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1981

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THE EFFECTS OF RADIO-FREQUENCY LESIONS OF THE NUCLEUS ACCUMBENS ON

D-AMPHETAMINE INDUCED LOCOMOTOR AND REARING BEHAVIORS IN RATS

A Thesis Presented

By

JOHN HERR KEHNE, JR.

Submitted to the Graduate School of the
University of Massachusetts in partial fulfillment
of the requirements for the degree of

MASTER OF SCIENCE

February   1981

Psychology

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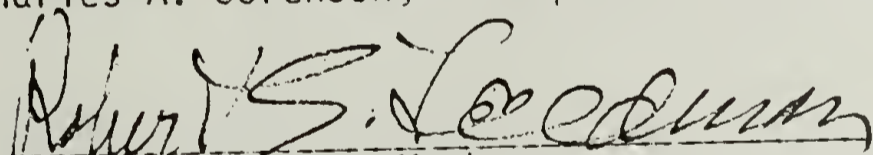
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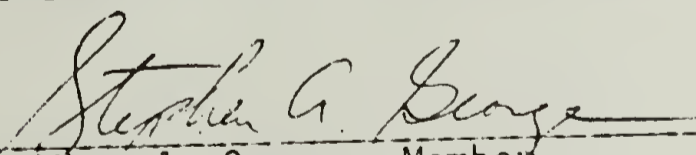
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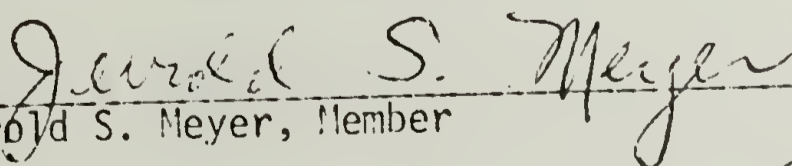
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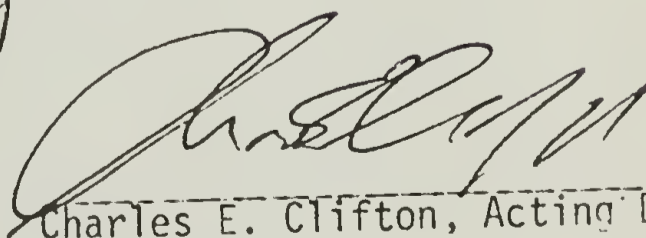
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DEDICATION

To Betsy, Nathan, and my parents,

for making me a proud brother, uncle, and son.

ACKNOWLEDGEMENT

ABSTRACT

A large body of evidence supports the conclusion that mesolimbic dopaminergic neurons, in particular those that innervate the nucleus accumbens (n.ACC), are important for the expression of d-amphetamine stimulated locomotor behavior (ASLB). However, one recent study has contradicted this conclusion, reporting that bilateral lesions of the n.ACC fail to block ASLB. It appears that this study contains a methodological flaw in that it employed a general measure of activity which did not distinguish between locomotion and rearing. In the present study, we used observer ratings of videotaped responses to determine the seperate effects of 2.0 mg/kg d-amphetamine on loco-motion and rearing in rats with either sham or radio-frequency lesions of the n.ACC. It was found that n.ACC lesions blocked the locomotor stimulation, but not the increased rearing, which follows d-amphetamine administration. Additionally, the time spent engaging in stereo-typed behaviors following administration of a high dose of the dopa-mine agonist apomorphine was not affected by the lesion. These results support the general conclusion that dopaminergic terminals in the n.ACC are important for the expression of ASLB, and further suggest that d-amphetamine-stimulated locomotion and rearing are mediated through different neural substrates.

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INTRODUCTION

Amphetamine as a Tool for Studying Catecholaminergic Neurons

In the past fifteen years, a wealth of literature has focused on
the study of brain dopamine- (DA) and norepinephrine- (NE) containing
neurons (collectively categorized as catecholamine- (CA) containing
neurons). By number, catecholaminergic neurons comprise only a fraction
of the total number of nerve cells in the brain, yet their significance
appears to be quite profound. From their cell bodies in the brainstem,
these neurons project widely throughout the neuraxis. Their reported
importance in the expression of a wide range of behaviors and behavioral
processes, e.g. aggression (Reis and Fuxe, 1969), sleep and arousal (An-
telman and Caggiula, 1977), self-stimulation (Stein and Wise, 1969),
food intake (Leibowitz, 1970), and their purported roles in the etiology
of psychopathological disorders (e.g. Snyder et al., 1974), is consistent
with the idea that CA-containing neurons are anatomically well-suited to
exert general modulatory or control influences over behavior.

The study of the function of central catecholaminergic neurons has
been aided tremendously by the development of specific pharmacological
tools for enhancing or blocking CA activity. The basic rationale
behind the psychopharmacological approach is that, by observing the
resultant behavioral effects of systematic pharmacological manipulation

(either alone or in combination with lesions produced by a variety of techniques) of NE- and DA-containing neurons, one can obtain an idea of the function that these neurons normally play in the control of behavior.

The drug amphetamine (AMPH) has proven to be an especially valuable tool for the study of catecholaminergic neurons. AMPH increases the functional activity of these neurons through multiple biochemical actions (Groves and Rebec, 1976 is an excellent review of the literature pertaining to these actions). A primary action of AMPH is its ability to release CAs from catecholaminergic nerve terminals (Anden and Svensson, 1973), thus resulting in a potentiation of neural activity by increased synaptic availability of the neurotransmitter. That blockade of CA synthesis with alpha-methyl-para-tyrosine (AMPT), but not disruption of vesicular storage of CAs with reserpine, prevents this releasing effect suggests that AMPH acts to release CAs from a "functional pool" of neurotransmitter maintained by de novo synthesis (Glowinski, 1973). Additionally, AMPH increases synaptic availability of CAs by blocking their reuptake into the terminal (Glowinski and Axelrod, 1964). At higher doses than those required to increase release and block reuptake, the drug inhibits monoamine oxidase (Glowinski et al., 1966; Coyle and Snyder, 1969), resulting in a decrease of terminal deactivation of the unbound transmitter. These three actions each serve to enhance the functional activity of NE- and DA-containing neurons.

AMPH exists in d- and l- isomeric forms. The two isomers have been found to have differential effects on blocking reuptake in dopa-

minergic vs. noradrenergic neurons, though the precise nature of those differences has been debated. It was first reported that the d-isomer was ten times more effective than the l-isomer in blocking noradrenergic uptake, whereas both isomers were found to be equipotent on dopaminergic neurons (Coyle and Snyder, 1969). The bulk of the evidence, however, supports the conclusion that the isomers are equipotent on noradrenergic neurons, while the d-isomer is five times more potent than the l-isomer in blocking uptake in dopaminergic neurons (Harris and Baldessarini, 1973; Thornburg and Moore, 1973). Although a number of investigators have attempted to correlate the potency differences between the two isomers with potency differences on behavior (e.g. Scheel-Kruger, 1972; Thornburg and Moore, 1973), the majority of the AMPH literature deals primarily with the action of the d-isomer.

The Behavioral Effects of d-Amphetamine

The intraperitoneal (i.p.) administration of d-AMPH results in a number of dose-dependent behavioral effects (see Groves and Rebec, 1976; Cole, 1967,1978 for reviews). Low dose administration (e.g. 1.5 mg/kg), in addition to producing hyperthermia, depression of food intake, and signs of autonomic arousal (references cited in Groves and Rebec, 1976), induces a prominent behavioral arousal. The frequency of specific motor behaviors, particularly locomotion and rearing (Cladel et al.,1966; North et al., 1974; Hanson, 1967; Segal, 1975) is greatly enhanced by the drug. Though it has been suggested that this activation reflects a general increase in exploratory activity, i.e. enhanced sensorimotor

reactions to novel enviornmental stimuli (van Rossum et al., 1977), it is more likely that the activation is motor in nature. Robbins and Iversen (1973), using an apparatus designed to differentiate increases in exploratory activity from general increases in locomotion, found that d-AMPH increased general motor activity while depressing exploratory responses. Their apparatus consisted of a rectangular open field with an alcove at one end, into which various objects were placed during the course of testing. 1.5 mg/kg of d-AMPH decreased the number and duration of observing responses and approaches to the novel objects while enhancing non-directed locomotion. Furthermore, a number of more recent studies have found that locomotion elicited by d-AMPH shows less variability than the spontaneously occuring behavior (Schiorring, 1979; Segal, 1975), suggesting that the drug is inducing a purely motoric stimulation.

At high doses (e.g. 5 mg/kg), a marked change in the behavioral pattern occurs. Immediately following injection, rats show enhanced locomotion and rearing, though these behaviors soon disappear and are replaced by a syndrome of "stereotyped" behaviors, e.g. repetitive licking, biting, sniffing and gnawing (Randrup and Munkvad, 1967; Costall et al., 1972; Creese and Iversen, 1972, 1973, 1974, 1975). There is virtually no locomotion or rearing throughout the period of intense stereotypies (the duration of which depends on the dose), and the animals are largely insensitive to changes in enviornmental novelty. As the stereotypies decrease, normal locomotion and rearing is restored, followed by a period of behavioral depression (Groves and

Rebec, 1976).

Catecholaminergic Mechanisms of d-Amphetamine Stereotypies

Though d-AMPH potentiates both NE- and DA-containing neurons, the literature has consistently emphasized a key role for dopaminergic neurons in the production of stereotypies. Disruption of CA synthesis with AMPT has been reported to block d-AMPH stereotypies (Fog et al., 1967; Hollister et al., 1974; Carlsson, 1966) whereas disruption of NE synthesis alone with the DA-beta-hydroxylase inhibitor diethyldithiocarbamate has been found to be unsuccessful in this respect (Scheel-Kruger and Randrup, 1967). Furthermore, a large body of evidence supports the conclusion that specific activation of the nigro-striatal dopaminergic pathway[1] is responsible for the development of d-AMPH stereotyped behaviors. Direct injection of d-AMPH (Ernst, 1967), DA (Ernst and Smelik, 1966), or the DA agonist apomorphine (Ernst, 1967) via cannulae into the

[1] Brain dopaminergic neurons are localized in four primary pathways: (1) the nigro-striatal pathway, with cell bodies in the pars compacta of the substantia nigra (the A9 cell group referred to by Ungerstedt, 1971) and terminal projections in the caudate-putamen (75-80% of brain DA is contained within this pathway); (2) the meso-limbic pathway, with cell bodies in the ventral tegmental area (A10) and terminals in the nucleus accumbens, olfactory tubercles, central amygdaloid nucleus, nucleus of the stria terminalis, and lateral septal area; (3) the meso-cortical pathway, also with cell bodies in the ventral tegmental area but with terminal projections to the fronto-medial and entorhinal cortices; (4) the tubero-infundibular pathway, a small dopaminergic tract from the tuberal nucleus of the hypothalamus to the stalk of the pituitary (infundibulum). Ungerstedt (1971) originally mapped the catecholaminergic pathways in the rat brain using the formaldehyde fluorescence technique, though the cortical pathway was later detected with the glyoxylic acid method (Lindvall et al., 1973).

neostriatum results in stereotyped behaviors. Intrastriatal injection

of para-hydroxy-amphetamine, which does not cross the blood-brain

barrier and thus does not diffuse via the vasculature to other parts of

the brain, produces stereotypies (Fog and Pakkenburg, 1971).

Furthermore, injection of the specific catecholaminergic neuro-

toxin 6-hydroxydopamine (6-OHDA) into the substantia nigra, which induces

a degeneration of striatal DA-containing terminals, blocks stereotyped

behavior induced by d-AMPH (Creese and Iversen, 1972). Electrolytic

lesions of the nigra have been reported both to block (Simpson and

Iversen, 1971) and to have no effect on (Costall et al., 1972) stereo-

typed behaviors elicited by the drug. However, it has been suggested

that the failure of electrolytic lesions of the nigra to attenuate

stereotypies was due to an incomplete lesion of dopaminergic neurons

and the development of denervation supersensitivity in the striatum.

Given the remarkable capacity for recovery of function in partially-

denervated CA-containing neurons (e.g. Stricker and Zigmond, 1976), it

is possible that the d-AMPH - induced release of DA from undamaged

nerve terminals onto supersensitive DA receptors resulted in a normal

drug response.

Specific lesions of DA-containing terminals innervating the striatum

achieved by intra-striatal injection of 6-OHDA have also been reported

to block d-AMPH stereotypies (Asher and Aghajanian, 1974). These

authors reported that relatively high levels of DA depletion were

necessary for this blockade to occur, supporting the idea that dener-

vation supersensitivity compensates for the reduced number of

dopaminergic neurons. In further support of this notion, it has been reported that administration of the DA agonist apomorphine (which, unlike AMPH acts directly on the postsynaptic DA receptor) to 6-OHDA-treated rats restored the full d-AMPH stereotypy response (Creese and Iversen, 1974).

Surprisingly, massive electrolytic lesions of the corpus striatum have been reported to have no effect on d-AMPH stereotypies (Marcus and Villablanca, 1974; Divac, 1972). Though it is possible that the lesions were incomplete (a possibility suggested by the immense size of the striatum), several studies suggest another possible explanation. 6-OHDA lesions (Costall et al., 1977) or electrolytic lesions (Costall et al., 1974) of the globus pallidus have been found to completely block the occurence of d-AMPH stereotypies. This finding is not surprising in that (1) such lesions disrupt ascending nigro-striatal fibers that course through the globus pallidus, and (2) the globus pallidus is considered to be the major output of the striatum (Carpenter, 1976). However, injection of apomorphine directly into the pallidus has been reported to result in stereotyped behaviors (Ernst and Smelik, 1966). A recent anatomical study using the sensitive glyoxylic acid technique has found that some of the fibers from the nigro-striatal dopaminergic pathway give off collaterals to the globus pallidus (Lindvall and Bjorklund, 1979). Though the innervation of the pallidus was reported to be sparser than that of the striatum, it was nonetheless significant in that "all large pallidal neurons could be contacted by these terminals." Taken together, these studies

suggest that, in addition to producing stereotyped behaviors by induc-
ing DA release in the striatum (whose output is through the globus
pallidus), d-AMPH may produce this behavioral effect by direct activa-
tion of nigro-pallidal fibers.

Catecholaminergic Mechanisms of d-Amphetamine Locomotor Stimulation

Although the mechanisms through which high doses of d-AMPH pro-
duce stereotypies are fairly well understood, the precise neurochemical
and anatomical pathway(s) through which low doses exert their activating
effects on behavior is less clear. A number of early studies attempted
to generally assess the relative roles of dopaminergic and noradrenergic
neurons in mediating d-AMPH-stimulated locomotor behavior (ASLB) using
several pharmacological approaches.

One approach was to selectively block the functional activity of
NE- **or** DA-containing neurons using pharmacological or lesion tech-
niques, and determine if d-AMPH still activated locomotor behavior.
Administration of the CA synthesis inhibitor AMPT, but not administra--
tion of the DA-beta-hydroxylase inhibitors U14,624 or FLA 63, blocked
ASLB, leading to the conclusion that release of DA, but not NE, was
critical for the d-AMPH effect (Hollister et al., 1974; Breese et al.,
1975). Creese and Iversen (1973) also suggested a primary role for
dopaminergic neurons, on the basis of their finding that 99% depletion
of brain DA in adult rats (injected neonatally with 6-OHDA) blocked
ASLB. However, significant whole brain depletions of NE were also
reported in this study, making it inappropriate to rule out a contribu-

tion of noradrenergic neurons. However, Hollister et al. (1975) have reported that selective depletions of whole brain DA, but not selective NE depletions, were successful in antagonizing the locomotor effect, supporting the conclusion of the Creese and Iversen (1973) study.

If d-AMPH enhances locomotion primarily through dopaminergic activation, then it would be predicted that independent (i.e. not using d-AMPH) pharmacological manipulation of dopaminergic activity would produce behavioral effects similar to those of d-AMPH. Geyer et al. (1975) have found that intraventricular infusions of DA or NE were successful in producing dose-dependent activation of locomotion. Furthermore, they have argued that noradrenergic activation was primarily responsible for both of these effects, on the basis of two findings: (1) pretreatment with low doses of haloperidol (which produces a selective DA receptor blockade) failed to antagonize either effect, whereas high doses (which additionally block NE receptors) successfully reduced both effects. (2) Pretreatment with the NE reuptake blocker imipramine blocked the effects of both DA and NE. The authors suggested that both infused CAs were inducing locomotor stimulation through the common activation of noradrenergic neurons.

It is important to note the authors' comments on the behavior of rats treated with NE or DA: NE produced "continuous motor activity with marked sniffing and chewing, and heightened reactivity to handling", whereas DA-infused rats often "lay flat and occasionally moved in a crawling posture." These descriptions make it unclear whether the locomotor stimulations produced by infusion of NE and DA were qualita-

tively similar or whether they were comparable to the locomotor activation produced by d-AMPH.

CA agonists have also been employed to determine whether noradrenergic and/or dopaminergic stimulation results in locomotor activation. It has been reported that administration of the DA agonist apomorphine stimulates locomotion in rats (Maj et al., 1972a; Ljungberg and Ungerstedt, 1977), though one recent study has reported a depressive effect (Isaacson et al., 1978). Furthermore, pretreatment with the DA receptor blocker haloperidol, but not pretreatment with the alpha-NE blocker phenoxybenzamine, antagonized this stimulation (Maj et al., 1972b). High doses of phenoxybenzamine did antagonize the apomorphine effect, though this may be due to non-specific sedative effects. Furthermore, the alpha-NE agonist clonidine has been reported to be ineffective in stimulating locomotion (Creese and Iversen, 1973), arguing against a noradrenergic contribution to this behavior. However, clonidine has been shown to additionally act on epinephrine receptors (Bolme et al., 1974), making it difficult to assess the precise role of NE-containing neurons from studies employing this drug. In summary, the apomorphine studies generally support the conclusion that dopaminergic stimulation results in locomotor activation, whereas the clonidine finding does not conclusively rule out a similar role for NE-containing neurons.

Though early studies generally argued against a contribution of NE-containing neurons to the locomotor activation by d-AMPH, there was little attention paid to the contribution of specific NE-containing

pathways. Creese and Iversen (1975), in contrast to their earlier 1973 study, did attempt to evaluate the potential contributions of the dorsal and ventral noradrenergic pathways to ASLB. They found that 6-OHDA injected into these pathways produced specific regional depletions of NE, though in neither case was ASLB affected. The authors concluded that noradrenergic neurons within these two pathways were not critically involved in the d-AMPH effect.

Creese and Iversen (1975), on the basis of their finding that 6-OHDA injected into the substantia nigra blocked the locomotor response to d-AMPH, suggested that activation of the nigro-striatal dopaminergic pathway was critical for this effect. However, these authors failed to control for the possibility that 6-OHDA may have destroyed cell bodies of the meso-limbic dopaminergic pathway, located rostro-medially to the substantia nigra in the ventral tegmental area (VTA). In fact, studies have since reported that specific degeneration of dopaminergic nerve terminals in the neostriatum, achieved by direct intrastriatal injection of 6-OHDA, effectively block the stereotypy, but not the locomotor, stimulating effects of d-AMPH (Kelly et al.,1975).

A variety of pharmacological and lesion studies have suggested that dopaminergic neurons of the meso-limbic pathway, particularly those that project from the VTA to the nucleus accumbens (n.ACC), play a major role in the mediation of ASLB. Direct injection of d-AMPH into the n.ACC produces a strong locomotor activation (van Rossum et al., 1977; Jackson et al., 1975) that is blocked by pretreatment with the CA synthesis inhibitor AMPT (Jackson et al., 1975). Given that the

n.ACC is also densely innervated by NE-containing neurons (Jacobowitz, 1973; Lindvall and Bjorklund, 1975), this procedure does not distinguish between noradrenergic and dopaminergic involvement. However, a key role for DA-containing neuron is suggested by the findings that intra-accumbens injections of the putative DA receptor blockers haloperidol (pijnenburg et al., 1975) or trifluoperazine (Jackson et al., 1975), antagonized the locomotor stimulation achieved by systemically administered d-AMPH. Additionally, direct injection of DA, but not NE, into the n.ACC stimulates locomotor activity (Pijnenburg et al., 1976). d-NE also stimulates locomotion when given in conjunction with nialimide, reserpine, and AMPT, though this locomotor activation is more successfully blocked by pretreatment with the DA receptor blocker pimozide than by the NE receptor blocker phenoxybenzamine (Anden, 1978).

Studies employing the use of lesion techniques to evaluate the role of the dopaminergic projection to the n.ACC are less consistent in their findings. DA depletion of the n.ACC achieved by intra-accumbens injection of 6-OHDA given alone (Kelly et al., 1975; Costall et al., 1977) or in conjunction with desmethylimipramine to protect NE-containing neurons (Kelly and Iversen, 1976; Iversen and Koob, 1977; Koob et al., 1978) has been found to attenuate or block ASLB. In contrast to these studies, it was recently reported that 6-OHDA injected into the adjacent antero-medial caudate nucleus, but not the n.ACC, attenuated ASLB (Fink and Smith, 1978). However, this last study used six ug of 6-OHDA injected bilaterally into the n.ACC, whereas other studies

used eight ug (Kelly et al., 1975; Koob et al., 1978). It is difficult to say whether this difference resulted in a less extensive DA deple-tion, since Fink and Smith (1978) used histofluorescence, rather than biochemical assay, to assess the extent of dopaminergic destruction. It is possible that a DA depletion sufficiently severe to block ASLB was not achieved. That supersensitivity may have developed is suggested by the finding that the n.ACC lesioned rats in the Fink and Smith (1978) study showed normal levels of spontaneous activity two weeks after 6-OHDA injection, but were hyperactive at five weeks. Others have re-ported that a consistent hypoactivity occurs during the first three weeks after injection (Iversen and Koob, 1977; Koob et al., 1978). Thus, a contribution of the dopaminergic innervation to the n.ACC to ASLB does not appear to be ruled out by the Fink and Smith (1978) study.

Wirtshafter et al., (1978) have recently reported that electrolytic lesions of the n.ACC, which presumably destroy the majority of affer-ents and efferents of this nucleus, have no effect on ASLB. This report clearly contradicts the notion that the dopaminergic projection to the n.ACC plays a major role in the mediation of ASLB.

However, it appears possible that the Wirtshafter et al. finding might depend upon the type of apparatus that was used to measure loco-motion. They used stabilimeters ("jiggle cages") calibrated to measure gross body movements. Pilot studies in our laboratory suggest that this device might have measured a d-AMPH-potentiated behavior other than locomotion, i.e. rearing, which might not require the presence of the n.ACC for its expression. The use of such a device would clearly

obscure a lesion-produced disruption of ASLB.

The purpose of the present study was to evaluate the behavioral effects of d-AMPH in rats with lesions of the n.ACC using a procedure which allowed the uniequivocal discrimination cf locomotion and rearing behaviors. Rats were videotaped in the open field, and observers objectively quantified their locomotion and rearing responses following treatment with d-AMPH or vehicle.

CHAPTER II
METHODS AND MATERIALS

Subjects

All subjects (Ss) were male albino rats of the Sprague-Dawley
strain, purchased from Berkshire Biological Laboratories (Florence, MA).
Ss were housed doubly in a colony room maintained on a 12/12 reverse
light-dark cycle (lights on from 8 P.M. to 3 A.M.). They were allowed
free access to food and water throughout the experiment. Weight range
at the time of operation was 250 - 350 grams.

Lesion Procedure

Approximately one week after receipt of the animals, lesioning
began. The rat was anesthetized with Ketamine HCl (60 mg/kg, intra-
muscularly) and Nembutal (21 mg/kg, i.p.). Both drugs were purchased
from the Central Veterinary Supply House, Springfield, MA. The scalp
was shaved, and the rat was then placed in a Kopf stereotaxic instru-
ment. A longitudinal incision was made in the skin covering the skull,
underlying connective tissue was removed with a bone scraper, and
bregma was visualized. A Radionics, Inc. RFG-4 radiofrequency lesion
maker was used to produce bilateral lesions of the n.ACC (n = 15), or
appropriate sham lesions (n = 11). A burr hole through the skull was
drilled at the following coordinates (using the skull landmark system
of Pelligrino and Cushman (1968), with the tooth bar set at 5 mm above

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the ear bar): 3.4 mm anterior from bregma, 2.0 mm lateral from the longi-
tudinal suture. The electrode was lowered 7.0 mm below dura. The current
was then slowly increased for 1 minute until a temperature of 65° C was
achieved, then adjusted to maintain this temperature for an additional
minute. The electrode was raised and the procedure repeated for the other
side of the brain. For sham operations, the same procedure was followed
except that the electrode was only lowered 5.5 mm (thus preventing
mechanical damage to the n.ACC) and the current was not turned on.
All coordinates and lesion parameters were derived from pilot studies.
Burr holes were filled with bone wax, the scalp sutured with wound
clips, and Mikedimide (.15 mg/kg, i.p.)(Ormont Drug) given to facilitate
recovery from anesthesia. Weight gain, monitored daily following the
operation, showed no significant difference between the two groups,
supporting the general observation that lesioned Ss were physically
indistinguishable from controls.

Apparatus

The apparatus for behavioral observation consisted of a videotaping
system and a modified open field chamber. The box was painted black,
and the floor marked off into a grid with white lines. A partition
divided the box into 2 rectangular chambers, each 93 x 44 x 28 cm high.
A wire screen covered the top of the box to prevent escape. The floor
of each chamber was marked off into a grid of 8 23.5 cm squares.
Illumination was provided by a 60 watt light bulb suspended 142 cm
above the floor of the cage. A transparent red filter minimized the

light reaching the Ss, and yet still allowed effective videorecording. Background white noise, generated by a Grason-Stadler white noise generator, was maintained at 60 db. The videocamera, placed 145 cm from the cage, allowed a complete view of the floors of both of the test chambers. Room temperature ranged from 22° to 25° C.

Testing

All rats were tested for their behavioral response to a low (2.0 mg/kg, i.p.) dose of d-AMPH sulfate (Sigma Chemical Co.), to a high (3.0 mg/kg, i.p.) dose of apomorphine HCl (courtesy of Michael Davis), and to the vehicle solution (physiological saline). The dose of d-AMPH chosen was the same as that used by Wirtshafter et al. (1978). It causes a reliable potentiation of locomotor activity without producing stereotyped behaviors. Administration of 3 mg/kg apomorphine, a specific DA agonist, produces stereotyped behaviors (sniffing, licking and gnawing), an effect which has been attributed to the stimulation of striatal DA receptors (see introduction). As a control for the possible disruptive effect of the n.ACC lesions on the neostriatum (in addition to routine histological controls), the effects of n.ACC lesions on the stereotypy-producing effect of apomorphine was measured. The measure of stereotypy used was the cumulative time spent engaging in stereotyped sniffing, licking, and/or gnawing.

Each rat was tested under all drug conditions (d-AMPH, apomorphine, or vehicle), with a period of 8 days between retesting. The order of drug injection was counterbalanced (i.e. the 6 possible orders,

d-AMPH/saline/apomorphine, saline/apomorphine/d-AMPH, etc., were ran-
domly assigned among rats). All testing was done during the middle of
the rats' dark cycle. Retesting was done in the same cage and at the
same time of day to minimize the effects of circadian fluctuations in
activity (Horlington, 1970) and CA levels (Lemmer, 1978). Prior to
testing, rats were weighed, injected with the appropriate drug, and
placed into the test chambers. Videorecording began immediately and
lasted for an hour, after which the rats were returned to their home
cages. The test chamber was washed and wiped dry in preparation for
the next test.

Behavioral Rating

The recorded tapes were played back on a television monitor, and
2 observers carried out the behavioral rating (1 observer per rat).
Locomotion and rearing were quantified with hand-held counters, and a
cumulative time clock was used to measure the amount of time spent
engaging in stereotypies. Two measures of locomotion were obtained.
The first, squares, was defined as forward movement from 1 square to
another, as indicated by placement of all 4 feet in the squares. Par-
tial excursions were not counted. The second measure, crosses,
referred to the number of times the rat moved from one half of the
cage to the other, along the long axis of the chamber. These measures
were used to determine whether activity was homogeneously distributed
throughout the entire length of the rectangular test chamber, or if it
was, under any condition, limited to one half of the cage. Fink and

Smith (1978) have reported that 6-OHDA lesions can selectively disrupt d-AMPH-induced full length traverses of the test chamber, while leaving shorter excursions intact. Rearing was counted every time the rat lifted its front feet off the floor and extended its body vertically (either freestanding or resting its front legs against the side of the chamber). These behaviors were quantified continuously for 1 hour, and individual scores for each measure were summed over 10 minute periods.

The behavioral rating in this experiment was not done totally blind. The rater was aware of the drug condition of the rat, since the information was recorded on tape at the onset of each test session. However, it is believed that observer expectation did not bias the data, since (1) although aware of the drug condition, the observers were blind as to whether the rats were shams or lesioned Ss (physically, the groups were indistinguishable); and (2) the inter-rater reliability calculated for a rat that was rated by both observers revealed very high correlations for all measures (squares, $r = .98$; crosses, $r = .99$; rears, $r = .99$).

Histology

At the end of testing, a routine histological analysis was performed. The rats were perfused with physiological saline, followed by 10% formalin. The brains were removed, placed in 10% formalin for 48 hours followed by 30% sucrose-formalin for about 24 hours. The brains were then rinsed, blocked, and mounted on a freezing stage with embed-

C H A P T E R I I I

RESULTS

d-Amphetamine Effects

Locomotion. The effects of 2.0 mg/kg d-AMPH or vehicle on locomotion
are seen in Fig. 1. An overall ANOVA revealed a significant drug effect
($F = 6.67$, df = 1/22, $p < .025$), a significant time effect ($F = 22.3$,
df = 5/110, $p < .001$), and a non-significant lesion effect ($F = .04$,
df = 1/22, n.s.). The lesion x time interaction ($F = .84$, df = 5/110,
n.s.) and drug x time interaction ($F = 1.43$, df = 5/110, n.s.) were
not statistically significant, though the lesion x drug interaction
approached statistical reliability ($F = 3.37$, df = 1/22, $.05 < p < .1$).
The drug x lesion x time interaction was not significant ($F = 1.43$,
df = 5/110, n.s.).

Subsequent within-group comparisons revealed that d-AMPH caused a
potentiation of squares in the sham group ($F = 6.69$, df = 1/10, $p < .05$)
but not the n.ACC lesioned group ($F = .43$, df = 1/12, n.s.). Addition-
ally, a comparison of the (d-AMPH minus saline) difference scores for
the sham vs. n.ACC lesioned groups revealed an overall difference that
approached statistical reliability ($F = 3.83$, df = 1/22, $.05 < p < .1$).
A closer look at the time course of the effect revealed that these
scores differed significantly over the last 30 minutes of testing
($F = 4.31$, df = 1/22, $p < .05$), but not over the first 30 minutes ($F = 2.2$, df = 1/22, n.s.). The lack of a difference over the first 30
minutes presumably reflected the initially high vehicle baseline scores

of both groups which resulted from the lack of a habituation period.
Taken together, these results suggest that the locomotor potentiating
effect of d-AMPH was blocked in the n.ACC lesioned group.

The within-group comparison of the sham group also revealed a signif-
icant time effect (F = 7.83, df = 5/50, p < .001) and a significant
squares x time interaction (F = 2.46, df = 5/50, p < .05), suggesting
that d-AMPH treatment resulted in less habituation to the test enviorn-
ment than did the vehicle treatment. In contrast to the shams, there
was a significant time effect in the lesioned group (F = 15.6, df =
5/60, p < .001), but no squares x time interaction (F = .33, df = 5/60,
n.s.), indicating equivalent habituation uder both d-AMPH and vehicle
treatments.

A comparison of the vehicle curves for the sham vs. lesion groups
revealed a baseline that averaged 33% higher in the lesioned group,
though the effect was not statistically reliable (F = 2.46, df = 1/22,
.1 < p < .2). This comparison also revealed a significant time effect
(F = 20.7, df = 5/110, p < .001) and a non-significant drug x time inter-
action (F = .34, df = 5/110, n.s.).

From general observation, it appeared that activity was distributed
homogeneously throughout the rectangular test chamber under all condi-
tiors. An analysis of the number of crosses made from one half of the
chamber to the other half revealed virtually identical results to the
squares measure (not shown here). Furthermore, squares and crosses were
found to be highly correlated (sham-vehicle, r = .94; sham-d-AMPH, r =
.95; lesion-d-AMPH, r = .92). These results suggest that the pattern

of locomotion (e.g. long vs. short locomotor sequences) was not differ-
entially affected by n.ACC lesions.

Rearing. The effects of d-AMPH and vehicle on rearing are seen in Fig.
2. An overall ANOVA revealed a significant drug effect ($F = 10.0$, df =
$1/22$, p $<.005$), a significant time effect ($F = 28.8$, df = $1/22$, p $<.001$),
and a non-significant lesion effect ($F = 1.75$, df = $1/22$, n.s.). The
lesion x time interaction ($F = .61$, df = $5/110$, n.s.), drug x time inter-
action ($F = .04$, df = $5/110$, n.s.) and drug x time x lesion interaction
($F = .21$, df = $5/110$, n.s.) were all statistically insignificant. There
was a reliable drug x time interaction ($F = 2.01$, df = $5/110$, p $<.025$).

Subsequent individual comparisons revealed that d-AMPH increased
rearing in the sham group ($F = 5.01$, df = $1/10$, p $<.05$) and in the
lesioned group ($F = 4.96$, df = $1/12$, p $<.05$). An analysis of the
(d-AMPH minus vehicle) difference scores for the two groups ($F = .11$, d.f.
$= 5/110$, n.s.) supports the conclusion that d-AMPH stimulated rearing
was not blocked by n.ACC lesions.

The within-group comparisons for the sham group revealed a signifi-
cant time effect ($F = 15.7$, df = $5/50$, p $<.001$) and a non-significant
drug x time interaction ($F = .98$, df = $5/50$, n.s.). The lesioned group
showed both a significant time effect ($F = 14.6$, df = $5/60$, p $<.001$) and
a significant drug x time interaction ($F = 2.63$, df = $5/60$, p $<.05$).

Finally, lesioned Ss showed an enhanced baseline of rearing when com-
pared to vehicle-treated shams ($F = 5.39$, df = $1/22$, p $<.05$). This com-
parison also resulted in a significant time effect ($F = 39.6$, df = $5/110$,

p <.001) and a non-significant drug x time interaction (F = .40, df = 5/110, n.s.).

Apomorphine Effects

The effects of 3.0 mg/kg apomorphine in sham and lesioned groups are seen in Fig. 3 (stereotypies, Fig. 4 (locomotion) and Fig. 5 (rearing). Apomorphine elicited stereotyped sniffing and licking in both sham and lesioned Ss. There was no statisitical difference between the two groups in the amount of time spent engaging in stereotypies (F = .05, df = 1/18, n.s.). Additionally, apomorphine significantly depressed locomotion in both sham (F = 24.2, df = 1/9, p <.001) and lesioned (F = 11.9, df = 1/11, p <.001) groups. Similarly, the drug depressed rearing in both the sham (F = 76.9, df = 1/9, p <.001) and lesioned (F = 117.0, df = 1/11, p <.001) groups.

The apomorphine results suggest that the n.ACC lesions did not disrupt the function of the nigro-striatal dopaminergic system, in that there was no difference in the amount of time spent engaging in stereotypies between the two groups. Furthermore, the same pattern of depressed loco-motion and rearing was seen in both groups. However, this control is not totally satisfactory, for two reasons. (1) Because videorecording was done under low-light conditions, it was difficult to differentiate between the exact behaviors being elicited by apomorphine. Thus it is not totally clear whether there were qualitative differences in the stereotypy exhibited by the two groups. (2) More importantly, the recent findings that suggest that stereotypies may occur independently

of the neostriatum question whether the measure employed here success-
fully assessed functional striatal damage.

Histology

Fig. 6 shows the extent of damage induced by a typical n.ACC
lesion. Variable damage to the n.ACC was found, averaging 75% at the
greatest extent of the lesion. Non-n.ACC structures were also variably
affected. Cortical damage from electrode entry was noted, and the ant-
erior commissure was consistently damaged. The medial boundary of the
anterior caudate was often damaged. Damage to the globus pallidus,
lateral preoptic area, piriform cortex, nucleus subthalamicus, and
anterior olfactory area was sometimes seen. Data from two lesioned
Ss were not used since their lesions were found to be unilateral.

C H A P T E R   I V

DISCUSSION

The finding that n.ACC lesions blocked ASLB is consistent with a number of other studies which have found that disruption of the meso-limbic dopaminergic innervation to the n.ACC attenuates or blocks ASLB (Kelly et al., 1975; Iversen and Koob, 1978; Koob et al., 1978). However, this finding directly contradicts the report that electrolytic lesions of the n.ACC failed to antagonize ASLB (Wirtshafter et al., 1978). An important methodological difference that apparently accounts for the discrepancy between our results and the results of the Wirt-shafter et al. study is the way in which locomotor behavior was quantified. Wirtshafter et al. used stabilimeters, which are sensitive to general changes in activity, whereas in this study a specific measure of locomotion was obtained through observer quantification of video-recorded behavior. The absence of a precise knowledge of the rats' behavior in the stabilimeters precludes a clear interpretation of the Wirtshafter et al. study.

The difficulty in interpreting stabilimeter data emphasizes the general importance of obtaining accurate quantifications of behavior and stresses the dangers of inferring changes in specific behaviors (e.g. locomotion) from data gathered using automated devices (Robbins, 1973; Fink and Smith, 1978). Stabilimeters are clearly not suitable for assessing changes in locomotion, nor does the commonly-used photo-cell method appear to be a completely reliable index of this behavior

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(Robbins, 1973; Fink and Smith, 1978). Photocell interruptions may result from partial excursions (e.g. moving into the beam and then turning around) (Fink and Smith, 1978) or from non-locomotor movements, such as head-waving or grooming (e.g. Brook and Iversen, 1975). The present study supports the use of the observational method for accurately quantifying changes in horizontal (locomotor) and vertical (rearing) activity, and suggests that studies utilizing automated measures should ideally be supplemented by this method.

A second explanation for the discrepancy between Wirtshafter et al.'s finding and ours is suggested by Teitelbaum et al. (1979). These authors, noting that the lesions in the Wirtshafter et al. study were primarily of the anterior n.ACC, found that posterior, but not anterior n.ACC lesions successfully blocked ASLB in mice. Our lesions produced variable destruction along the full extent of the n.ACC, though no clear relationship between locomotor blockade and placement of the lesion was evident.

Because our lesions non-specifically destroyed neural tissue in the n.ACC, it is not possible to differentiate between a dopaminergic or noradrenergic involvement in mediating ASLB. However, taken together with the large body of literature cited in the introduction, our findings support the general conclusion that the meso-limbic dopaminergic input to the n.ACC is important for the occurrence of ASLB.

In light of the total blockade of ASLB seen in rats with n.ACC lesions (present study) and in rats with haloperidol injected into the n.ACC (Pijnenburg et al., 1975), it would appear unnecessary to postu-

late the existence of other neural systems in the brain on which d-AMPH acts to stimulate locomotion. However, the findings of several studies suggest that d-AMPH can stimulate locomotion through more caudal pathways not involving the n.ACC. ASLB has been reported to occur in rats devoid of ascending catecholaminergic pathways, e.g. in decerebrate rats (Baez and Petroff, 1977) and in rats with midbrain knife cuts (Sorenson and Kee, 1976). The mechanism through which this activation occurs is unknown, though one suggestion is that it is mediated through a noradrenergic pathway that descends from the locus coeruleus into the spinal cord (Sorenson and Kee, 1976; Sorenson et al., 1978). If it is assumed that d-AMPH induced activation of this system also gives rise to increased locomotion in the normal animal, then the question arises as to why, in rats with the meso-limbic dopaminergic input to the n.ACC functionally blocked (either by n.ACC lesions or by DA receptor blockade), a locomotor stimulation is not seen.

A hypothesis that would account for this inconsistency is that, in the normal rat, d-AMPH simultaneously activates several distinct neural systems which exert antagonistic influences on locomotor behavior, and that the extent of the locomotor behavior is a function of the balance between these excitatory and inhibitory influences. According to this notion, in the intact rat d-AMPH stimulates locomotion through a preponderance of excitatory influences (e.g. meso-limbic dopaminergic and descending noradrenergic systems). In the n.ACC lesioned rat, however, the activation of a remaining inhibitory system by d-AMPH would be sufficient to counteract the excitatory descending pathway, resulting

in no net locomotor stimulation. In the reduced preparation, the inhibi-
tory component would additionally be absent, resulting in locomotor
stimulation through the descending noradrenergic system.

This hypothesis may clarify the recent finding that electrolytic
lesions of the VTA, which produce an 80% depletion of DA in the n.ACC,
fail to block ASLB (Sessions et al., 1980). This finding is in clear
contrast to the blockade of ASLB reported to occur following 6-OHDA
injections into the n.ACC (Koob et al., 1978; Iversen and Koob, 1977),
despite similar levels of DA depletion. If VTA lesions simultaneously
disrupt the A10 projection to the n.ACC and a neural system through
which d-AMPH exerts an inhibitory influence on locomotion, then ASLB
might occur through the unchecked activation of descending noradrener-
gic neurons. In fact, VTA lesions disrupt a number of ascending systems
through which d-AMPH might exert an inhibitory influence on locomotion.
These lesions produce depletions of forebrain serotonin (5-HT) and
cortical DA (Sessions et al., 1980; Le Moal et al., 1977). d-AMPH has
been shown to potentiate serotonergic activity (Azzarro and Rutledge,
1973), and this activation appears to exert an inhibitory effect on
activity (Hollister et al., 1975). Le Moal and his colleagues have
attributed the spontaneous hyperactivity that accompanies VTA lesions
to a disruption of a tonically-inhibitory meso-cortical dopaminergic
pathway (Le Moal et al., 1977; Tassin et al., 1978; Galey et al., 1977).
That a d-AMPH induced increase in the functional activity of these
neurons may produce an inhibition of locomotion is supported by the
finding that DA injected into the frontal cortex produces catalepsy

(Carter and Pycock, 1978).

If abolition of an excitatory dopaminergic projection and an in-hibitory (5-HT and/or meso-cortical dopaminergic) component by VTA lesions allows the expression of locomotor stimulation through the net activation of a remaining excitatory descending noradrenergic sys-tem, then two predictions would follow. First, ASLB shown by VTA-lesioned rats should be blocked by reducing noradrenergic transmis-sion (e.q. using NE receptor blockers). Second, n.ACC lesioned rats should show a restoration of ASLB following a concomitant disruption of ascending 5-HT neurons (e.g. with the 5-HT synthesis inhibitor para-chloro-phenyl-alanine or with raphe lesions) and/or disruption of fronto-cortical dopaminergic terminals (achieved by frontal inject-ions of 6-OHDA).

It is also possible that the reported failure of VTA lesions to block ASLB could be attributed to the development of denervation super-sensitivity in the n.ACC. Consistent with this interpretation is the fact that Sessions et al. (1980) tested their rats 1-2 months following lesioning, whereas studies reporting a blockade of ASLB in rats with 6-OHDA lesions of the n.ACC carried out testing 1-3 weeks after 6-OHDA injection. This hypothesis could be tested by determining if rats injected with 6-OHDA into the n.ACC (using a dose sufficient to exten-sively deplete DA within that nucleus) develop a restored d-AMPH response over time, and to see if, shortly following electrolytic lesioning of the VTA, rats show a blocked locomotor response to d-AMPH.

In addition to finding that n.ACC lesions blocked ASLB, we report

the novel finding that these lesions failed to antagonize the stimula-
tion of rearing behavior elicited by d-AMPH. The ability of low doses
of d-AMPH to potentiate this behavior is well-documented (Fog, 1972;
Segal, 1975; Groves and Rebec, 1976; Schiorring, 1978; Mumford et al.,
1978; Russell and Pihl, 1978), yet there are few studies which have
investigated the mechanism through which this activation occurs. Our
results clearly show that, although the n.ACC appears to exert a tonic
inhibitory effect on rearing (indicated by the significant increase in
spontaneous rearing seen in the lesioned group), this nucleus does
not seem to be critical for the d-AMPH induced stimulation of this
behavior. Haber et al.,(1980) have recently suggested that different
neural mechanisms mediate d-AMPH stimulated locomotion and rearing,
on the basis of their finding that pretreatment with the opiate antag-
onist naloxone selectively blocked the rearing activation. The authors'
suggestion that the circuit mediating d-AMPH stimulated rearing may
involve a central CA - endorphin interaction warrants the further study
of this behavior. .

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APPENDIX
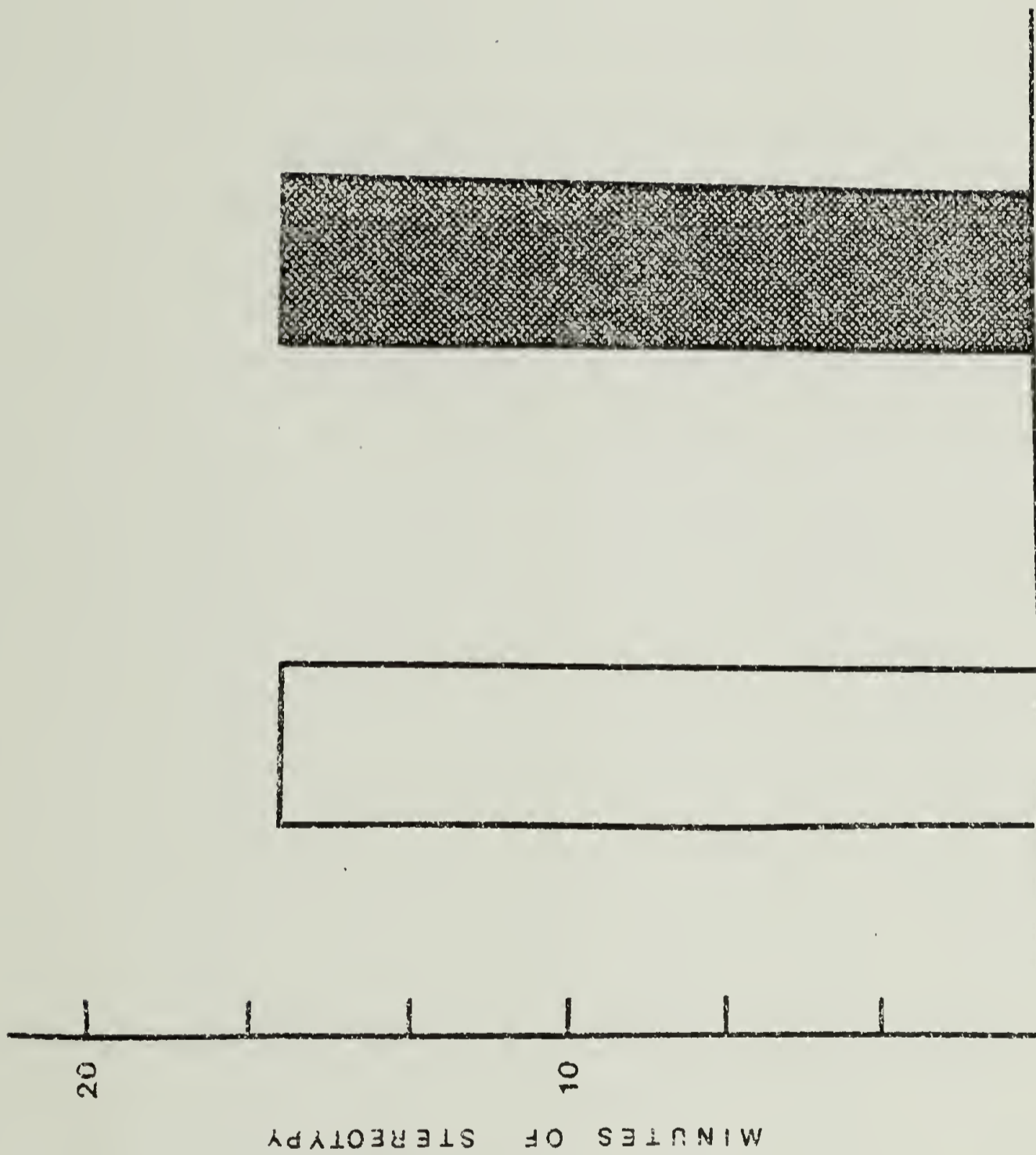
Fig. 1. Mean number of squares entered during 1 hour testing following i.p. injection of 2.0 mg/kg d-AMPH (⊛) or vehicle (★) in sham (━━) or n.ACC lesioned (━ ━) Ss.
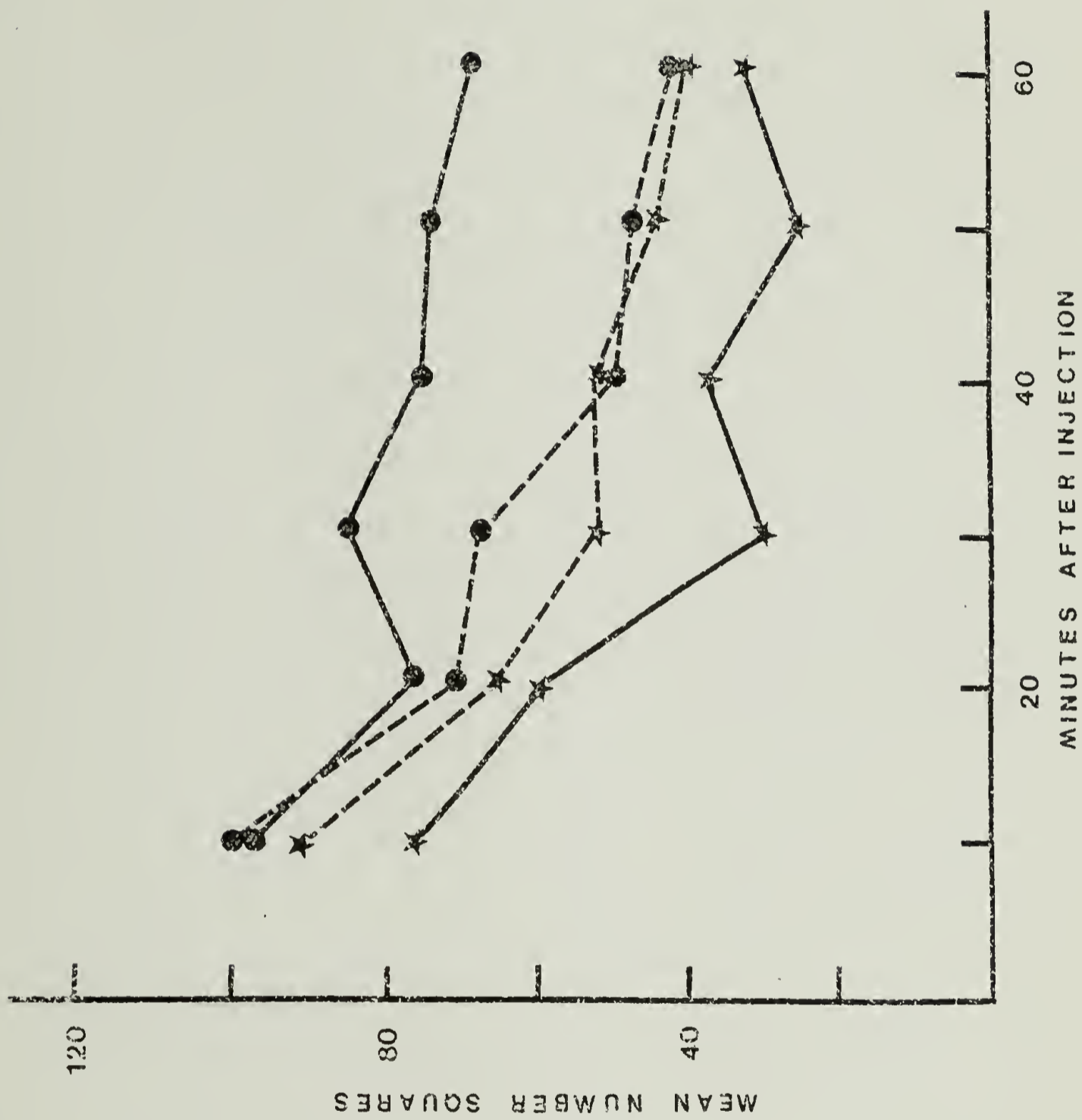
Fig. 1

Fig. 2.   Mean number of rears during 1 hour testing following i.p. injection of 2.0 mg/kg d-AMPH (●) or vehicle (★) in sham (——) or n.ACC lesioned (— —) Ss.
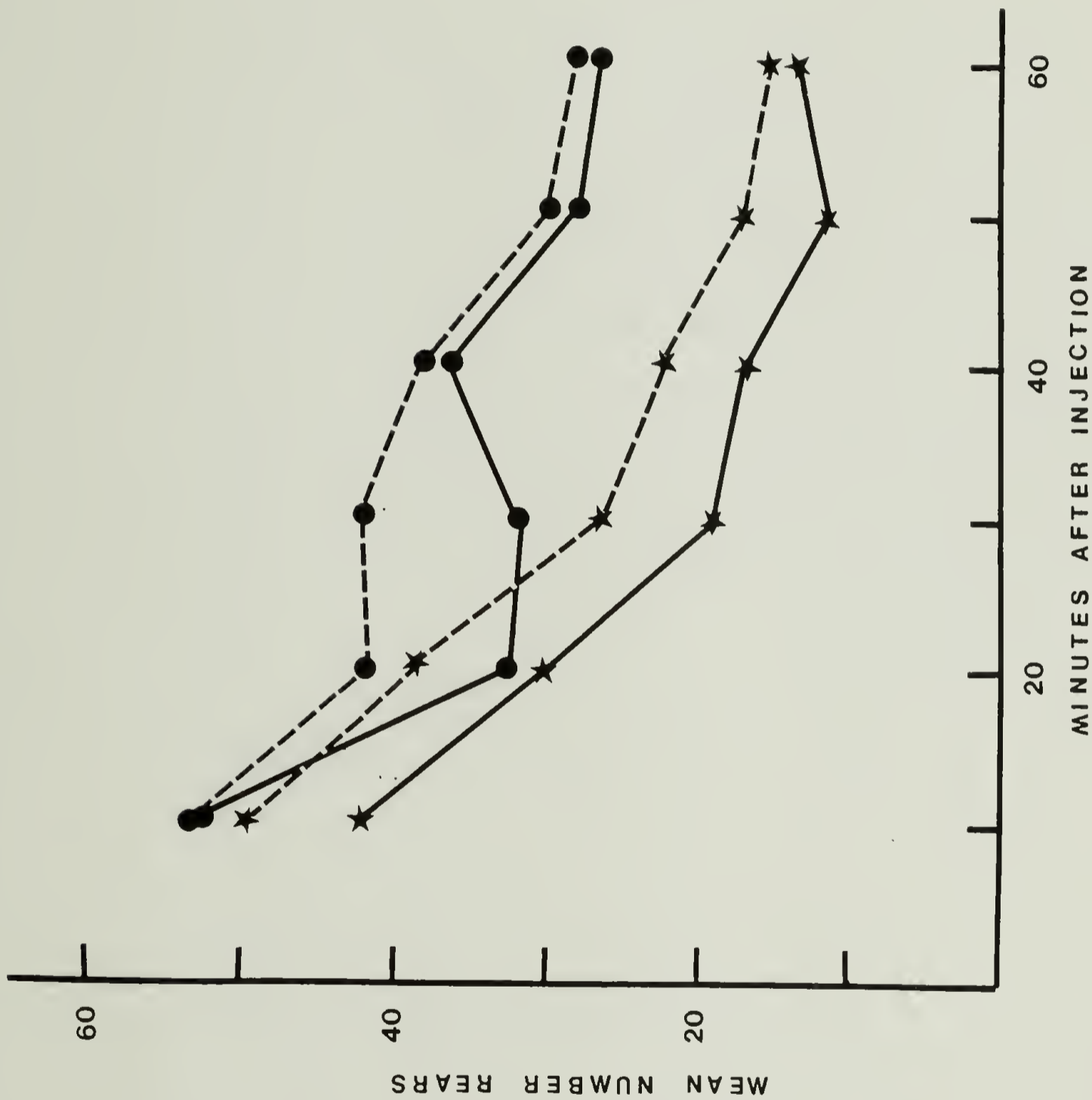
Fig. 2

Fig. 3. Mean amount of time (minutes per hour testing) spent engaging in stereotyped behaviors following treatment with 3.0 mg/kg apomorphine in sham (open bar) and n.ACC lesioned (solid bar) Ss. There was no statistical difference between the two groups.

Fig. 3

Fig. 4. Mean number of squares entered during 1 hour testing following i.p. injection with 3.0 mg/kg apomorphine (stippled bar) or vehicle (open bar) in sham and n.ACC lesioned Ss. (* p <.001, when compared to saline scores).
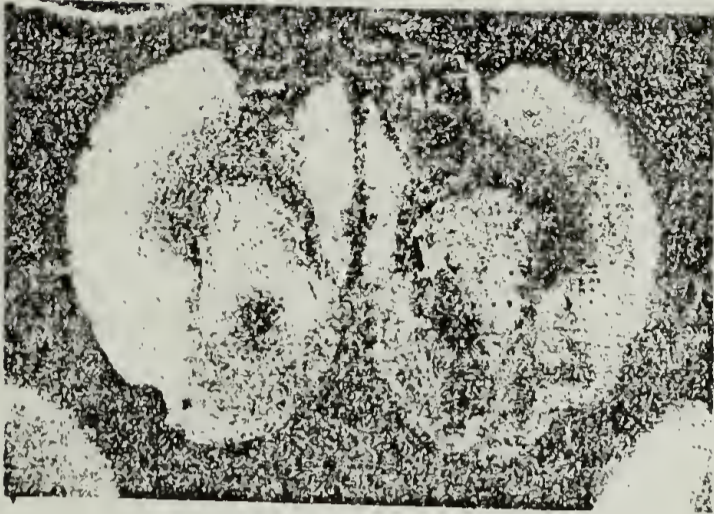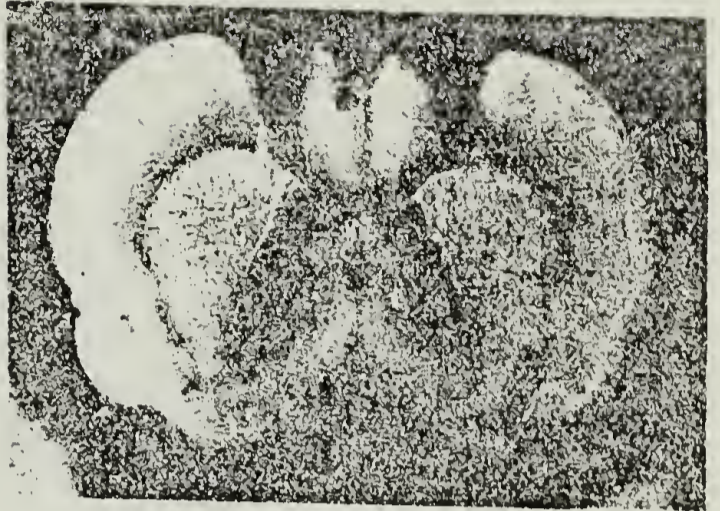
Fig. 4

NUMBER SQUARES
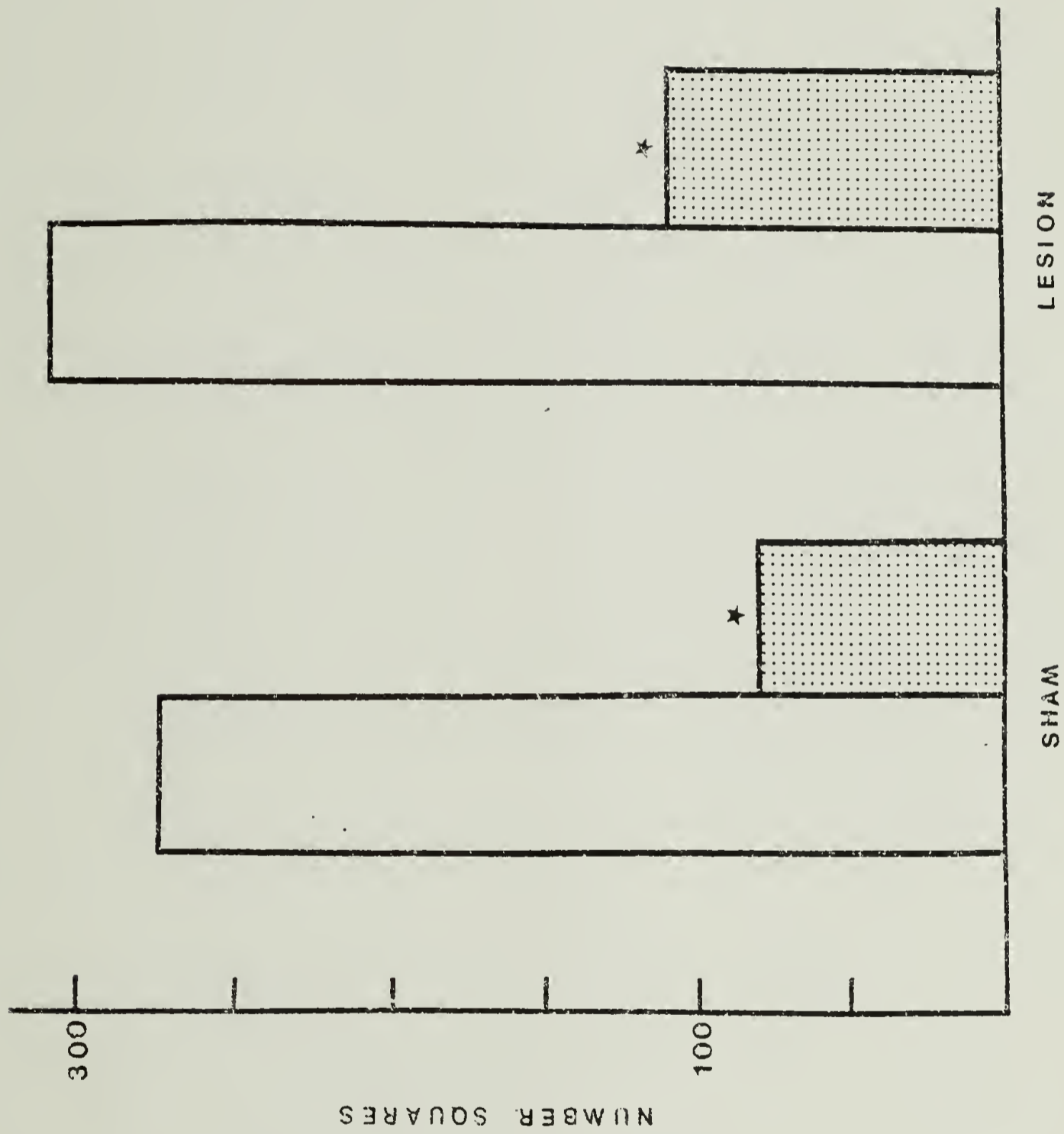
Fig. 5. Mean number of rears during 1 hour testing following i.p. injection with 3.0 mg/kg apomorphine (stippled) or vehicle (open bar) in sham and n.ACC lesioned Ss. (* p < .001, when compared to saline scores).
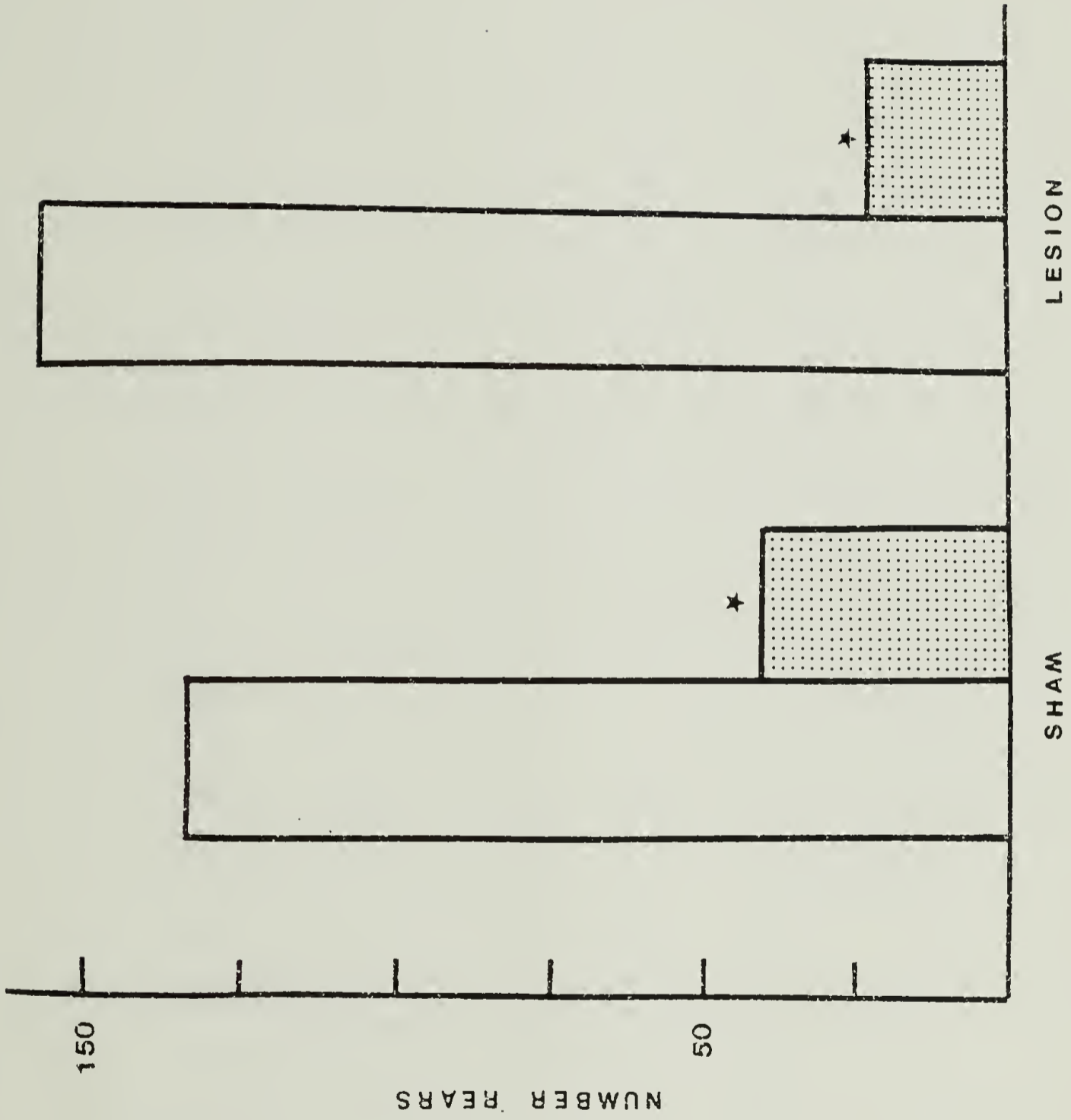
Fig. 5

Fig. 6. Photograph of serial sections of a typical n.ACC lesion. Cortical damage seen is due to the entry of the lesioning electrode.
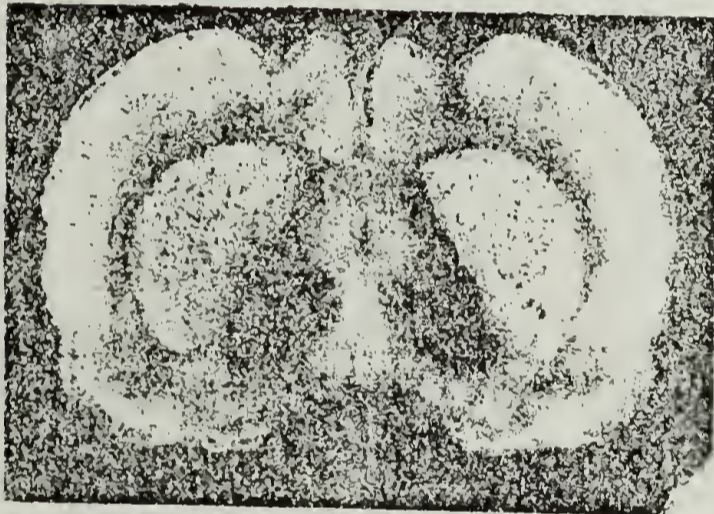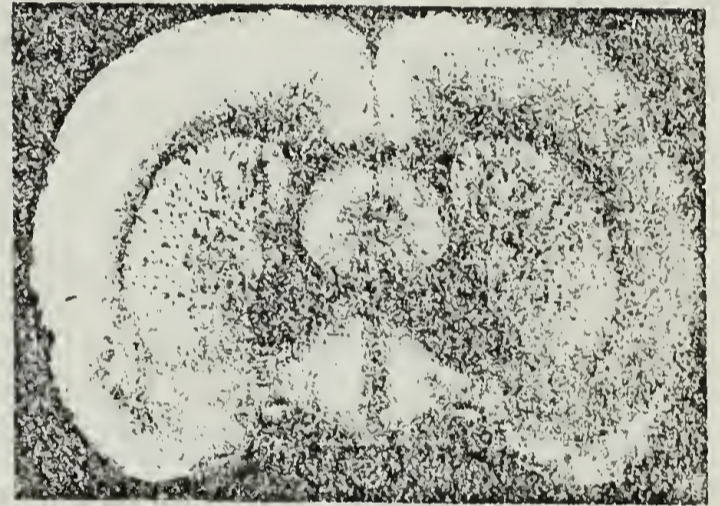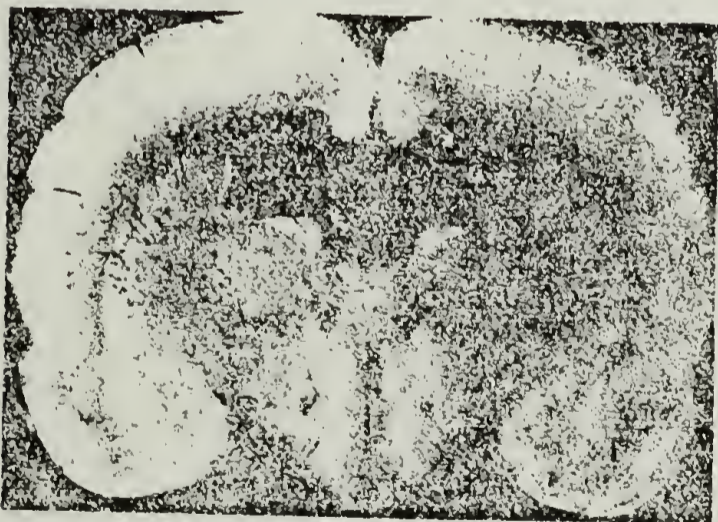
Fig. 6