gnaw, lick, and groom for the duration of the stimulation only (these are behaviors described as stereotypy). Bilateral stimulation with both electrodes below rotation threshold produced no observable effect; stimulation at currents identically higher than threshold exacerbated the stereotypy. When the subjects were stimulated with one electrode at rotation threshold and the second electrode below threshold, the subject rotated contralateral to the first electrode. Similarly, with one electrode above threshold and the second at threshold, rotation was contralateral to the first electrode.

Experiment 2. Stimulation-elicited rotation as an animal model for drug effects on the nigrostriatal system

Part A. Amphetamine dose-response curve

This experiment was designed to assess the pharmacological effect of amphetamine, which causes spontaneous rotation in normal rats (Jerussi

and Glick, 1974), on stimulation-elicited rotation. To begin, a dose-response curve for the effect of amphetamine on rotation threshold was generated.

Subjects (n=5-6 per dose) were implanted unilaterally in the CD and tested for rotation as described in the General Methods. Four hours after the rotation test, subjects received an i.p. injection of saline or d-amphetamine: doses used were 0.125, 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, or 16.0 mg/kg. At 30 minutes post-injection subjects were retested for rotation.

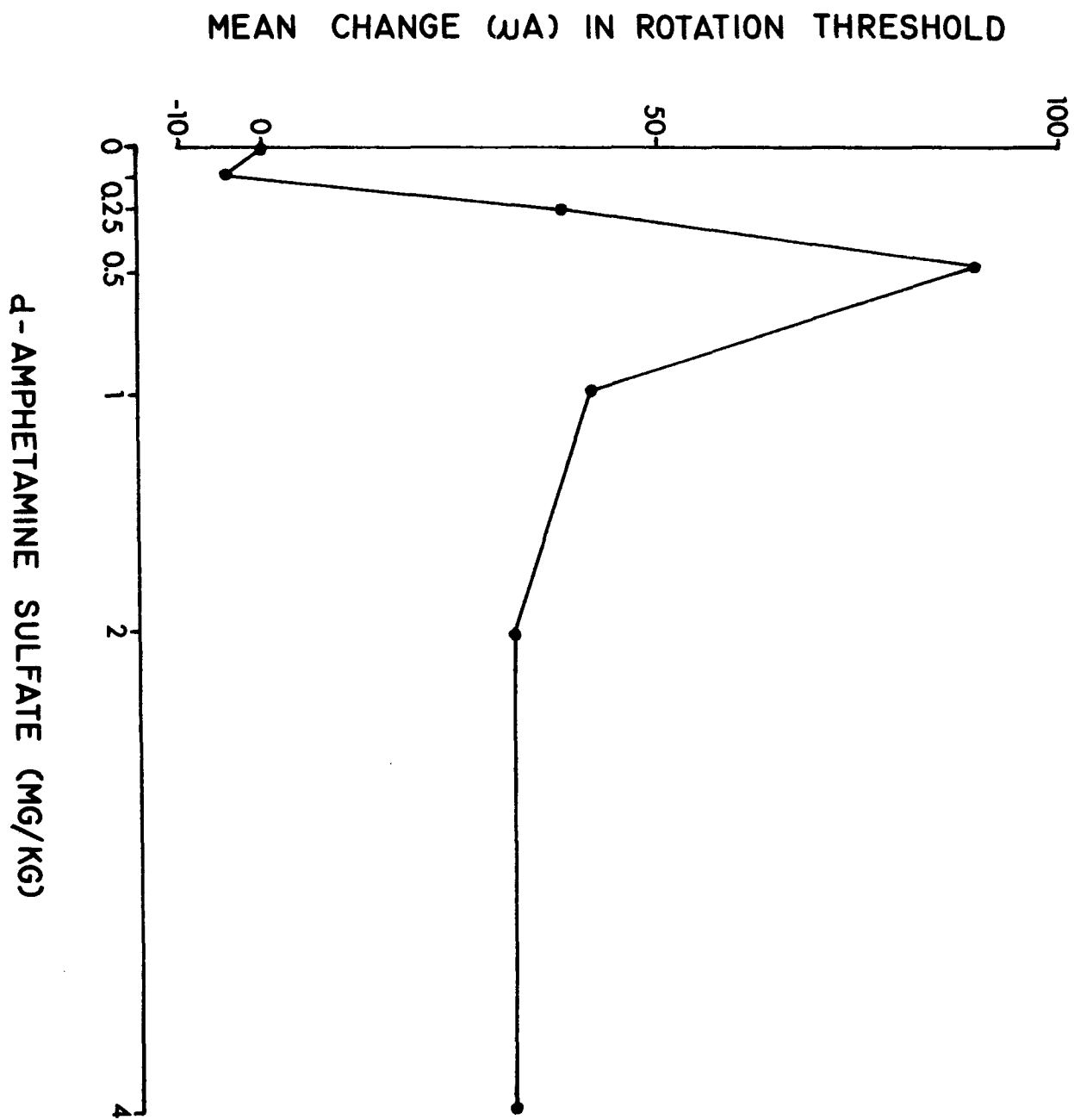
d-Amphetamine was found to increase the threshold for rotation induced by CD stimulation at 0.25, 0.5, 1.2, and 4 mg/kg, as seen in the percent change in threshold or in the difference in absolute means ($p < .05$, t test). These results are shown in Figure 3. At 8 or 16 mg/kg the animals were observed to be highly active with periods of stereotyped behaviors. They were also observed to rotate towards the side of the implanted electrode. During stimulation, the animal would turn straight ahead instead of towards the electrode. Rotation threshold determination was therefore impossible because the animal's baseline behavior was so erratic.

Part B. Spontaneous rotation experiment to explain amphetamine dose-response curve.

The expected results of Part A were that amphetamine, a dopaminergic stimulant, would decrease the intensity of stimulation required to activate the nigrostriatal system on the side of the electrode, thus lowering the rotation threshold. Surprisingly, the opposite effect was

FIGURE 3

Mean change in rotation threshold (in μA) after administration of d-amphetamine sulfate (0.125 to 4.0 mg/kg) in contralateral rotation elicited from unilateral stimulation of the caudate nucleus in rats.



observed. Because the high doses of this drug caused spontaneous rotation ipsilateral to the electrode, it was theorized that perhaps the placement of the chronic electrode was creating an effective lesion in the CD, and that the increased threshold for electrically-induced contralateral rotation was due to a competing spontaneous ipsilateral rotation. To test this hypothesis, the following experiment was conducted.

Bipolar electrodes were implanted unilaterally in the CD of six subjects and the subjects were allowed to recover, as described in General Methods. Implantation sites were verified by a rotation test. Two days later, the subjects were tested in an automated rotometer (Glick and Greenstein, 1973). This apparatus is a white opaque Plexiglas sphere, 30 cm in diameter. A flexible stainless steel wire, connected to a cam positioned on the vertical axis on the outer surface of the sphere, was wrapped around the thorax of the rat. As the rat rotated, the cam closed one of two micro switches that were positioned so as to indicate left or right turns, which were recorded automatically on a BRS POC-112 print-out counter. The subjects were placed individually in the rotometer for 15 min., and then received an i.p. injection of 0.5 mg/kg d-amphetamine and were tested for one hour.

The results of this experiment are shown in Table 2. All animals showed a rotational preference towards the side of the electrode.

The artifact indicated by the results of Part B made it necessary to abandon the use of stimulation to study drug effects on the nigrostriatal system. Stimulation, however, was still thought to be a useful way to artificially activate the system in studies of associative behaviors. The first behavior chosen for study was side preference in the two-lever Skinner box.

TABLE 2

ROTATION INDUCED BY D-AMPHETAMINE (0.5 mg/kg) IN RATS WITH A
UNILATERAL CD ELECTRODE

<u>Subject</u>	<u>Electrode Placement</u>	<u>% Left Rotations</u>
1	right	6
2	right	35
3	right	43
4	left	52
5	left	62
6	left	62

Experiment 3. Effect of unilateral stimulation on side preference

Testing in this experiment involved the use of an additional apparatus, the operant test chamber (Lehigh Valley) or Skinner box. This chamber was equipped with two levers, at the right and left of a center reward spout, and responses on either lever were reinforced with 0.01 cc water. A connecting cable was suspended from a commutator within the test chamber and when attached to an implanted electrode allowed free movement of the subject. Electrical stimulation could be delivered to the cable from a constant voltage sine wave stimulator, in 0.7 sec. pulses, 2.0 sec. apart. The animal's behavior was observed on a closed circuit video monitor mounted within an isolation chamber surrounding the test cage. In addition, responses on left and right levers were recorded on an event recorder and on digital counters.

Subjects ($n=7$) were deprived of water two days before the beginning of this experiment, and received 15 min. of water after each test session for the remainder of the experiment with the exception of the recovery period, when they received free water. The subjects were trained to barpress for water reward on a continuous reinforcement schedule (each press on either lever was rewarded). Training continued for four weeks, at which time all rats exhibited consistent side preferences. The rats were then bilaterally implanted in the caudate nucleus and allowed to recover, as explained in General Methods. They were then tested for rotation in the standard stimulation chamber; as expected, unilateral stimulation of either electrode individually produced contralateral rotation for the duration of the stimulus. The rats were then again deprived

of water, and retested for two weeks in the operant chamber under the same conditions as pre-implantation. There were no significant changes in performance (response rate) or side preference as a result of the electrode implantation.

The subjects were then tested for the effects of unilateral stimulation on their side preference. The animals were tested under the following paradigm: The subject was allowed to emit 150 responses with no stimulation delivered via the connecting cable; 150 responses during stimulation, and 150 responses with no stimulation again. Each subject received this stimulation test for at least three separate sessions, with at least three days in between test sessions with the cable connected but no stimulation delivered. Current intensity was set at 10% below rotation threshold, which was determined again under the new stimulation parameters, and could be observed on the video monitor. At the completion of the experiment, rotation threshold was determined as earlier, and found unchanged. The sites of implantation were verified histologically for each subject.

The results of this experiment are shown in Table 3. Stimulation of the caudate nucleus on the same side as the side preference caused a reversal of side preference to the opposite lever, as illustrated in Figure 4. Stimulation of the caudate nucleus on the side opposite to the preferred lever had no significant effect on side preference (only subjects 4, 5, 6 and 7 were tested, and their baseline preference was very strong and therefore an increased side preference may have been undetectable). Thus an electrically-induced increase in activity in one-half of the nigrostriatal system results in a preference for the opposite side.

TABLE 3

EFFECT OF UNILATERAL CAUDATE STIMULATION ON SIDE PREFERENCES

MEAN % RESPONSES ON PREFERRED BAR				
SUBJECT (PREF.)	TRAINING	PRE-STIM.	STIM.	POST-STIM.
1 (L)	75	73	26	68
2 (R)	67	62	16	83
3 (R)	95	71	10	21
4 (L)	99	92	18	100
5 (R)	98	100	56	90
6 (L)	99	100	86	100
7 (R)	91	60	03	55
COMBINED MEANS	89	80	31*	74

*Significantly different from PRE-STIM. and POST-STIM. at
 $p < .001$, t - test

FIGURE 4

Representative event recording showing the effect of unilateral caudate stimulation on bar-pressing; stimulation was administered to the caudate ipsilateral to the initial (PRE-STIM.) side preference (t = time with 15 sec. between markers; L = left lever; S = stimulation; R = right lever).

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Experiment 4. Effect of unilateral stimulation on passive avoidance learning

The results of experiment 3 indicated that an electrically-induced asymmetry of the nigrostriatal system can affect a spatially-related behavior. This experiment was designed to extend these findings into a seemingly non-spatial task, a passive avoidance test. A paradigm was used which was identical to that described in previous studies of the effects of bilateral CD stimulation on passive avoidance behavior (Wyers et al., 1968; Wyers and Deadwyler, 1971; Wyers et al., 1973).

Subjects (n=23), unilateral implantation of electrodes in the CD, and rotation testing proceeded as in General Methods. Rats were deprived of water for two days prior to the beginning of the experiments, and received one half-hour of water each day after the test session. At the completion of the experiment, histological verification of implantation sites was performed as usual.

The passive avoidance test utilized a drinking tube located on one wall of the rotation test chamber. A $\frac{1}{2}$ inch diameter hole, $2\frac{1}{2}$ inches from the floor, permitted access to the tube which was attached to a graduated water bottle. Each time the animal's tongue made contact with the tube, a lick was registered on a BRS MV-45 lickometer. Latency for 10, 50, 100 and 300 licks was counted on a BRS serial printout counter PO902. Each lick also delivered water to the subject from the graduated cylinder attached to the tube. A 0-500 volt AC microamp shock source was set up to deliver 0.4 mA shock through the drinking tube to the subject's tongue.

The experiment was conducted on four consecutive days. On days 1 and 2 (training days) the subjects were allowed to make 300 licks, with their electrodes connected to the cable but no stimulation on. On day 3 (Test Day), after the 300th lick, the shock was turned on for five minutes. Every touch of the tongue to the tube during that 5 min. resulted in a shock to the animal. Subjects received between three and six shocks. After the shock period, the animals received either no stimulation (n=5), below threshold stimulation (n=8) or threshold intensity stimulation (n=6) (one 2 sec. pulse with parameters the same as in rotation testing). Four additional animals served as unimplanted controls; they were trained and tested as above, but had no implantation of electrodes. On day 4 (Retest Day), the subjects were placed in the rotation chamber with the cables connected, and again allowed to lick for water. The latency to emit 10 licks on the Retest Day was defined as the retention latency; the greater the latency, the greater the retention of the shock on the previous day.

The results of Experiment 4 are shown in Table 4. There were no significant differences between the unimplanted controls and the implanted controls. There was also no significant difference between either of the control groups and the below threshold group. There was a significant decrease in retention latency in the group stimulated at rotation threshold vs. the control groups. However, there was no significant difference between the threshold group and the below threshold group; this seems to indicate that the latter group was indeed between the control and threshold groups in retest retention, and that the large variability in the below threshold group was due to the

TABLE 4

EFFECT OF UNILATERAL STIMULATION OF THE CD ON RETENTION OF
A PASSIVE AVOIDANCE TEST IN RATS

<u>Group</u>	<u>Mean latency $\pm$ S.D. (sec) to emit</u>
	<u>10 licks on Day 2</u>
Threshold	54.2 $\pm$ 39.5*
Below Threshold	220.7 $\pm$ 246.5
Implant Control	463.4 $\pm$ 120.5
Control	365.0 $\pm$ 149.5

*Significantly different from both control groups ($p < .001$,
t-test)

stimulation of some subjects at intensities closer to rotation threshold than others. These results demonstrate that unilateral stimulation of the striatum is effective in impairing passive avoidance learning as is bilateral stimulation. The relationship between nigrostriatal asymmetry and passive avoidance learning was further explored in a nonstimulation paradigm.

II. T MAZE EXPERIMENTS

Pilot Study: Stability of side preferences in a T Maze

Acknowledging the limited value of stimulation to pursue the central problem of this thesis, a decision was made to devise a better model for the study of the role of the nigrostriatal asymmetry in behavior. The results of Experiment 3 had indicated that side preference could be altered by a unilateral activation of the nigrostriatal system. Thus a simple and reliable paradigm for determining side preference was designed using a T maze.

The apparatus and method of testing in the T maze is described fully in the General Methods. This pilot study attempted to evaluate the stability of side preference behavior using the T maze test. Three separate groups of eight rats each were tested either every day for a week, every week for a month, or twice, a month apart. A fourth group of 32 rats was tested only once. Left or right choices on each of the ten trials in the test were recorded to analyze patterns of responding in the fourth group.

Ninety-two percent of the rats had a preference (defined as unequal number of left and right choices out of the ten trials per test) on the first test. Over each of the three time intervals examined, 83 to 85% of all rats preferred the same side on subsequent tests as they had on the first test ($p < .005$, chi-square test). Analysis of response

patterns in the fourth group revealed several interesting results. A significant percentage of animals alternated arms from the first to the second trials (72% alternation rate, $p < .05$, chi-square test). This alternation rate decreased with subsequent trials, and by the tenth trial a significant percentage chose the same arm as in the preceding trial (26% alternation rate, $p < .05$, chi-square test). Also, it was observed that 81.5% of the rats chose the same direction on the first trial as their overall left or right preference ($p < .002$, chi-square test).

Experiment 5. Neuroanatomical basis of side preference; effect of unilateral caudate lesions on T maze side preferences

Having established the stability of T maze side preferences, the first question asked was whether side preference in this apparatus was similar to side preference in the two-lever Skinner box in that it would be affected by an exaggerated asymmetry of the nigrostriatal system. If so, the theorized link between an intrinsic asymmetry and side preference would be strengthened.

All subjects (6 rats per group, total $n=18$) were tested in the T maze on Day 1. Four days later, the animals were divided into three groups ($n=6$ rats per group) and treated in the following way: Group 1 received unilateral CD lesions ipsilateral to their preference in the T maze; Group 2 received unilateral CD lesions contralateral to their preference; and Group 3 received sham lesions (electrodes lowered, no ipsilateral or contralateral lesion made). On Day 7, all rats were retested in the T maze for side preference.

The results of Experiment 5 are shown in Table 5. All rats with lesions had side preferences ipsilateral to the lesion, regardless of pre-operative preference. Subjects with lesions on the preferred side had a significant increase in preference ($p < .005$, t-test), and those with lesions on the non-preferred side had a significant reversal of preference ($p < .005$, pre-op- post-op difference; t-test). Subjects in Group 3, (sham-operated) had side preferences in the same direction as they had a week earlier, with no change in degree of preference. Figure 5 shows the minimal and maximal extent of the lesions.

Experiment 6. Neurochemical correlate of side preference

The previous experiment indicated that animals with unilateral caudate lesions will turn to the side of the lesion in a T maze, just as animals with the same lesion will rotate ipsilaterally in the rotometer (Ungerstedt, 1971b). Since this laboratory had demonstrated that animals without lesions will also rotate in the rotometer (Jerussi and Glick, 1974), and that the direction of rotation was correlated with an imbalance in dopamine levels in the striatum (Glick et al., 1974a), the next question posed was whether there was also a relationship between side preference behavior and a neurochemical imbalance between left and right striata.

Subjects in this experiment were four groups of rats. Group 1 (n=23) was tested in the T maze as usual (General Methods) and then immediately killed (approximately 30 sec.). Group 2 (n=8) was also tested in the T maze as usual, but these subjects were killed ten days after testing. Subjects in Group 3 (n=8) were placed in the long arm of the T maze and received the same amount of footshock as groups 1 and 2,

TABLE 5

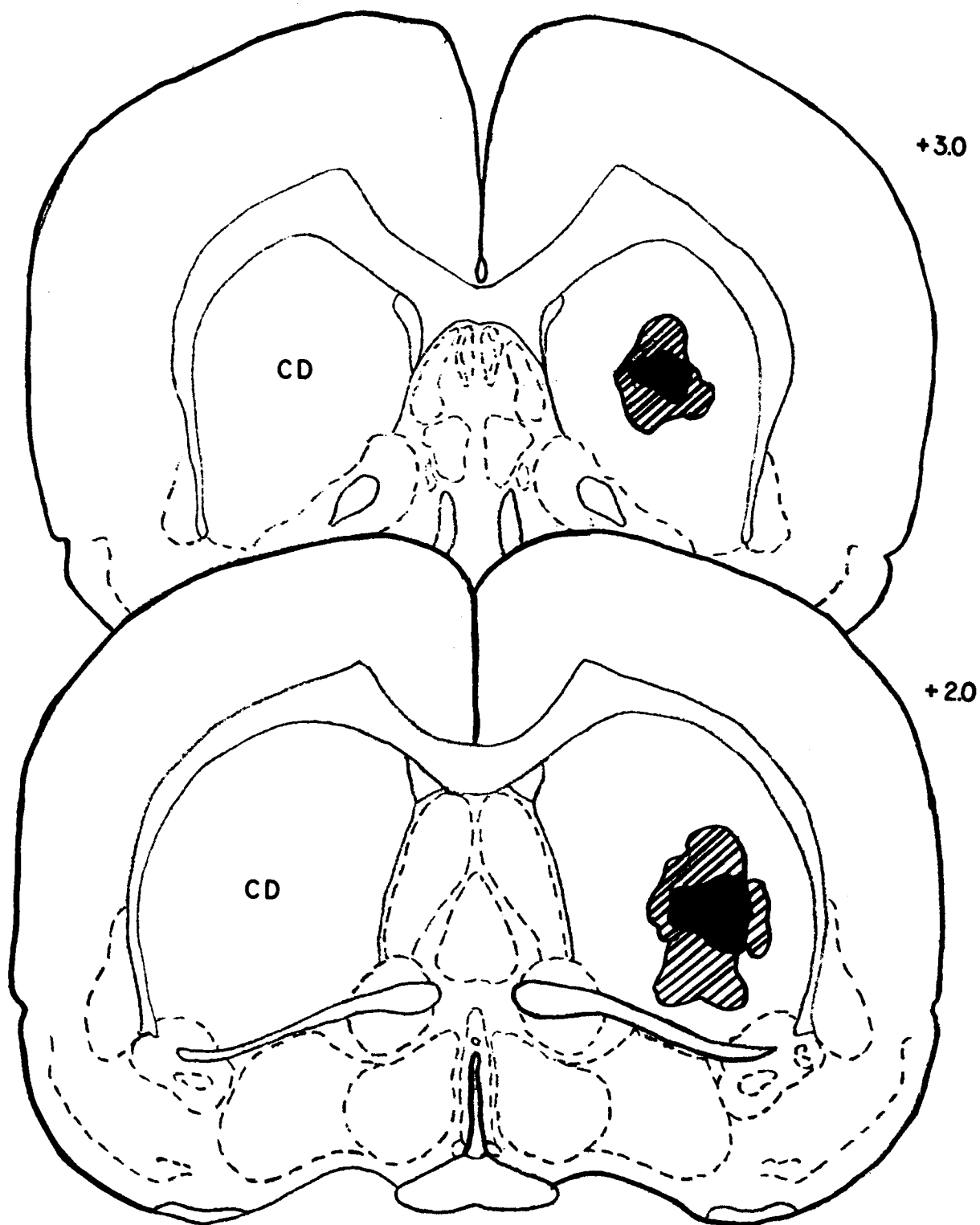
EFFECT OF CAUDATE LESIONS ON T MAZE SIDE PREFERENCE

<u>Group</u>	<u>Mean Side Preference (%)</u>	
	<u>Pre-op</u>	<u>Post-op</u>
Lesion: Preferred side n = 6	71.7	91.7*
Lesion: Nonpreferred side n = 6	70.0	5.0*
Sham n = 6	75.0	68.3

*Significant pre-op - post-op difference at $p < .005$, t-test

FIGURE 5

Unilateral electrolytic lesions (15 sec.) of the caudate nucleus (CD) in rats: dark areas represent the minimal extent of lesion; striped areas the maximal extent. Coordinates (+ 3.0, top section; + 2.0, bottom section) are from Pellegrino and Cushman, 1967.



but they were not allowed to enter the arms to escape the shock. The animals in Group 4 (n=8) were placed and contained in the T maze for the same amount of time as the other groups, but received no shock. Groups 3 and 4, like Group 1, were killed immediately after testing. Animals were killed by decapitation and the brains were assayed for dopamine and norepinephrine according to the Neurochemical Methods.

Results of Experiment 6 are shown in Table 6. Mean dopamine and norepinephrine levels were computed in three ways: left and right sides; the side with the higher levels and the side of lower levels; and the side ipsilateral to the side preference and the side contralateral to the side preference. Mean high to low ratios were also computed. There were no significant differences ($p > .1$, analysis of variance) among the four groups in any of the measures computed. Within each group, there was a significant difference in striatal dopamine concentration between the high and low sides ($p < .01$, paired t-test) but not between left and right sides ($p > .05$). In the two groups tested for side preference, there was a significant difference in striatal dopamine levels between the ipsilateral and contralateral sides ($p < .02$ for Group 1, $p < .05$ for Group 2), with dopamine concentrations higher in the contralateral side. There were no significant differences ($p > .1$) between any of these measures for tel-diencephalic norepinephrine levels, and the high/low ratios of all groups were significantly greater for dopamine than for norepinephrine ($p < .05$).

Experiment 7. Relationship between side preference and rotation

The results of Experiment 6 suggested that there may be an intrinsic

TABLE 6

UNILATERAL DOPAMINE (DA) AND NOREPINEPHRINE (NE) LEVELS IN RATS

TESTED IN THE T MAZE

Mean Striatal DA $\pm$ S.D. ($\mu\text{g/g}$)*

Group	Left	Right	High	Low	Pref.	Nonpref.	Ratio (H/L)
1. Pref.- 2 min.	7.26 ± 1.11	7.56 ± 1.16	7.87 ± 1.07	6.95 ± 1.06	7.00 ± 1.08	7.82 ± 1.07	1.13 $\pm$ 0.09
2. Pref.- 10 day	7.51 ± 1.20	7.13 ± 1.18	7.74 ± 1.10	6.90 ± 1.05	6.94 ± 1.06	7.70 ± 1.11	1.12 $\pm$ 0.06
3. Shock	7.29 ± 1.19	7.33 ± 1.24	7.82 ± 1.11	6.80 ± 1.09	--	--	1.15 $\pm$ 0.08
4. Control	7.97 ± 1.28	7.58 ± 1.21	8.25 ± 1.15	7.30 ± 1.07	--	--	1.13 $\pm$ 0.09

Mean Tel-diencephalic NE $\pm$ S.D. ($\mu\text{g/g}$)**

Group	Left	Right	High	Low	Pref.	Nonpref.	Ratio (H/L)
1. Pref.- 2 min.	.411 $\pm .051$	.421 $\pm .056$	.428 $\pm .064$	.404 $\pm .058$	.420 $\pm .050$	.412 $\pm .059$	1.06 $\pm$.05
2. Pref.- 10 day	.417 $\pm .061$	.428 $\pm .058$	.433 $\pm .055$	.412 $\pm .059$	.414 $\pm .060$	.431 $\pm .054$	1.05 $\pm$.05
3. Shock	.404 $\pm .048$	.416 $\pm .057$	.420 $\pm .072$	.400 $\pm .051$	--	--	1.05 $\pm$.04
4. Control	.405 $\pm .052$	.423 $\pm .061$	.426 $\pm .062$	.401 $\pm .058$	--	--	1.06 $\pm$.06

* There were no significant differences (analysis of variance and t tests, $p > .1$) among the four groups in left, right, high or low DA levels or in H/L ratios. Within each group, there was a significant difference (paired t-tests) between high and low sides ($p < .01$) but not between left and right sides ($p > .05$). In both groups tested for preferences, the difference between the preferred and non-preferred sides was significant (paired t tests, $p < .02$ and $.05$ for the 2 min, and 10 days groups, respectively). For each group, DA H/L ratios were significantly greater (paired t-tests, $p < .05$ in each case) than NE H/L ratios.

TABLE 6 (CON'T)

****There were no significant preferences (analysis of variance and t-tests, $p > .1$) among the four groups in left, right, high or low NE levels or in H/L ratios. Within each group, there was no significant differences (paired t-tests, $p > .1$) between left and right sides, between high and low sides, or between preferred and non-preferred sides in the groups tested for preferences.**

asymmetry of the dopaminergic nigrostriatal system with functional significance, i.e. just as rats will rotate towards the side of lower dopamine levels in the striatum, they will also prefer the side of lower dopamine in the T maze. The neuroanatomical and neurochemical basis for side preference and rotation appeared to be identical from the preceding two experiments, and this experiment was designed to directly test the relationship between these two spatial behaviors.

Part A. Spontaneous rotation and side preference

The apparatus used in this experiment were the T maze and the rotometer, and testing procedures for each have been described previously. Eighteen rats were used as subjects. The rats were tested first in the T maze, then injected with d-amphetamine sulfate 1.0 mg/kg and placed in the rotometer for one hour (the 1.0 mg/kg dose of amphetamine was known to produce consistent rotation, viz. Jerussi and Glick, 1974).

Rats were observed to preferentially rotate in the same direction in the rotometer as the direction of side preference in the T maze (direction was the same in 78% of the rats, $p < .05$, chi-square test).

Part B. Effect of amphetamine on side preference

Since amphetamine is thought to induce rotation by increasing the asymmetry of the nigrostriatal system (Glick et al., 1974a), it was of interest to see if amphetamine would increase side preference in the T maze.

A group of 14 rats were the subjects in this experiment. They were tested on Day 1 in the T maze. On Day 2, they received an i.p.

injection of d-amphetamine sulfate (1.0 mg/kg), and 15 minutes later each rat was again tested in the T maze.

Amphetamine was found to significantly increase side preferences of rats, when compared to each subject's own preference without drug on the previous day. The mean preference on day 1 was 68.6%; the mean preference on day 2 was 76.4% ($p < .02$ paired t-test). When compared to the mean preference of a group of rats tested on two consecutive days, with no drug administration (group 1 of T maze pilot study), there was also a significant difference between drug and non-drug animals on day 2 (76.4% drug vs. 64.2% non-drug; $p < .05$, t-test).

Experiment 8. Relationship of initial side preference to learned spatial behavior in the T maze

The preceding T maze experiments suggested that side preference is a behavioral correlate of an intrinsic asymmetry of the nigro-striatal system. The next problem posed was the role of side preferences in learning. The first associative behavior chosen for study was learned spatial behavior in the T maze.

Part A. T maze learning experiment

The subjects used in this experiment were two groups of 12 rats each. All rats were tested in the T maze on day 1. On day 2, the subjects were again tested in the T maze, but in this test one of the two arms (left or right) was deemed "safe". When the rat entered the "safe" arm, shock was terminated as usual. If the rat chose the "unsafe" arm, however, the shock was not terminated and a correction was allowed. In both cases the animal was then removed from

the arm and placed in the stem for the next trial. Testing continued in this manner until the subject had made the last nine out of ten choices to the safe arm. The number of trials required to reach this 9/10 criterion was taken as a measure of the rate of learning. The two groups were equated for degree of side preferences on day 1. On day 2, one group was trained with the preferred side "safe", and the other group with the nonpreferred side "safe."

The group that was trained to choose the same arm as their previous side preference had a mean number of trials to criterion of 21.5; the group trained against their preference had a mean number of trials to criterion of 35.9. The first group learned at a significantly faster rate ($p < .025$, t-test). In each group the same number (6) of subjects went to the correct side on the first choice, thus eliminating that factor as a possible determinant of the difference between groups.

Part B. Retesting experiment

The second part of this experiment was designed to examine the comparative strength of the spontaneous side preference in the T maze vs. the learned side preference.

Twelve rats were the subjects for this experiment. They were tested in the T maze on day 1. On day 3, subjects were all trained to enter the arm opposite to their initial side preference, as in Part A of this experiment. These subjects were then retested one month later with both arms "safe", that is, the same testing procedure as on day 1.

The results of this experiment were that the number of trials required to reach criterion on day 3 was negatively correlated with the percent preference to the trained side during free choice retest one month later, with a significant correlation coefficient of $-.56$ ($p < .05$, t-test). This means that an animal who required a greater number of trials to learn to go to its nonpreferred side was less likely to maintain its preference to the trained side on subsequent retesting with free choice of arms, and more likely to revert to its original preference.

Experiment 9. Relationship of side preference to active avoidance learning

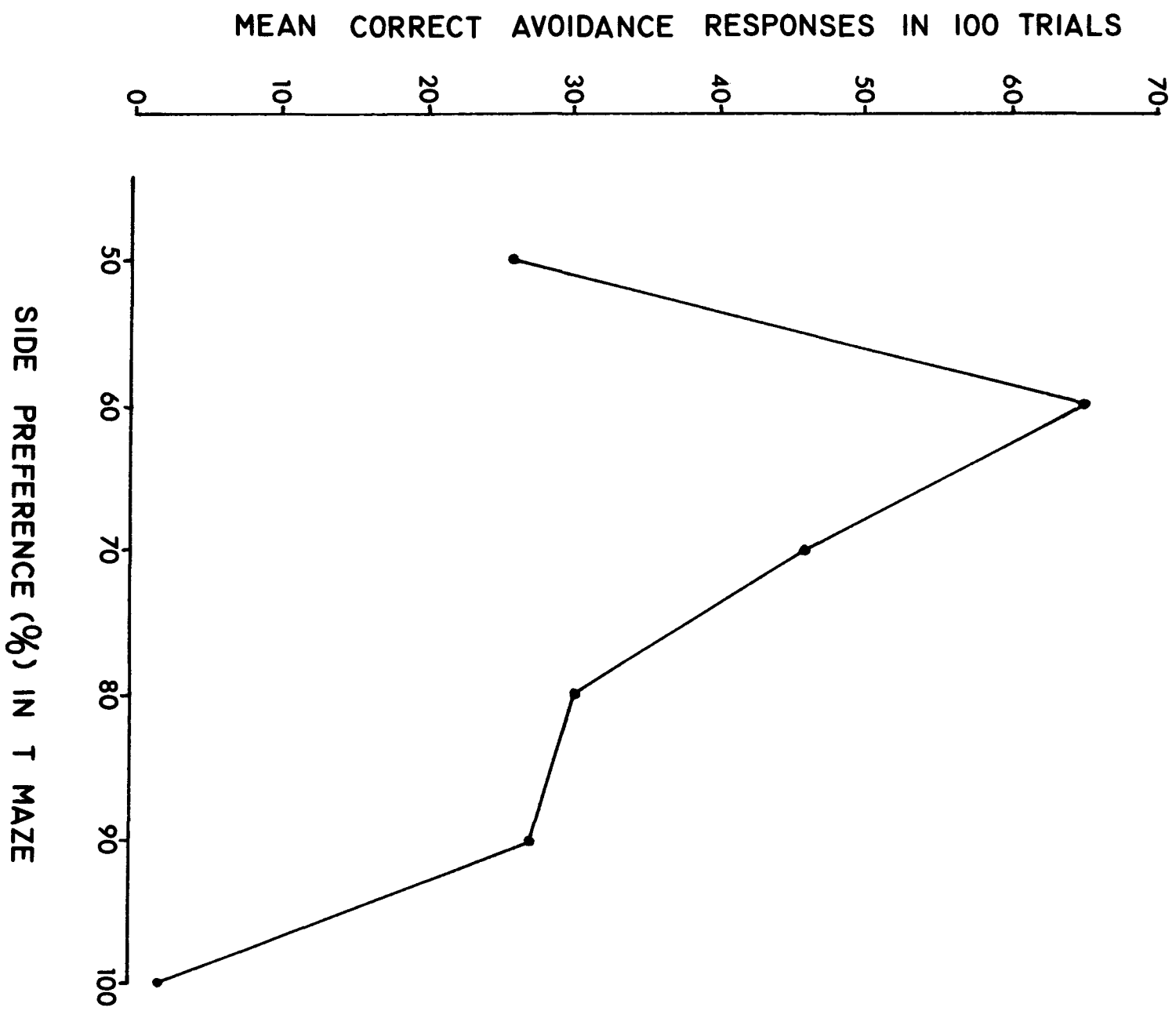
The results of the previous experiment suggested that an animal's intrinsic side preference interacted with its learning of a spatial task. The next question was its role in learning of tasks not obviously spatial in nature. The disruptive effects of bilateral lesions of the striatum on active avoidance learning, discussed in the introduction, may be due to a selective damage of the nigrostriatal system. Thus the relationship of the intrinsic asymmetry of this system to active avoidance learning was investigated in this experiment.

Subjects were 33 rats. On day 1, they were tested in the T maze for side preference. On day 4, they were placed in the shuttle box for 100 trials to assess active avoidance learning.

The results of this experiment are shown in Figure 6. In animals exhibiting side preferences, active avoidance learning was optimal in animals with moderate side preferences, and decreased with increasing preference (correlation coefficient = $-.61$, $p < .001$, t-test). Animals with no side preference also had difficulty learning the task, and were significantly different from rats with a 60% side preference ($p < .01$, t-test). Rats with a 60% side preference showed significantly better

FIGURE 6

Relationship of strength of side preference in a T maze (% left or right choices) to mean correct avoidance responses in 100 trials in rats trained in a two-way shuttle box.



learning than those with 80, 90% or 100% preferences ($p < .05$, $.025$, and $.01$ respectively).

Experiment 10. Relationship of side preference to passive avoidance learning

Another behavior, not obviously spatial in nature, which is disrupted by lesions of the striatum is passive avoidance learning. The relationship of the intrinsic asymmetry of the nigrostriatal system to the learning of this task was the next problem examined.

Subjects were 32 mice. They were divided into two equal groups which received identical treatment but received the treatments in reverse order. Each group was tested in the T maze for side preference, either two weeks before or after, and in the step-through box for passive avoidance learning. The passive avoidance footshock level used in both was 150 uA.

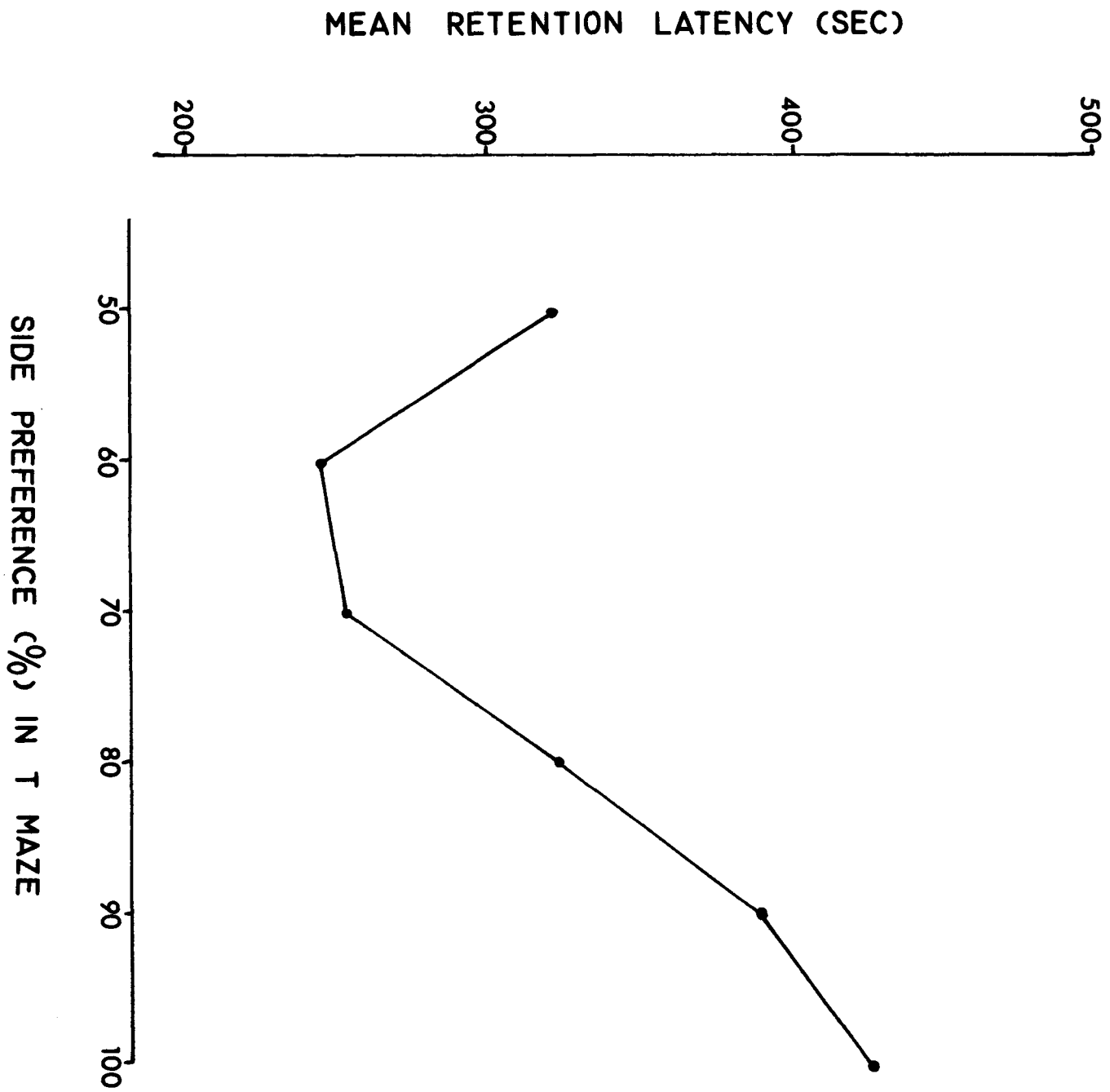
The results of this experiment are shown in Figure 7. Since there were no significant differences between the two groups, the results were combined. There was a significant positive correlation between side preference and day 2 latency in passive avoidance retention (correlation coefficient = 0.5, $p < .01$, t-test). Subjects with a 100% side preference learned significantly better than those with 60 or 70% side preferences ($p < .05$, t-test). Thus animals with stronger side preferences were more likely to exhibit better retention of the passive avoidance task.

Experiment 11. Relationship of side preference to spontaneous locomotor activity

Another behavior associated with striatal dysfunction and with alterations in dopaminergic function is locomotor activity. Activity is also an

FIGURE 7

Relationship of strength of side preference in a T maze (% left or right choices) to mean passive avoidance retention latency (sec.) on day 2 in mice tested in a step-through apparatus.



index of behavioral arousal, which may be an important factor in learning, as discussed in the Introduction. It was therefore of interest to examine whether there was a relationship between side preference and activity.

Subjects in this experiment were 24 mice. Again, half of the subjects received testing in reverse order, i.e. activity test or T maze test on day 1, than T maze or activity test on day 14.

There was no significant differences between the two groups, so order of testing was not a factor and the results were combined. The results are presented in Figure 8. There was a significant negative correlation between the degree of side preference and the total activity counts (correlation coefficient = - 0.56 $p < .01$, t-test). Thus more active mice had weaker side preferences. There was no significant relationship between side preference and habituation rate, as measured by the rate of decrease in activity in each 5 minute period over the total half-hour test session.

Experiment 12. Pharmacological analysis of side preference.

In order to assess the relative importance of dopaminergic and cholinergic mechanisms in spatial behavior, the effects of drugs affecting such mechanisms were studied in this experiment.

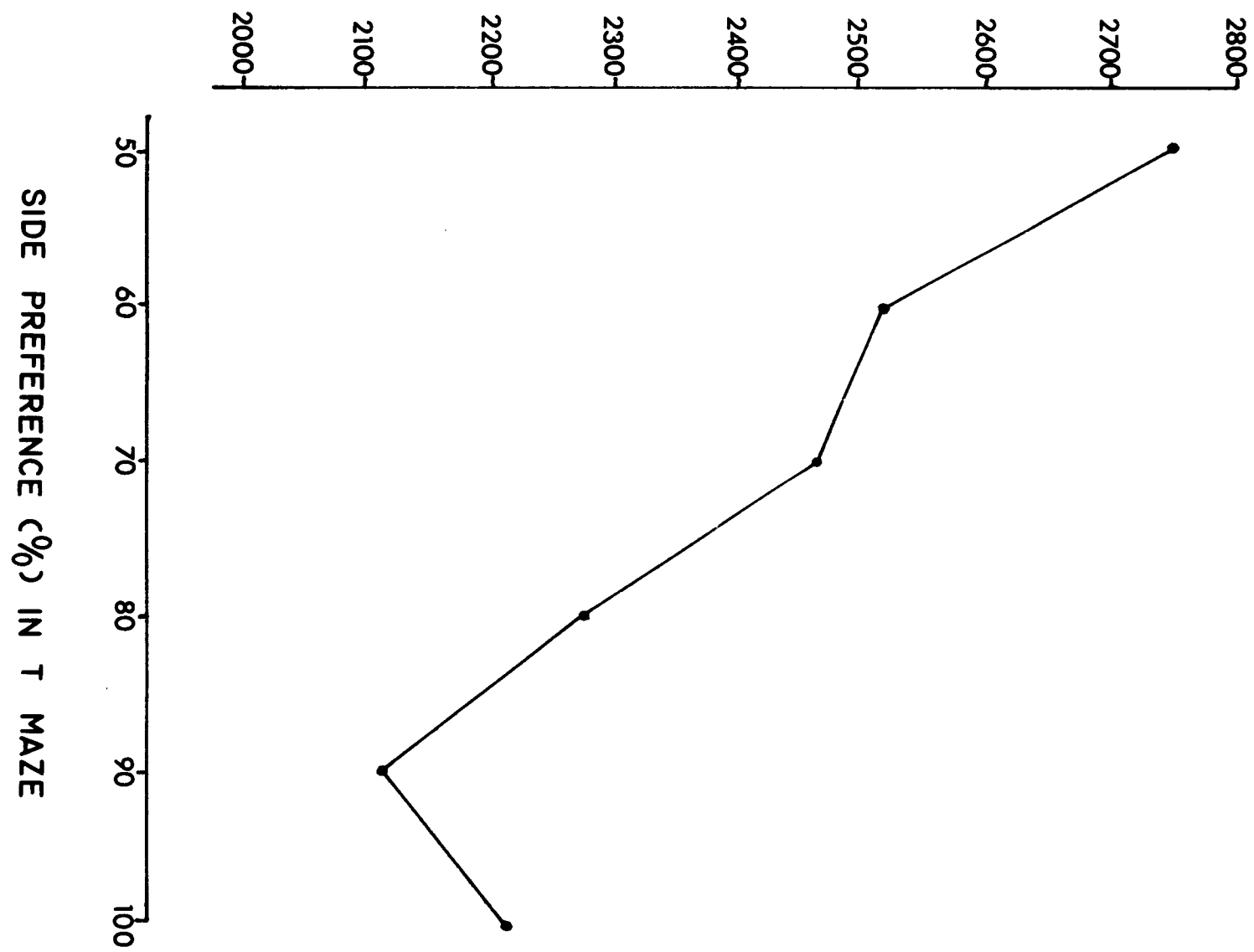
Subjects were mice (8 mice per dose of drug; 16 mice for saline). Subjects were tested for side preference in the T maze on day 1. On day 2, they received an i.p. injection of saline or drug 30 minutes prior to a retest in the T maze. When drug interactions were studied, the subjects received both drugs simultaneously.

Four drugs were chosen for this investigation: apomorphine hydrochloride (dopaminergic agonist), haloperidol (dopaminergic antagonist),

FIGURE 8

Relationship of strength of side preference in a T maze (% left or right choices) to mean activity counts in mice tested for 30 min. in a photocell activity box.

MEAN ACTIVITY COUNTS IN 30 MINUTES



pilocarpine nitrate (cholinergic agonist) and scopolamine hydrobromide (cholinergic antagonist). Doses used for each drug are shown in Table 8.

Dose-response relationships for apomorphine, haloperidol, pilocarpine, and scopolamine are presented in Table 7. On day 1, all groups had mean % side preferences of 70.0 % to 71.2%. On day 2, only two drugs caused significant changes in side preference; saline had no effect. Apomorphine significantly increased side preference at 1 mg/kg ($p < .05$, Wilcoxon signed rank test), significantly decreased side preference at 5 mg/kg ($p < .02$), and had no effect at 10 mg/kg. Haloperidol caused a significant decrease in side preference at 1 and 2 mg/kg ($p < .05$); 10 mg/kg had no effect. Mice treated with pilocarpine or scopolamine showed no significant change in side preference at any dose tested as compared to saline.

The results of the drug interactions are shown in Table 8. Although the dose of apomorphine used increased side preference when given alone, when given in combination with haloperidol or scopolamine, mice showed no net change in side preference as compared to saline-treated mice. When apomorphine and pilocarpine were administered jointly, there was a significant decrease in side preference as compared to saline-treated subjects ($p < .02$, Wilcoxon rank sum test); this decrease was also significantly different from the effect of apomorphine given alone ($p < .01$) but not from pilocarpine alone.

When administered alone, haloperidol, at 1 mg/kg, decreased side preference, but when administered with apomorphine there was no significant difference from saline. When given with pilocarpine, the mean percent side preference was significantly lower than saline ($p < .02$), but was

TABLE 7

EFFECT OF APOMORPHINE, HALOPERIDOL, PILOCARPINE, AND SCOPOLAMINE
ON T MAZE SIDE PREFERENCE

<u>Drug</u>	<u>Dose (mg/kg)</u>	<u>Mean % Side Preference (towards the Day 1 pre- ference) on Day 2</u>
Saline	--	71.2
Apomorphine	1	83.3*
	5	51.2* *
	10	72.5
Haloperidol	1	42.5*
	2	43.8*
	10	60.0
Pilocarpine	1	71.2
	5	71.2
	10	61.2
Scopolamine	0.5	71.2
	2.5	58.5
	5	61.2
	10	53.8

*p < .05 } significant increase or decrease in side preference, day 2 vs day 1
 **p < .02 } and drug vs saline, Wilcoxon signed rank test and Wilcoxon rank sum
 test, respectively.

TABLE 8
 DRUG INTERACTIONS AND T MAZE SIDE PREFERENCE

Mean % Side Preference (towards the Day 1
 preference) on Day 2 when given in
 combination with:

<u>Drug</u>	<u>(Dose, mg/kg)</u>	<u>Alone</u>	<u>Apomorphine</u>	<u>Haloperidol</u>	<u>Pilocarpine</u>	<u>Scopolamine</u>
Apomorphine	(1)	83.3 ^{**}	X	71.2	52.5 ^{*,**}	67.5
Haloperidol	(1)	42.5 ^{**}	71.2	X	53.7 ^{**}	51.1 ^{***}
Pilocarpine	(10)	61.2	52.5 ^{*,**}	53.7 ^{**}	X	57.5
Scopolamine	(.5)	71.2	67.5	51.1 ^{***}	57.5	X

*significantly different from Apomorphine alone, $p < .01$, Wilcoxon rank sum test

**significantly different from saline, $p < .02$, Wilcoxon rank sum test

***significantly different from Haloperidol alone, $p < .05$, Wilcoxon rank sum test

not different from the effect of haloperidol alone. When haloperidol and scopolamine were administered in combination, there was no longer any significant difference from saline-treated controls, and the effect was significantly different from haloperidol alone ($p < .05$).

In the last interaction, pilocarpine and scopolamine administered jointly, there was no significant change in side preference behavior as compared to saline treated mice or to either drug alone.

Experiment 13. Pharmacological analysis of passive avoidance learning

After establishing a relationship between side preference behavior and passive avoidance learning in Experiment 10, and comparing dopaminergic and cholinergic influences on side preference in Experiment 12, it was of interest to perform a similar pharmacological analysis of passive avoidance learning using the same four drugs.

Subjects were mice ($n=16$ per dose of drug or saline). The two-day paradigm for passive avoidance testing was followed as described in the Genral Methods, except that each subject received an i.p. injection of saline or drug, or injection of two drugs, 30 minutes prior to training day day 1. Drugs used were apomorphine hydrochloride, haloperidol, pilocarpine nitrate, scopolamine hydrobromide, and methylscopolamine hydrobromide (peripheral anti-cholinergic agent). Footshock level in this experiment was 350 μ A. Saline control groups were run every time a drug group was tested; apomorphine at 5 mg/kg was repeated twice.

The effect of varing doses of apomorphine, haloperidol, pilocarpine, or scoplamine on passive avoidance learning are presented in Table 9. Significant impairments in learning, as measured by the latency to enter the dark chamber on day 2, were seen after administration of 5 mg/kg

TABLE 9

**EFFECT OF APOMORPHINE HALOPERIDOL, PILOCARPINE AND SCOPOLAMINE ON PASSIVE
AVOIDANCE RETENTION**

<u>Drug</u>	<u>Dose (mg/kg)</u>	<u>Latency (Sec.) Day 1</u>	<u>Latency (Sec.) Day 2</u>
Saline		20.7	600+
Apomorphine	2.5	18.1	423.6
	5	18.9	408.1*
	7.5	60.0*	482.0
	10	124.5*	498.7
Haloperidol	.5	29.8	597.3
	1	28.9	503.8
	2	29.6	600+
Pilocarpine	2.5	19.9	600+
	5	34.0	600+
	10	134.5*	211.5*
Scopolamine	.5	19.9	242.8**
	2.5	47.0	207.3**
	10	49.3	96.7**

* $p < .05$ } significantly different from saline, Wilcoxon rank sum test
 ** $p < .05$ }

of apomorphine ($p < .05$, Wilcoxon on rank sum test), 10 mg/kg of pilocarpine, ($p < .05$) and all doses tested of scopolamine ($p < .01$). However, on day 1, the initial latency to enter the dark chamber was also significantly greater than that of saline-treated mice for pilocarpine at 10 mg/kg and apomorphine at 7.5 and 10 mg/kg ($p < .05$).

The drug interactions on passive avoidance learning are shown in Table 10. The significant decrease in latency seen with apomorphine alone was absent when haloperidol was also administered (significantly different from apomorphine alone, $p < .05$, not significantly different from haloperidol alone or saline). When apomorphine was given in combination with pilocarpine, there was a significant impairment in learning ($p < .01$ from saline-treated mice) that was significantly different from the effect of apomorphine alone ($p < .01$) but not from pilocarpine alone. Scopolamine and apomorphine together caused a decrease in retention latency that was significantly greater than either drug alone as well as significantly lower than saline ($p < .01$ in each case).

Pilocarpine, at a dose that impaired learning was unaffected by the simultaneous administration of haloperidol (decrease in latency was significantly different from saline, $p < .01$, and haloperidol, $p < .01$, but not from pilocarpine alone). When pilocarpine and scopolamine were administered together, the decrease in latency seen with either drug alone was absent (not significantly different from saline but significantly different from pilocarpine or scopolamine alone, $p < .05$). Similarly the decrease in latency observed when scopolamine was administered alone was no longer present when given with haloperidol (significantly different from scopolamine alone, $p < .05$, but not from haloperidol or saline).

TABLE 10

DRUG INTERACTIONS AND PASSIVE AVOIDANCE RETENTION

Drug	(Dose, mg/kg)	Median Day 2 latency (sec.) when given in combination with:				
		Alone	Apomorphine	Haloperidol	Pilocarpine	Scopolamine
Apomorphine	(5)	408	X	596 ^b	93 ^{a,b}	66 ^{a,b,e}
Haloperidol	(1)	503	596 ^b	X	104 ^{a,c}	400 ^e
Pilocarpine	(10)	211 ^a	93 ^{a,b}	104 ^{a,c}	X	427 ^{d,e}
Scopolamine	(.5)	243 ^a	66 ^{a,b,e}	400 ^e	427 ^{d,e}	X

a) significantly different from Saline, $p < .01$, Wilcoxon rank sum test

b) significantly different from Apomorphine alone, $p < .05$, Wilcoxon rank sum test

c) significantly different from Haloperidol alone, $p < .01$, Wilcoxon rank sum test

d) significantly different from Pilocarpine alone, $p < .05$, Wilcoxon rank sum test

e) significantly different from Scopolamine alone, $p < .05$, Wilcoxon rank sum test

When pilocarpine (10 mg/kg) was administered with methylscopolamine (0.5 mg/kg), the median latency was 440.7 sec. which was not significantly different from pilocarpine alone, or from saline. When pilocarpine, apomorphine (5 mg/kg) and methylscopolamine were administered together, the median latency was 147.3 sec., which was not significantly different from pilocarpine alone or apomorphine alone, or pilocarpine plus methylscopolamine or pilocarpine plus apomorphine but was significantly different from saline ($p < .01$).

DISCUSSION

The preceding experiments have indicated that there may be an important role of an intrinsically asymmetric nigrostriatal system in the associative behaviors of side preference, learning, and activity. Through the use of several behavioral and pharmacological tools this role has been analyzed; by no means exhaustively but as an initial examination of a potentially important approach to the problem of individual variance in behavior.

Side Preference

In recent years the study of asymmetrical behavior has centered around unilateral dysfunction of the nigrostriatal system. The model of this behavior was the persistent circling of an animal in a fixed direction, or rotation (Anden et al., 1966; Ungerstedt, 1971b; for example). More recently this rotation model has been used to demonstrate that asymmetrical behavior occurs after the systemic administration of certain drugs affecting the nigrostriatal system in animals without unilateral lesions or unilateral brain stimulation (Jerussi and Glick, 1974; Glick et al., 1975b). The present investigation carries the examination of asymmetrical behavior to the next step--the demonstration that an asymmetrical behavior, side preference, exists in an untreated animal. Concurrently, the important links to the previous studies were pursued. Side preference was found to have the same neurochemical and neuroanatomical basis as rotation; the conclusion drawn is that rotation is an extreme form of side preference elicited by the testing procedure.

The first steps in this study of side preference were methodological. A map of electrically-elicited turning sites in the brain was generated in Experiment 1A. The location of turning sites in the brain followed the course and distribution of the nigrostriatal system (with the exception of frontal cortex, which will be discussed separately later). Within the striatum, a functional localization of contralateral rotation was found. As the electrodes were placed further from where the nigrostriatal bundle entered the caudate nucleus the less likely would stimulation elicit turning, perhaps because fewer fibers were stimulated. This localization suggested that the rotatory effect of caudate nucleus stimulation was presynaptic. This hypothesis was confirmed in Experiment 1B. Animals no longer rotated in response to caudate nucleus stimulation after substantia nigra lesions, and began to rotate again only after nigral recovery appeared. The presynaptic basis of striatal stimulation-induced rotation may help to explain a perplexing problem in the rotation model. If, as many investigators suggest, dopamine is an inhibitory transmitter in the striatum, stimulation of the substantia nigra should not cause rotation in the same direction (contralateral) as stimulation of the striatum. However, if the rotation effect is presynaptic, the problem is resolved.

The second methodological approach was the design of a T maze test for side preference. Rats were found to have spontaneous and stable left or right side preferences in a T maze. Although the T maze is used routinely for spontaneous alternation and learning experiments in behavioral pharmacology, side preference has been only causally noted, if at all, and not studied for its own sake. As expected, the rats did have a significant alternation rate in the first few choices. However, when the subjects were

tested for ten trials, a side preference was detectable. Side preferences were shown to be consistent over weeks. The only continuing drawback to this T maze test was the use of footshock. Preferably, a test of spontaneous side preference would be free of such an extreme treatment, since footshock can elicit rotation in the rotometer (Glick et al., 1975b) and has been found to alter catecholamine levels (Bliss et al., 1968, Thierry et al., 1968). However, the footshock used in these studies was much greater and administered over a longer time. A pilot study was conducted with water reward at the ends of the two arms of the T maze. The rats also exhibited spontaneous side preferences in this paradigm, but again the animal had an extreme treatment, water deprivation, and, as a further drawback, this paradigm was more time consuming than the initial footshock procedure. Rats tested in the T maze without footshock also exhibited spontaneous side preferences, but since they rapidly habituated to the apparatus it took considerable time for the rats to finish ten trials. Thus it became expedient in light of the large number of animals to be tested to continue with the use of footshock, and to control for its effects as much as possible.

Using the T maze test devised here, the role of the nigrostriatal system in side preference behavior was sought. The most definitive of the experiments establishing a direct relationship between side preference and an intrinsic asymmetry in the nigrostriatal system was the demonstration in Experiment 6 that side preference is correlated with a bilateral difference in dopamine levels between the two striata. In both groups tested for side preference (one just prior to killing, one ten days prior to killing) there was a significant association of the high/low dopamine ratios with nonpreferred/preferred side ratios: rats exhibited a side

preference towards the side opposite the striatum with higher dopamine levels. This asymmetry was not elicited by the footshock, since the group tested without shock had significant high/low dopamine ratios as well, and these ratios were not significantly different from those in the tested groups (catecholamine levels were also no greater in this non-shock group vs. the shock groups). Similarly, the asymmetry was not elicited by the movements of the animal within the testing apparatus since the group shocked in the T maze but not tested for side preference also had high/low dopamine ratios not significantly different from the three other groups. Some neurochemical specificity was also demonstrated: there was no significant differences between high and low tel-diencephalic norepinephrine levels in any of the four groups.

These findings support the postulation of an intrinsic nigrostriatal asymmetry (Glick, 1973; Glick and Jerussi, 1974); all groups regardless of treatment have a significant difference between the high and low striatal dopamine levels on the two sides and these high/low ratios were the same for all groups. The relationship of the asymmetry to side preference mirrors the association seen between high/low dopamine ratios and contralateral/ipsilateral rotation (Glick et al., 1974a) suggesting that the intrinsic asymmetry subserving spontaneous rotation (e.g. nonlesioned) (Jerussi and Glick, 1974; 1975) is also the basis for side preference. The studies demonstrating that a rat will rotate to the side opposite to its higher dopamine level in the striatum (as discussed fully in the Introduction) all looked at rotation following drug administration. In the experiment reported here, however, the relationship between side

preference and an intrinsic asymmetry of striatal dopamine levels was found present without any drugs, and therefore provides direct evidence that the asymmetry is intrinsic and not drug-induced.

One problem encountered in the above neurochemical experiment was the inability to find a quantitative correlation between the degree of asymmetry in dopamine levels and the degree of side preference; those animals with the greatest side preferences were not necessarily those with the greatest high/low dopamine ratios. There are several reasons which may account for the lack of such a finding. First, the dopamine asymmetry is small (approximately 12%) and the variability in the methods may mask a correlation that is present. It is also possible that the dopamine asymmetry normally fluctuates around a set point, and since the behavioral and neurochemical measurements cannot be taken simultaneously, the correlation cannot be shown but may exist for that moment in time in the behavioral test. Alternatively, the nigrostriatal asymmetry may set the direction of the side preference (left or right) but another system may modulate the mechanism for the degree of asymmetry. The solution to this problem is being pursued by the use of more exacting neurochemical techniques, such as the measurement of turnover and metabolite levels (Jerussi and Glick, in progress). The problem does not however, mean that experiments in this investigation relating degree of asymmetry in the T maze to other behaviors are invalid; the conclusions must just be qualified to relate to the behavioral asymmetry and are valid as such.

Two methods of exaggerating nigrostriatal asymmetry, stimulation and ablation, were employed to further establish the role of the asymmetry

in side preference behavior. In Experiment 3, rats were found to choose the lever contralateral to the side of unilateral electrical stimulation of the striatum. Thus, an electrically-induced increase in activity in one half of the striatum resulted in a preference for the opposite side. At higher intensities, the stimulation which had changed the side preference elicited contralateral rotation. The results of this experiment indicate that the intrinsic asymmetry of the nigrostriatal system expressed in rotation may also be responsible for a spontaneous side preference in the two-lever Skinner box. As proposed earlier (Glick, 1973; Glick and Jerussi, 1974), variations in the degree of nigrostriatal asymmetry may account for individual differences in normal side preference in this apparatus. Unilateral lesions in the caudate nucleus or the globus pallidus have been reported to selectively block lever pressing with the forepaw contralateral to the lesion in a two-lever Skinner box (Hansing et al., 1968; Levine et al., 1971). The results of the present stimulation experiment can be seen as the converse of this previous work.

The results of Experiment 5 provide additional support for a direct role of nigrostriatal asymmetry in side preference; regardless of pre-operative preference, all rats with unilateral caudate lesions chose the side ipsilateral to the lesion in the T maze. Again, the side with greater nigrostriatal activity was opposite to the side preference. The effects of unilateral caudate lesions on side preference behavior in this experiment are identical to its effects on rotation (e.g., Ungersstedt, 1971b). However, since the T maze model does not require drug administration, as does the rotation model, this experiment is more direct. Experiment 7A demonstrated that animals will rotate in the same direction as their side preference in the T maze. Hence the suggestion

that rotation is an extreme form of side preference is further supported.

The role of the nigrostriatal system in side preference was also investigated by using drugs as pharmacological tools. In Experiment 7B, rats which received d-amphetamine (1.0 mg/kg) had increased side preferences in the T maze. This drug has been shown to enhance the intrinsic asymmetry of striatal dopamine levels (Glick et al., 1974). Amphetamine may increase activity more in the normally more active side, possibly through the greater release of dopamine from more active terminals (Von Voightlander and Moore, 1973) and thus cause an increase in contralateral tendencies. Alternatively, the 1.0 mg/kg dose of amphetamine may decrease dopamine turnover to a greater extent in the less active side (Jerussi and Glick, unpublished results); this would have the same net effect of increasing the difference in activity between the normally more and less active sides, and therefore increasing side preference. The suggestion that low doses of amphetamine may decrease dopaminergic activity through a decrease in turnover via a feedback inhibition (Besson et al., 1971; Bunney et al., 1973) might also help explain the apparently paradoxical effects of Experiment 2A. In this experiment, amphetamine was found to raise the threshold of stimulation-induced contralateral rotation, whereas one would have expected a decrease in threshold based on a stimulant action of the drug. Interestingly, the greatest rise in threshold was seen with a low dose of the drug (0.5 mg/kg) (higher doses, 1, 2, and 4 mg/kg, had the same but lesser effect). As amphetamine decreases dopamine turnover in the implanted side, the amount of current necessary to cause contralateral rotation would increase because this rotation is based on a pre-synaptic effect (as shown in Experiment 1B where substantia nigra lesions blocked contralateral rotation from

caudate stimulation). Alternatively, the implanted electrode does cause a small but significant lesion in that side; experiment 2B demonstrated that this lesion was large enough to cause competitive ipsilateral rotation after 0.5 mg/kg d-amphetamine administration. It is impossible to determine if this artifact is totally responsible for the rise in threshold seen after amphetamine.

Mice were also found to exhibit side preferences in the T maze, and a pharmacological analysis of this behavior was undertaken in Experiment 12. The results dose response curves were confusing and possible explanations are presented as follows. Only agents which alter dopaminergic function affected side preference behavior; cholinergic agents had no effect as compared to saline when given alone. Apomorphine, a dopamine receptor stimulant (Anden et al., 1967) increased side preferences at 1 mg/kg. The action of this drug may have been to activate more receptors in the normally more active nigrostriatal system, thereby increasing nigrostriatal asymmetry and, as a result, enhancing side preferences. At 5 mg/kg, apomorphine decreased side preferences. One explanation of this result is that apomorphine also acts as a partial antagonist (Bieger et al., 1972) and this action may be first manifested on the more active side. At an even higher dose (10 mg/kg) apomorphine produced no change in side preference. This suggests that both sides of the nigrostriatal system are now equated for agonist and/or antagonist actions of the drug, resulting in a net asymmetry equivalent to the non-drug state.

Haloperidol, an agent which blocks dopamine receptors (Rossum, 1966) reversed side preferences at 1 and 2 mg/kg. The drug may more readily block more receptors in the more active nigrostriatal system. This

suggests, as does the apomorphine data, that there may be a post-synaptic asymmetry as well as a presynaptic asymmetry. At a higher dose, 10 mg/kg haloperidol had no effect on side preference. Again, this suggests that all receptors are now saturated, resulting in an asymmetry equivalent to the non-drug state.

The action of apomorphine to enhance side preferences, and that of haloperidol to diminish side preferences, agrees with the finding that apomorphine will cause consistent rotation in normal rats (Glick and Jerussi, 1975). In rats or mice with unilateral 6-hydroxydopamine-induced damage to the nigrostriatal system, apomorphine elicits contralateral rotation (Ungerstedt, 1971c; Thornberg and Moore, 1974) because it has a relatively greater effect on the supersensitive denervated side. Haloperidol in low doses (0.125 mg/kg) also induces rotation in normal rats (Jerussi, 1974). In addition, haloperidol has been shown to antagonize the rotatory effects of apomorphine in both nonlesioned rats (Jerussi, 1974) and in unilaterally lesioned animals (Ungerstedt, 1971c; Kehr et al., 1972). In Experiment 12 the combined administration of apomorphine and haloperidol resulted in an antagonism of either drug's effect alone. The opposite and antagonistic actions of apomorphine and haloperidol at those doses support two major premises of the preceding experimentation on side preferences: first, that the behavior is correlated with dopaminergic activity in an asymmetric nigrostriatal system, and second, that side preference and rotation are both behavioral manifestations of this activity differing only quantitatively.

The results of the administration of cholinergic agents indicate that there is some pharmacological specificity in mechanisms of side preference. Scopolamine and pilocarpine had no effect on side preference when given alone or in combination as compared to saline. At 2.5, 5,

and 10 mg/kg of scopolamine, however, the preferences were also no different from chance (50%). This indicates that at these doses there may be a tendency for a decrease in side preference. One possible explanation of these results is that the action of scopolamine in another system, perhaps hippocampal, to block habituation (Carlton, 1968) interferes with the measurement of its effect on side preference. The block of habituation would increase the likelihood of an animal's choosing the left or right arm by chance. If habituation is impaired, the animal reacts to the choice at the end of the stem as novel on every trial; the association of side and cues necessary for side preference behavior is thus severed and the resulting performance would tend towards chance. A similar explanation has been advanced to account for the decrease in spontaneous alternation after scopolamine (Douglas and Isaacson, 1966; Carlton, 1968) and hippocampal lesions (Douglas, 1967); the animal which normally alternates in response to novel stimuli is now, after drug or lesion, continuing to respond to old stimuli as new ones and thus has an equal chance of re-entering the original arm as of entering the alternate arm.

Few conclusions can be drawn from the drug interactions studied in Experiment 12. Scopolamine did appear to antagonize the reversal of side preference seen induced by haloperidol when given together, and this result is compatible with a dopamine-acetylcholine reciprocity in the striatum. However, scopolamine did not enhance apomorphine's increase in side preference when administered co-jointly. Similarly, pilocarpine did not enhance the haloperidol effect. This suggests that the nigro-striatal system is primarily involved in the generation of side preferences and the cholinergic effects are mediated elsewhere, as discussed above.

The most perplexing result was that of the combined administration of apomorphine and pilocarpine. There are three possible interpretations of the data. The decrease in side preference after the two drugs was significantly different from apomorphine alone, and could therefore be seen as an antagonism of the apomorphine effect, and thus support a dopamine-acetylcholine reciprocity. However, the decrease was also significantly different from saline, and reduced to chance level. Since a higher dose (5 mg/kg) of apomorphine also reduces side preference, one could also conclude that pilocarpine enhances the effect of apomorphine on side preference. Finally, since the result obtained with the two drugs was not significantly different from that of pilocarpine alone, perhaps the effect of pilocarpine masked any joint effect. In sum, it appears that the T maze is not a particularly fruitful tool for the study of drug effects on side preference.

These results indicating that animals have intrinsic side preferences raise important methodological considerations for behavioral pharmacology. For example, the T maze is routinely used to study the effects of particular treatments (e.g. drugs or lesions) on spontaneous alternation and spatial learning. Frequently a "position bias" or "position habit" is observed in experimental subjects; such subjects are usually discarded from the experiment or occasionally the side preference is ignored. Discarding the subject may result in a skewing of the distribution of "normals" towards those with the least side preference and thus may bias the results of the experiment. Ignoring the side preference, and randomly placing unilateral lesions in either side of the brain regardless of intrinsic side preference, a very common practice, may also confound results. The assumption that both halves of the rat brain are equal and the frequent use of one side as a control (as in neurochemical studies) must now be questioned. Recently, Jerussi and Glick (1975) found that the placement of lesions in the dominant or non-

dominant hemisphere can indeed produce different results. Rats initially tested for rotation after 10 mg/kg of apomorphine were unilaterally lesioned in the caudate nucleus either ipsilateral or contralateral to the initial preference. Post-operatively, all rats rotated towards the side of the lesion, but rotation in the ipsilateral group was twice that of the contralateral group. Thus one can no longer assume that a lesion in one hemisphere will produce effects identical to those of a lesion in the other hemisphere. The knowledge of a subject's inherent bias will therefore not only help to explain individual variations, but will also lead to a more exact interpretation of results involving spatial tasks.

Learning and Memory

The evidence for involvement of an intrinsic asymmetry of the nigrostriatal system in learning and memory is not as direct as that for its involvement in side preferences. Based on the relationship between side preference and nigrostriatal asymmetry established in the experiments discussed above, the role of this asymmetry in learned behaviors was inferred by utilizing side preference as a behavioral manifestation of the asymmetry. Albeit with indirect evidence, there does appear to be an important role for nigrostriatal asymmetry in the learning of both spatial and nonspatial tasks in rats and mice.

Spatial learning was studied in the T maze in Experiment 8. Typically, when other investigators use a T maze for learning experiments, they randomly assign half of the animals to learn a left discrimination, and half to the right. This experiment was designed to determine if an animal's intrinsic side preference is an important variable in learning a left-right discrimination in this apparatus. In part A of this study, rats were found to learn a left-right discrimination faster when the correct

choice was the same as their spontaneous choice. When rats had to chose their nonpreferred side, the task was more difficult. If side preference is a result of greater responsivity to cues on one side of the animal's environment, then there would follow a quicker association of these stimuli with the escape response and thus better learning. Part B of this experiment showed that the original preference reasserts itself on subsequent free-choice retesting. There was a significant negative correlation between number of trials required to reach criterion on the training day, and number of choices to the trained side when retested with free choice. Thus although the animals had more experience with the cues on the forced, nonpreferred side during training, their intrinsic preference, which is related to their nigrostriatal asymmetry, was a stronger factor governing their subsequent behavior in the testing situation.

Deficits in the learning of spatial tasks after caudate lesions have been reported since 1956 (Rosvold and Delgado, 1956; Gross et al., 1965; Mikulas, 1966; Potegal, 1969). These lesions studies attribute a critical role for the striatum in spatial learning. The relationship between nigrostriatal asymmetry and the learning of the spatial task suggested here may help explain how the striatum is influencing spatial learning. In the lesioned animals, the intrinsic asymmetry is disrupted, and a relatively quicker association of cues on the preferred side which could occur during training in normal animals is thwarted (evidence for a role of the nigrostriatal system in sensory processing is discussed later). This association may be important in order for the subjects to make a "comparison" of the left and right choices in a spatial task; thus learning becomes more difficult for these animals. In addition,

the damage to the two sides of the striatum may not be equal, and even if equal, damage to the dominant side may be functionally different than damage to the other side. As discussed earlier, rats with caudate lesions on the side opposite to their pre-operative direction of rotation were much less sensitive to apomorphine postoperatively than rats with lesions on the same side (Jerussi and Glick, 1975). A symmetrical placement of bilateral lesions, or functionally unequal damage, would produce an artificial asymmetry in place of the normal intrinsic asymmetry. This artificial asymmetry would yield a choice bias in the direction opposite to the more active side, and would be expected to interfere with spatial learning to the extent that the artificial asymmetry deviates from the normal asymmetry. Schwartzbaum and Donovanick (1968) noted, for example, that subjects with bilateral caudate lesions persisted in responding to the inappropriate side of the box. It would seem to be even more difficult to train a subject against a lesion-induced side preference than an intrinsic one, since the possibility of modulation is restricted by the damage. As a group, animals in this experiment learned the task as rapidly as control groups in lesion studies; the individual differences in learning among these subjects, as related to the initial influence of their intrinsic asymmetry, is the critical finding.

An even more intriguing possibility suggested by the results of further experiments is that the intrinsic asymmetry of the nigrostriatal system may influence learning in general, not only learning of spatial tasks. Since the striatum had been implicated in the learning of avoidance behavior (Thompson, 1959; Thompson and Mettler, 1963; Fox et al., 1964; Green et al., 1967; Winocur, 1974; Kirkby and Polgar, 1974), the relationship between nigrostriatal asymmetry and active and passive

avoidance learning was investigated. In Experiment 4, rats which received post-trial unilateral electrical stimulation of the caudate nucleus at rotation threshold showed deficits in passive avoidance learning, whereas those receiving below-threshold currents were not impaired. The mechanism for this post-trial effect is not revealed by this experiment; however, this effect of unilateral electrical stimulation of the caudate nucleus is similar to that reported in earlier studies using bilateral stimulation (Wyers, 1968; Wyers and Deadwyler, 1971; Gold and King, 1972; Wyers et al., 1973; Haycock et al., 1973). In studies using bilateral stimulation, no attempt was made to equate stimulation on each side in terms of efficacy to induce rotation. Thus the stimulation-induced amnesia in these studies may be due to asymmetrical effects of the stimulation rather than to the stimulation per se. In this respect, the direct relationship shown here between the threshold current to induce rotation and amnesia is important. Here, as in Experiment 3, where stimulation reversed side preferences, the normal modulation of the intrinsic asymmetry of the striatum altered. In Experiment 3, the stimulation was continuous and the effect lasted only while the stimulation was being administered, just as one observes stimulation-elicited rotation. In Experiment 2, the paradigm was quite different; stimulation was administered only once, and its effect was revealed a day later. Perhaps the asymmetry of the stimulation disrupted the storage of the engram by forcing the animal to respond to spatial cues that had no relevance for retention of the test, and thus was a distracting influence. The closer the intensity was to rotation threshold, the greater distraction.

A second examination of the relationship between nigrostriatal asymmetry (as measured by side preference) and passive avoidance learning was described in Experiment 10. There was a positive correlation between the degree of side preference and the retention of a passive avoidance response in a group of normal, nonlesioned mice. Those mice with stronger side preferences were better learners of the passive avoidance task. All mice learned the task, but the observation that individual differences in learning among the mice were related to side preferences implicates nigrostriatal asymmetry as a factor in the learning of the task, as it was in the learning of the spatial task. The mice may be using spatial cues in the task although these cues are not a requisite; they may position themselves within the small lit chamber so that certain cues "in space" in relation to their body position become associated with that position. The ability to form stimulus-position associations more readily on one side of the body via a dominant nigrostriatal system may, possibly, be an important part of the learning experience. Those mice with a greater functional difference between the two nigrostriatal systems (as measured by degree of side preference) may have better use of this association system, and are thus better learners of the passive avoidance response.

A similar comparison between side preference (as indicative of nigrostriatal asymmetry) and learning was undertaken in Experiment 9. The active avoidance paradigm was studied in rats because of the conflicting reports of the effect of striatal lesions on this type of learning; deficits reported by one group of investigators (Green et al., 1967; Kirkby and Polgar, 1974; Winocur, 1974) were not confirmed by a second group (Fox et al., 1984; Albert and Bignami, 1968; Winocur and

Mills, 1969). The results of Experiment 9 demonstrated an interesting relationship between active avoidance learning and side preferences. In those animals having side preferences, there was a negative correlation between the degree of side preference and the learning of a two-way shuttle response. Animals with no side preferences, however, were also poor learners. Thus as the asymmetry (as indicated by side preference) increased beyond a minimal degree, learning of this task decreased. This result is opposite to the positive correlation seen in passive avoidance learning and side preferences. However, it is consistent with the fact that several studies in experimental treatments (drugs, lesions, electroconvulsive shock) have been reported to have opposite effects on passive and active avoidance learning (e.g. Vanderwolf, 1963; McGaugh, 1966; Kulkarni, 1968; Bohdanecky and Jarvik, 1967; Glick and Greenstein, 1973). Species difference may be a factor in the contrasting results, though this seems unlikely since the particular strains of rats and mice used in these experiments behave similarly in a wide variety of tasks. An alternative explanation can be based on the influence of spontaneous motor activity on the learning of either task. In Experiment 11, a negative correlation between activity and side preference was demonstrated in mice. In passive avoidance learning, an animal must inhibit its activity and remain in the small compartment. Those animals with the greatest asymmetry are least active and also best learners of passive avoidance. In contrast, learning of active avoidance requires a great deal of activity by the subject in the shuttling back and forth between chambers. Therefore an animal with a moderate degree of side preference (asymmetry) also has a moderate level of spontaneous locomotor

activity, and may learn this task better than an animal with lesser activity albeit with a greater asymmetry. Interestingly, those animals with no asymmetry (as indicated by the absence of spontaneous side preferences) are the most active but are relatively impaired on both tasks; perhaps too much activity interferes with adequate stimulus-response pairing.

Experiment 13 investigated the neuropharmacology of one of the learned behaviors apparently related to nigrostriated asymmetry. In contrast to the dopaminergic effects on side preferences, the predominant influence on passive avoidance learning appears to be cholinergic. The demonstration of learning impairments following administration of an anticholinergic agent confirms several earlier studies on passive avoidance behavior (e.g. Bohdaneky and Jarvik, 1968; Dilts and Berry 1969; Glick and Zimmerberg, 1971). The greatest deficits in passive avoidance retention were found after administration of scopolamine, in a dose-dependent manner. Pilocarpine also impaired passive avoidance learning, but only at a dose that affected day 1 latencies; its effect on retention can probably be attributed to a performance deficit, in as much as methylscopolamine, an anticholinergic agent having little or no action in the central nervous system (Goodman and Gilman, 1975), blocked effects on both initial (Day 1) and retention (Day 2) latencies. It is likely, therefore, that as a result of peripheral effects, pilocarpine grossly interfered with behavior on Day 1 and secondarily impaired learning as a consequence. The lower dose could not facilitate learning because only impairments can be demonstrated at this shock level. The cut-off point of 600 seconds was chosen because it maximizes the possibility of detecting impairments.

Apomorphine administration resulted in a small but significant impairment at 5 mg/kg; higher doses had no effect. Haloperidol had no effect on passive avoidance learning at the doses tested, but it did antagonize the apomorphine-induced impairment. With the exception of pilocarpine, the drug interactions indicated a dopamine-acetylcholine reciprocity. Apomorphine and scopolamine synergized to produce a greater deficit than with either drug alone, whereas haloperidol antagonized the scopolamine-induced deficit. These results support the dopaminergic-cholinergic "balance" theory. However, apomorphine did not antagonize, and haloperidol did not potentiate, the deficit caused by pilocarpine, a result which is consistent with the suggestion that the effect of pilocarpine is mediated by its peripheral actions.

The results of the pharmacological analysis of passive avoidance learning revealed more about the complexity of the field than any definitive evidence for a role of the nigrostriatal system in this learned behavior. The drugs affect the total activity of the system, not just the asymmetry. Furthermore, there is no proof of anatomical specificity; cholinergic systems in the hippocampus and the ascending reticular formation are also thought to contribute to the disruption of learning and memory caused by scopolamine (Pradhan and Dutta, 1971; Glick et al., 1973). The absence of a major effect by apomorphine, and lack of effect by haloperidol, is interesting in terms of the present hypothesis of asymmetrical influence. Both drugs alter the intrinsic asymmetry of the nigrostriatal system, as demonstrated in the changes in side preferences in the T maze experiment

described above. Non-drug-treated animals with increased asymmetries, or side preferences, had better retention of the passive avoidance task when compared to group-mates with lesser side preferences, as shown in a further experiment. In the drug study, a higher shock level was used than in the previous study correlating side preference with passive avoidance learning. Thus a low dose of apomorphine which increased side preferences resulted in no effect on passive avoidance learning, perhaps because only impairments can be demonstrated as discussed above. But a middle dose of apomorphine, which completely blocked side preferences (51.2% side preference) impaired the subjects in passive avoidance learning. This result is consistent with the finding that animals with no asymmetry are the poorest learners on both types of avoidance tests. However, doses of haloperidol which had no effect on passive avoidance learning also blocked side preferences. It seems likely, from all these results, that the influence of an animal's intrinsic asymmetry is not the major factor involved in learning. It may, however, be of value as an explanation for individual variance in behavioral testing situations. The intrinsic asymmetry of the nigrostriatal system can thus account for individual differences within the group but not for group changes after drug treatments that affect the group as a whole.

The relationship between learning and side preferences shown here is similar to that reported in other studies with different schedules of reinforcement in the two-lever Skinner box. On a fixed ratio (FR 30) or a fixed interval (FI 15) schedule, there is a direct relationship between the strength of side preferences and baseline rates of responding (Glick and Jerussi, 1974); on a differential reinforcement of low rates (DRL 16) schedule, however, side preferences are inversely related to rates of responding (Glick et al., 1975a). This

apparent discrepancy among schedules actually has adaptive significance: on FI and FR schedules, higher rates of responding yield more reinforcements whereas on DRL schedules higher rates yield less reinforcements. Thus on all schedules, animals with the greatest side preferences are also those who receive the most reinforcements and have therefore "learned" the appropriate responding pattern best.

To summarize, the functional significance of nigrostriatal asymmetry in learning appears to be not as a basic mechanism for learning per se, but as an important influence. The mediation of this influence may be via its effect on arousal, or in its relation to the importance of spatial cues and tendencies in the particular testing situation. Both of these possibilities are consistent with the results of this thesis, and are not incompatible. There may be an important three-way relationship between arousal, learning, and the function proposed here to be mediated by nigrostriatal asymmetry--the comparison of spatial cues in the animal's environment.

One recent study supports the hypothesis that the striatum is involved in the use of spatial cues in learning rather than in basic learning mechanism generally. Livesey and Rankine-Wilson (1975) found that stimulation of the caudate nucleus in cats during delayed-response testing severely impaired performance. However, when an exteroceptive cue signalled the correct location of the reward, these animals performed normally. The temporal pattern of responding was not affected by caudate stimulation, only the ability to remember the last location of the reward. In this experiment, unilateral as well as bilateral stimulation was found to impair learning. The

impaired animals all displayed circling responses (contralateral) with unilateral stimulation and one consistent direction with bilateral stimulation (probably contralateral to more active side, as predicted by Experiment 1C). Thus this study seems to lend support to the proposed relationship between striatal asymmetry and learning.

Relationship to Frontal Cortex

The finding that unilateral stimulation of the anterior cortex in rats also causes contralateral rotation (Experiment 1A) is consistent with previous work demonstrating ipsilateral rotation after lesions of the frontal cortex in rats (Glick and Greenstein, 1973b; Cowey and Bozek, 1974), and raises the question of the relationship of the striatum to frontal cortex in terms of spatial behavior. Sensory neglect in the visual modality has been reported after frontal lesions (Kennard, 1939; Welch and Stuteville, 1958), leading to the use of the term "frontal eye fields". Recently, Kinsbourne (1975) suggested that the frontal eye field may actually be frontal turning fields, and this suggestion is confirmed by the rotation elicited by electrical stimulation as reported here. In addition, unilateral ablation of frontal cortex in rats has been found to decrease contralateral turns in a Y maze (Cowey and Bozek, 1974), a result which is similar to the T maze results reported here after unilateral caudate lesions (Experiment 5). Cowey and Bozek, in fact, did not think that there was a true sensory neglect after the unilateral frontal cortex lesions, but rather that "the neglect . . . reflects a preference for the ipsilateral side and not an inability to turn contralaterally" (Cowey and Bozek, 1974). Green and co-workers (1970) had earlier reported that rats with unilateral frontal, but not occipital or

parietal, cortex lesions chose the ipsilateral arm of a T maze.

In addition to the above data implicating the frontal cortex and the striatum in spatial behavior, there is substantial evidence linking these two structures in the mediation of delayed alternation learning (e.g. Divac, 1972; Goldman, 1973). This similarity in lesion effects as well as the known anatomical relationship between the frontal cortex and the striatum led Divac and co-workers to theorize that "the caudate nucleus would subserve the functions of the cortex in its absence" (Divac et al., 1967). Recently there has been evidence of a functional specialization of the two structures because of differences found in rate of recovery and severity of deficit for the two lesions (Schmaltz and Isaacson, 1968, DRL; Livesey and Rankine-Wilson, 1975, delayed alternation).

The similarity, although not identity, between the functions of the frontal cortex and the caudate nucleus are probably subserved by the intimate connections between these two structures (Nauta, 1964; Knook, 1965; Leonard, 1969). Further research is thus indicated to parcel out the functions of the striatum in spatial behavior from those of the frontal cortex; however, duplication of function seen in the denervated animal does not invalidate a primary role for one structure in the intact state. In this regard, it should be emphasized that changes in side preference and rotation following unilateral caudate lesions are much more profound than those occurring after frontal cortical lesions (Glick and Greenstein, 1973b).

Evolution of Asymmetrical Function

The observation here that a physically symmetrical animal can display asymmetric behavior is not new; according to Wilson (1968)

there is an "old and extensive, but apparently forgotten literature on asymmetrical behavior in structurally intact organisms of several phyla". Jerussi (1974) suggests that asymmetric function may have originated in the taxis of primitive life; Chapple (1975) proposes the independent movement of appendages as the first step towards asymmetry. The Gastropods exhibit a marked asymmetry in the constant direction of spiral in their shells. Interestingly, the Decapods who inhabit these discarded shells have an asymmetry in the front chela on the same side as the direction of circling of the shell. Wilson (1968) noted the asymmetry in the motor output pattern of the flying locust, and reported that in the absence of light these animals will roll consistently in one direction. The milkweed bug also has a strong turning bias when tested in either infrared light or on a Y maze globe (Wilson and Hoy, 1968). Flies have been reported to make circling movements when deprived of food (Dethier, 1957). A well-known circling habit is visible in the "round dance" of the honeybee (Frisch, 1967).

Asymmetry of function in vertebrates has also been reported in the literature. During relaxed wakefulness, the pilot whale has both frequency and amplitude asymmetries in EEG recordings of the two cerebral hemispheres (Serafetinides et al., 1972). In birds, Nottebohm (1971, 1972) observed a lateralization of vocalization in songbirds. Rabbits show an asymmetric EEG that shifts in non-REM versus REM sleep, during bar-pressing for food, and after administration of psychoactive drugs (Goldstein, 1975). Susceptibility to audiogenic seizures also is an asymmetric function; a significant difference between left

and right ear susceptibility was found in DBA mice (Collins and Ward, 1970).

Since handedness is an obvious asymmetric function in humans, there has been a search for a similar manifestation in lower mammals. Stable and consistent paw preferences were reported in rats (Peterson, 1934) which could be reversed by either forced practice or contralateral frontal cortex ablation (Peterson, 1934; Peterson and Barnett, 1961; Peterson and Devine, 1963). Most mice have been found to be strongly left or right pawed when tested in a reaching-for-food chamber (Collins, 1968). This paw preference also was shown to be maleable; changing the bias of the testing chamber switched the preference of 90% of the animals. Collins concluded after numerous breeding experiments that the direction (i.e. left or right) of paw preference was not genetically determined in mice, but that the strength of laterality (i.e. a strong or weak preference) may be genetically intrinsic (Collins, 1975). The direction and degree of paw preference in cats and monkeys has also been reported to remain stable over time and in different testing conditions (Webster, 1972) although there is no consistent dominance of the left or right hemisphere as in man (Hamilton et al., 1974).

The preferential use of one hemisphere in learning in cats and monkeys has also been studied, using the split-brain paradigm, with conflicting results concerning the presence or absence of dominance (Webster, 1975; Sechzer, 1975; Hamilton, 1975; Ettlinger and Dawson, 1969; Butler and Francis, 1973; to name a few). The explanation for these conflicting reports, suggests Stamm (1975), is that hemispheric

dominance in these studies was assumed to be related to handedness, as it appears to be in humans. Recording evoked potentials in frontal cortex in intact monkeys during performance of a delayed response task, Stamm found that a significant left/right difference was not related to the preferred hand or to the hand used in training. What the electrophysiological asymmetry did correlate with was a "clear-cut spatial orientation preference". When learning the task, the monkeys were observed to develop individual and consistent position preferences, with a resulting ten-fold difference between error to the left or to the right. The visible position preference was quantitated through recordings of lateral eye movements. Each animal preferentially attended to one side during the inter-trial interval, and only when the cues came on did the animal look to the other side. These observations are consistent with my hypothesis presented earlier that preferential association of cues to one side may be responsible for the rodent's behavior in the T maze and perhaps in other learning situations. Whether the preferred spatial orientation indeed is intrinsic from birth or learned is a difficult question to answer experimentally. Anecdotally, baby chimps have preferred side preferences when learning to crawl (Doty, 1975), 80% of human babies lie with their heads to the right and turn to the right after release from midline (Turkewitz, 1975), and ducklings are more responsive to tactile stimulation on one side of the body, an effect which is related to their body position in the shell (Turkewitz, 1975).

Asymmetrical Functions in Humans

Although the highly specialized skill of writing leads one to focus on handedness as a manifestation of lateralization in humans,

other forms of asymmetric function may be more related to the type of spatial behavior studied in animals here. Asymmetry of motion around the vertical axis (body rotation) was studied in adult males, and they were found to have directional preferences (Ruisel, 1973). Preferred direction of body rotation has been observed in sports, such as skiing, diving, gymnastics, and track events (Ruisel, 1973). Significant side preferences were observed in adult females in a spontaneous alternation test (Manning and Artman, 1973). A phenomenon reminiscent of rats' rotation in the rotometer is the observation that people lost in fogs find that they walk in complete circles (Howard and Templeton, 1966). Experimentally, consistent direction of "veering" and preferred direction of descending a twin spiral staircase have been reported (Howard and Templeton, 1966).

The question of the mechanism responsible for asymmetrical spatial behavior was first posed over a hundred years by Ernst Mach, who wrote:

The idea that the distinction between right and left depends upon an asymmetry, and possibly in the last resort upon a chemical difference, is one which has been present to me from my earliest years. I gave expression to it in the first lectures I ever delivered, in 1861 . . . I learned by chance from a retired army-officer that on dark nights or in snow-storms, when external landmarks are absent, troops will move approximately in a circle of large radius so that they almost return to their point of departure . . . Human beings and animals that have lost their direction move, almost without exception, nearly in circle, of which the centre lies sometimes on the left hand of the individual travelling along the circumference, and sometimes on his right, according to the individual and the species. According to Guldberg we have here a teleological device to help parents to find their hungry young again when they have been lost.

(Mach, 1885)

This thesis proposes that the "chemical difference" suggested by Mach to be present in the central nervous system to mediate problems of "right and left" is indeed real, and may be found in the asymmetry of the

dopaminergic nigrostriatal system. The mechanisms by which this sensory-motor integration occurs, and its intimate connection with arousal will now be considered.

Sensory Neglect and Spatial Orientation

One of the ways to study spatial orientation is to think of it as a dual-track attention system, in which the animal is geared to respond appropriately to stimuli on the left or right. Thus there may be a dual-track orienting response in the left-right plane. According to Pavlov (1928) the orienting response, or reflex, occurs when "in the surroundings of the animal there appears some new agent . . . the corresponding receptor surfaces of the organism becomes focused on it, in a manner which will bring about the most favorable stimulation." There is obvious adaptive significance in the ability of an animal to locate a stimulus in space; food searching and escape from prey are two immediately apparent examples. The lateral duality of the orienting response may be seen in a syndrome in which one side no longer responds appropriately to stimuli presented on that side. This syndrome, sensory neglect, is found after several types of unilateral damage to the central nervous system. Unilateral mesencephalic reticular formation lesions in monkeys causes tactile, visual, auditory olfactory neglect on the contralateral side (Watson et al., 1973b). Multimodal sensory neglect is seen after inferior parietal lesions in monkeys (Watson et al., 1973a), and superior collicular lesions in rats (Kirvel et al., 1974). Contralateral neglect is also seen after unilateral lateral hypothalamic lesions (Marshall et al., 1971), which probably included damage to the nigrostriatal system, and after

ablation of the ansa lenticularis, an efferent projection of the striatum via the globus pallidus (Marshall and Teitelbaum, 1974). Most important in terms of this thesis is the finding by Ungerstedt (1974) that unilateral destruction of the nigrostriatal system by 6-hydroxydopamine produces unilateral sensory neglect to visual, tactile, olfactory and auditory stimuli. The finding that there is gradual recovery of some modalities, but at differing rates, indicates that the lack of orienting response is due to a deficit in sensory-motor integration or stimulus recognition rather than to a mere motor deficit.

If unilateral damage to the dual attention system blocks half of the animal's orienting response, then unilateral stimulation of the same areas should elicit the contralateral orienting response. The head and body turning reported here and elsewhere (Arbuthnott and Ungerstedt, 1969; Arbuthnott and Crow, 1971; Laursen, 1963, for recent studies) after unilateral caudate stimulation has been interpreted as a "searching" motion that appeared to be a complex behavioral pattern rather than a mere motor response (Laursen, 1962a). The interpretation, from experiments discussed earlier, that contralateral turning in rats represents an exaggerated unilateral orienting response, has also been suggested by investigators working with cats. Ursin and co-workers (1969) reported that electrical stimulation of the caudate nucleus, at the same frequency used in the present experiments, cause a contralateral orienting response in unanesthetized, freely moving cats. The movement of the head described in the Ursin study was identical to the response described here in rats, and was defined by these authors as an orienting response because "it was impossible for us to tell from

the observed behavior whether a given orienting response is being elicited by external stimulation or brain stimulation" (Ursin et al., 1969). In Experiment 3, rats were observed to reverse their side preferences in the two-lever operant chamber after unilateral caudate nucleus stimulation. The suggestion of a dual-track attention system operating via the asymmetric nigrostriatal system is therefore supported by findings of neglect from unilateral lesions, and orientation elicited by stimulation. Thus perhaps the reversal of side preference shown here can be seen as sensory "overattention" to the opposite side. With increased attentiveness to stimuli present on the contralateral side, the animal presses the lever on that side more frequently. A side preference exhibited spontaneously may therefore be the result of a normal imbalance between the left and right nigrostriatal systems, with the greater activity in one system producing greater attention to the opposite side. And the ability to form such associations of stimuli and motor responses may help to explain the relationship between an animal's side preference and its performance on learned tasks. Each task will require an optimum amount of attention to spatial cues, perhaps maximized in maze learning and minimized in active avoidance learning.

Sensory Neglect and Spatial Orientation in Humans

Anosognosia, the denial or unawareness of illness (particularly left hemiplegia), may be a clinical correlate of sensory neglect. First defined by Babinski in 1914, this syndrome of neglect occurs in patients whose other brain functions (memory, attention, judgement) remain intact. Not only are the patients seemingly unaware of their disability,

but figures and objects drawn by such patients are asymmetric and show distortions and omissions on the side mirroring the patients' deficit. This syndrome was studied by Weinstein and Kahn (1955) and their anatomical and physiological research concluded that "anosognosia occurred with frontal, parietal or temporal lobe lesions when these invaded the medullary center of the cerebral hemisphere and the corpus striatum and diencephalon" (Weinstein and Kahn, 1955). Although this study did not specifically indict the striatum in this syndrome, it did reject causation by the cortex alone.

Parkinson's Disease provides a good clinical correlate of experimental alterations in the nigrostriatal system in two ways:

- (1) it represents a parallel to nigrostriatal lesion in animals and
- (2) the problems of l-dopa pharmacotherapy may also mimic overstimulation of the system, especially in its long-term use. In both situations alterations in arousal and cognitive functions have been reported. Parkinson patients scored higher on the depressive scale of the Minnesota Multiphasic Personality Inventory than controls (Marsh et al., 1971; Horn, 1974). L-dopa treatment has been shown to cause a wide range of disturbances in arousal: irritability, insomnia, nervousness, agitation, hypomania, and depression (Knopp, 1970; Murphy, 1973; Martin et al., 1974). One study which dealt directly with the question of l-dopa and disturbances in arousal found that the drug increased skin conductance levels and fluctuations, increased electromyographic activity in frontalis muscle, and increased reactivity and decreased habituation to loud noises in Parkinson patients (Horvath and Meares, 1974). Barbeau (1971) noted that there was a gradual decrease in the attention span after two years of l-dopa administration.

Short-term administration of l-dopa to Parkinson patients increased alertness as measured by the Critical Flicker Frequency (CFF) test, but long term l-dopa use (two years) decreased CFF scores (Maskin et al., 1973). No studies have been conducted on the few cases of unilateral Parkinsonism; it would be interesting to see if a syndrome comparable to sensory neglect were present. Parkinson patients have been shown to be deficient on two tasks requiring spatial orientation, map-walking and adjusting a vertical line (Proctor et al., 1964; Bowen et al., 1972).

In addition to deficits in arousal and spatial orientation in Parkinsonism there is evidence of intellectual impairment (Warburton, 1967; Loranger et al., 1972b). The mental deterioration has been best correlated with the akinetic component of the disease, which in turn is best correlated with deficits in dopamine (Barbeau, 1974). Short-term l-dopa treatment seemed to improve intellectual functioning, as measured by the Weschler Adult Intelligence Scale (Loranger et al., 1972a). When these studies were extended as the duration of treatment continued for two years, however, it was observed that the improvement in cognitive function was not maintained (Donnelly and Chase, 1973; Loranger et al., 1973). In fact, some investigators think that l-dopa therapy on a long term basis may actually worsen cognitive function, and in some cases result in permanent dementia (Sachs et al., 1972; Wolf and Davis, 1973; Pearce, 1974). The conflicting reports of increases and decreases in both arousal and cognitive function after l-dopa treatment may be related, perhaps, to individual difference in the effects of the drug on nigrostriatal asymmetry; as indicated in this thesis, such differences might result in differential effects on arousal (e.g. locomotor activity), spatial behavior (e.g. side preference) and cognition (e.g. avoidance learning).

Other Implications-Minimal Brain Dysfunction

These observations which relate the nigrostriatal asymmetry to many aspects of behavior may be helpful in understanding the etiology and current treatment of "minimal brain dysfunction" (MBD), a disorder in children characterized by hyperactivity and learning difficulties. It has been noted that MBD is frequently associated with poor cerebral dominance (Gazzaniga, 1973). Learning and motor disabilities as well as electrophysiological abnormalities may appear asymmetrically (Reitan and Boll, 1973; Conners, 1973). Gazzaniga (1973) suggested that the fundamental problem in MBD is related to the failure of normal cerebral dominance to develop. Amphetamines and related drugs have been found to be particularly useful in treating MBD, especially when neurological evidence of minimal but real brain damage is demonstrable (Satterfield et al., 1973; Millichap, 1973). It may be speculated, therefore that amphetamine's therapeutic effects in MBD are attributable to enhancement of nigrostriatal asymmetry and/or of cerebral dominance generally. The small percentage of animals having no striatal asymmetry as measured here may be a suitable model for MBD. These animals are hyperactive and appear to have overall impairments in learning ability. These animals have also been shown to be hypersensitive to amphetamine-induced depression of locomotor activity, a finding consistent both with the rate-dependent principle of behavioral pharmacology and with the empirical "sedative" effect of amphetamine in MBD (Glick and Milloy, 1973). It can be predicted that amphetamine would facilitate asymmetry to a more optimum degree. Hopefully the use of this model for further experimentation will contribute to the therapeutic input of behavioral pharmacology.

SUMMARY

Normal rats were found to have spontaneous and stable left or right side preferences in a T maze. The possible relationship of this side preference to an intrinsically asymmetric nigrostriatal system was examined in several ways. First, the side preference was found to be contralateral to the striatum with higher dopamine levels. Second, rats rotated following d-amphetamine in the same direction as their non-drug side preferences in the T maze. Third, d-amphetamine, which induces rotation in normal rats by potentiating the intrinsic dopamine asymmetry, also potentiated side preferences. Side preferences in animals with experimentally-induced asymmetries were also studied. Unilateral caudate lesions, which cause ipsilateral rotation, produced ipsilateral side preferences. Unilateral electrical stimulation of the caudate nucleus, which was shown here to elicit contralateral rotation with neuroanatomical specificity to the nigrostriatal system, also elicited contralateral side preferences in a two-lever operant task. These results indicated that side preferences reflect a normal asymmetry in nigrostriatal function.

Side preference, as a correlate of nigrostriatal asymmetry, was then investigated for its relationship to associative behaviors previously shown to be related to striatal function. The initial side preferences of rats were found to influence their subsequent learning of a left-right discrimination in the T maze. Strength of side preferences was shown to be inversely related to the rate of learning of an active avoidance response in a two-way shuttle box. Conversely, in mice, strength of side

preference in mice was also positively correlated with spontaneous locomotor activity. Animals with no side preferences were found to have the greatest activity and were poor learners of either avoidance task. The results of these experiments indicated that there may be an important role of nigrostriatal asymmetry in the learning of both spatial and nonspatial tasks.

A pharmacological analysis of the effects of four drugs on side preference and passive avoidance in mice was undertaken. A dopaminergic stimulant (apomorphine), a dopaminergic blocker (haloperidol), a cholinergic stimulant (pilocarpine) and a cholinergic blocker (scopolamine) were used. Side preference was found to be primarily a dopaminergic function, although cholinergic systems may modulate its manifestation. Passive avoidance learning, conversely, was shown to be primarily affected by the cholinergic agents, with lesser effects by dopaminergic drugs. The results of drug interactions on both tasks were inconclusive, although there was some support for dopamine-acetylcholine reciprocity in the striatum.

The results of this thesis suggest that individual differences in degree of nigrostriatal asymmetry may be responsible for individual variations in behavioral responses to pharmacological or surgical treatments. The intrinsically asymmetric nigrostriatal system may function as mechanism for the comparison of spatial cues in an animal's environment, and, as such, may influence associative behaviors in general. This hypothesis was discussed in relation to the evolution of asymmetric function and studies on sensory neglect and spatial orientation in animals and man.

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