AN ABSTRACT OF THE THESIS OF
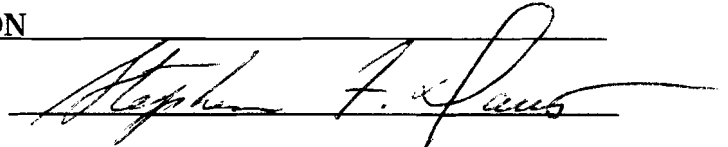
 Kyle Damon Wood   for the Degree of Master of Science

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Title: ODOR-MEDIATED PERFORMANCE IS AFFECTED BY

CADMIUM INGESTION

Abstract approved by: _____

Eighteen male Holtzman rats served as subjects. One group of 9 rats (Group CAD) was maintained on a .15 % saccharin solution having 90 ppm cadmium chloride for 80 days. Another group of 9 rats (Group SAC) served as a comparison group and was maintained during the same period on a .15 % saccharin solution. All animals had access to the fluid on an ad libitum basis. Group CAD and SAC received double alternation, reward(R)-nonreward(N) runway training. When only olfactory cues could be used as discriminative stimuli (Phase 1), just the SAC animals were capable of mastering the RRNNRRNN pattern. When a tactile discriminative stimulus was added (Phase 2), both groups of animals displayed appropriate patterned responding. Removal of the tactile cue (Phase 3) resulted in the immediate disruption of patterned responding in CAD animals. A separate split-plot ANOVA incorporating groups (CAD vs. SAC) as a between-subjects factor and days and type of trial (R_1, N_1, R_2, and N_2) as within-subjects factors was performed on the run and goal-approach speeds for the last 3 days of Phase 1, Phase 2, and Phase 3. The results of these analyses support the view that chronic

cadmium exposure inhibits olfactory ability; Group CAD was clearly inferior to Group SAC in acquisition of the olfactory discrimination.

ODOR-MEDIATED RUNWAY PERFORMANCE
IS AFFECTED BY CADMIUM INGESTION

A Thesis

Presented to

the Division of Psychology and Special Education

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by

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CHAPTER 1

INTRODUCTION

Our environment has been and continues to be poisoned by toxins from various sources such as the heavy metal industry and by-products of industries associated with technological development. Many of these toxins are heavy metals such as lead and cadmium which humans contact and ingest. Therefore, a better understanding of the effects of ingesting such heavy metals on humans is important. Hence, research on such toxic metals as lead and cadmium has increased in recent years.

A substantial body of literature delineating the effects of lead has been established. For example, Davis, Freeman, and Nation (1993) conducted two experiments investigating the effect of chronic lead exposure on taste-aversion learning. Results of both experiments indicated that significantly stronger aversions are developed by the lead-exposed animals. These findings are attributed to the increased reactivity of the lead-exposed animals which allowed additional associations to be formed between the taste conditioned stimuli and heightened reactivity and between the taste-reactivity state stimuli and illness.

Additional research on the effects of lead toxicity also reported heightened reactivity to primary and conditioned aversive stimuli following chronic exposure to the toxicant (Davis, Nation, & Mayleben,

1993; Flynn, J., Flynn, E., & Patton, 1979; Nation, Baker, Taylor, & Clark, 1986; Nation, Clark, Bourgeois, & Rogers, 1982). Thus, one effect of lead exposure appears to be an increase in emotionality or stress reactivity.

Further evidence of the stress-enhancing effects of lead contamination was found when rats exposed to lead consumed greater amounts of ethanol in a free-access situation (Nation, Baker, Fantasia, Ruscher, & Clark, 1987; Nation, Baker, Taylor, & Clark, 1986). Nation and his colleagues suggested that the elevated stress levels attributed to lead ingestion stimulated increased consumption of ethanol, which in turn reduced stress in the animal. Of direct relevance to the present project is research on the effects of cadmium.

Cadmium Effects

Unfortunately, research on cadmium and its effects has lagged behind that of lead. However, several effects have been established. Cadmium (Cd) exposure may influence sensory abilities. For example, Adams and Crabtree (1961) suggested exposure to Cd may impair olfactory ability based on clinical reports of workers exposed to Cd dust developing anosmia. Indirect support for this view was reported by Smith, Pihl, and Garber (1982), who reported that Cd-exposed rats learned a spatial T-maze discrimination more rapidly than did normal rats. They reasoned that impaired olfactory ability of the Cd animals

decreased competing investigatory behaviors typically engendered by olfactory stimuli, thus, discrimination performance improved. However, Hastings (1990) reported that even though rats chronically exposed to aerosol Cd for 20 weeks had a build up of Cd in the olfactory epithelia and olfactory bulbs, they did not display anosmia. Clearly, additional research on the relationship between Cd exposure and the olfactory sense is needed.

Cadmium exposure may also influence learning and memory. For example, Holloway and Thor (1988) found when rats were injected with two milligrams (mg) of Cd, their social memory was affected. As adults, the Cd rats failed to learn the identity of a strange rat in a social recognition test; they investigated familiar and strange rats for equal amounts of time. Untreated control groups investigated unfamiliar rats for considerably more time than they did familiar rats. These results suggest that Cd exposure in infancy affects social memory processes long after the treatment period.

Low levels of Cd have been found to affect cognitive functioning in children. Thatcher, Lester, McAlaster, and Horst (1982) found that the amount of Cd and lead detected in children's hair was negatively correlated with intelligence and school achievement scores. Possibly subclinical concentration levels of toxins such as Cd and lead may lead to impairments in children's cognitive development.

Cadmium exposure may have facilitated T-maze performance by reducing olfactory based competing stimuli (Smith et al., 1982). Similarly, Pelletier and Satinder (1991) reported that rats exposed to Cd mastered one-way avoidance tasks significantly better than did control rats. An increase in reactivity to pain likely facilitated this behavior (Gabbiani, Gregory, & Baic, 1968).

Past research also indicated that infant rats exposed to medium levels of Cd tended to be hyperactive, have more aggressive play, and have significant changes in locomotor activity (Holloway & Thor, 1988; Lehotzky, Ungvary, Polinak, & Kiss, 1990; Smith, Pihl, & Farrell, 1985). The toxic effects of Cd in heavy doses is well documented, whereas the effects of low level doses of Cd are not as well substantiated.

Because the results of Cd research are somewhat limited and at times contradictory, the need for continued research is apparent. Data from animal learning laboratories showing that rats exude conspecific odors that may be used as discriminative stimuli in learning tasks offers a unique opportunity to combine the two lines of research.

Odor Effects

Psychologists conducting laboratory experiments using animal subjects have traditionally assumed that the performance of one subject on a given trial is functionally isolated from the subsequent performance of conspecifics. According to this perspective, any improvement in

performance from one trial to the next must be attributed to the use of memory or some such construct. However, in 1966 this conception was directly challenged.

In an experiment on differential reward conditioning, McHose and Ludvigson (1966) reported that nondifferentially reinforced (control) rats, tested in a straight runway, ran faster when they were preceded by discrimination animals receiving reward than when preceded by discrimination animals receiving nonreward. This differential responding on the part of the control animals was attributed to odors exuded by the discrimination animals which, presumably, served as discriminative cues for the control animals. Since this initial observation, research designed to investigate odor-based discrimination has expanded rapidly.

From the research dealing with odor-based responding, two general attributes have become evident. First, odor cues serve to signal upcoming goal events. For example, Ludvigson and Sytsma (1967) demonstrated that rats were capable of learning to respond appropriately (fast to reward, slow to nonreward) on a double-alternation (DA) pattern of reward (R) and nonreward (N) (i.e., RRNNRRNN) when they were trained under homogeneous trial-administration conditions, an odor-maximizing technique. Rats also were not capable of learning the DA pattern under odor-minimizing conditions. Other studies have confirmed the discriminative property of such intra-specific odors (e.g.,

Davis, 1970; Morrison & Ludvigson, 1970; Prytula, Cox, & Bridges, 1973). Further testing of rats in a fixed order (an odor-maximizing technique) has shown that odor-based responding occurs when the animals receive the same reward condition on a given trial (Davis, 1973; Ludvigson, 1969; Taylor & Ludvigson, 1983).

The second general attribute that has emerged as a result of this accumulated research involves the elicitation of unconditioned approach and avoidance responses by R and N odors. Mellgren, Fouts, and Martin (1973) demonstrated that naive rats approached a location where another rat had been rewarded faster than they sought to escape from that location. Likewise, they showed that rats escaped more rapidly from a location where another rat had not been rewarded than they approached that location. Collerain and Ludvigson (1972) also reported studies suggesting that R and N odors may elicit unconditioned approach and avoidance responses. Employing a forced-choice, T-maze test, they found rats avoided the arm of the maze in which nonreward odor was present.

As research involving R and N odors expanded, several studies were conducted in order to ascertain an anatomical source for these odors (e.g., McNeese, 1975). Attempts were made to implicate the preputial gland, androgen-sensitive glands (testes), urine, and feces. McNeese (1975) found no evidence that these glands or emissions were

responsible for the odors in question. The harderian gland has also been considered as the source for R and N odors. Harderian gland secretions are thought to be responsible for thermoregulation of body temperature and allowing female rats to assess the reproductive competence of male rats. A study by Nash, Anderson, Reed, Parrish, and Davis (1986) found that rats with the harderian gland removed still established appropriate odor-based responding. This finding indicates that the harderian gland is not the anatomical source of R and N odor.

Other studies have been concerned with delineating the physiological and/or theoretical nature of these odors. For example, Voorhees (1980) found that differential responding of cells in the medial olfactory-bulb occurred when reward and nonreward odors from donor animals were presented to the test animals.

Studies by Collerain (1978) and Collerain and Ludvigson (1972, 1977) attempted to demonstrate that the production of the odor of nonreward is linked to the occurrence of frustration. According to Amsel's (1958, 1962) frustration theory, receipt of nonreward in a previously rewarded situation results in an emotional reaction (frustration) with the magnitude of that reaction depending upon the strength of the expectation of reward. The T-maze study conducted by Collerain and Ludvigson (1972) is instructive. In this study, rats avoided the arm of a T-maze in which other rats had previously experienced

frustrative nonreward. They also reported that as few as two or four reinforced trials were sufficient to elicit nonreward odor by the donor subjects.

The effect of reward magnitude on odor production also has been studied. If rats exude different odors for R and N trials, then they should exude different odors for large and small rewards, respectively. Past data indicated that rats encountering small reward at the onset of a goalbox-confinement period in a straight runway did not display appropriate odor-based patterning. However, appropriate odor-based patterning has been shown by rats receiving the small reward at the end of the confinement period and rats that had the time of reward delivery shifted from the beginning to the end of the confinement duration (Burns, Thomas, & Davis, 1981; Davis & Weaver, 1981; Davis, Whiteside, Bramlett, & Petersen, 1981). These results were surprising in light of the results of previous studies (Bower, 1961; Ludvigson & Gay, 1967) reporting evidence of distinctive odor emissions under the frustration-evoking procedure of large- versus small-reward contrast. Davis et al. (1981) suggested although large- versus small-reward contrast fails to produce appropriate odor-based DA patterning, entrance into an empty goal box prior to a delivery of a small reward does result in such responding. Rather than accompanying frustration, operative odors may be signaling the absence of reward. Voorhees and Remley (1981)

suggested a simple food versus no food hypothesis as an alternative to the frustration odor interpretation. They proposed that rats may emit an ethologically significant odor when they encounter food to signal the location of the food. Conversely, if the rat does not encounter food, it will exude a qualitatively or quantitatively different odor signaling the absence of food.

Just as numerous studies have investigated rats' abilities to produce and utilize R and N odors, the ability to disrupt and/or control such odors has been investigated. For example, Seago, Ludvigson, and Remley (1970) showed that rats rendered surgically anosmic by removing the olfactory bulbs were incapable of learning the DA pattern of behavior. Similarly, Phillips and Bloom (1971) and Bloom and Phillips (1973) demonstrated that exhausting the runway air, thereby eliminating odor cues, resulted in a disruption of DA performance. Even the simple procedure of running the animals in an apparatus having a hardware cloth top that allowed the natural dissipation of odors was sufficient to eliminate DA patterning (Pitt, Davis, & Brown, 1973).

Rationale for the Present Research

Although learning/performance may be facilitated in Cd-exposed animals by reducing competing responses and/or heightening reactivity to aversive stimuli, is the acquisition of responses that are dependent on olfactory cues disrupted by Cd exposure? The present research seeks to

add to the body of knowledge by using the odor-based DA task to evaluate the olfactory effects of exposure to Cd.

Two groups of animals, one Cd-exposed and one control, were given odor-based DA runway training (Phase 1). If Cd exposure interfered with olfaction, then the ability to master this task would be attenuated, possibly eliminated, in the Cd-exposed animals. The addition of a nonolfactory discriminative stimulus to the runway during Phase 2 would provide cues that could be used by the Cd animals to establish appropriate responding. The removal of the nonolfactory discriminative stimulus during Phase 3 would result in the elimination of patterned responding by the Cd animals because of a return to cue salience of the olfactory stimuli.

CHAPTER 2

METHOD

Participants

Eighteen albino male laboratory rats purchased from the Holtzman

Company (Madison, WI) participated in this study. All animals were 40

days old upon arrival and were housed in individual, suspended wire-

mesh cages.

Apparatus

A single straight runway (11.4 cm wide X 12.7 cm high) served as

the experimental apparatus. A gray startbox (28.1 cm) and a black

goalbox (30.5 cm) were separated from a black runway section (91.4 cm)

by guillotine doors. Run and goal-approach latencies produced by a

series of photoelectric cells (located 15.2, 92.4, and 116.8 cm,

respectively, beyond the start door) were recorded on each trial by digital

electric timers (Lafayette model 54030). A plastic receptacle mounted

into the end wall of the goalbox served as the goal cup. To ensure that

conspecific odors were confined to the apparatus, a thin sheet of

transparent plastic covered the entire top of the apparatus (see Davis,

Thomas, & Prytula, 1981).

Procedure

Upon arrival from the supplier, the animals were randomly

assigned to the Cd-exposed (Group CAD) or saccharin exposed (Group

SAC) group. Following four rest days, Cd exposure was begun for Group CAD by mixing .25 grams of Cd chloride (see Cory-Slechta & Weiss, 1981) per liter of saccharin solution (.15% w/v). In view of previous research demonstrating that rats find the taste of Cd in solution aversive (Cory-Slechta & Weiss, 1981), the Cd was presented in a saccharin solution to make it more palatable. This procedure yielded a solution having a concentration of 90 parts per million Cd. Fifty ml of this solution were administered to each subject in the CAD group via graduated, polypropylene centrifuge tubes on a daily basis for the duration of the experiment. Subjects in group SAC received similar access to a .15 % saccharin solution. All animals were weighed every three days for the duration of the experiment.

Fifty-three days following the inception of Cd exposure, a food deprivation regimen was implemented and pretraining was begun. Food deprivation consisted of restricting food intake such that each animal was maintained at 85% of its free-feeding body weight. Maintenance feeding took place at the conclusion of the daily sessions.

Pretraining was begun 24 hours following the inception of food deprivation. On each of the six pretraining days, all animals were handled and tamed for one minute each. Following the handling period, each animal received a 2 minute exploration period in the baited (12, 45 mg. Noyes pellets) runway. All animals received additional habituation to

the reward pellets in the home cage following the exploration period.

Throughout the entire experiment, runway training was administered to all animals under a daily DA RRNNRRNN schedule. Reward always consisted of 12, 45 mg Noyes pellets, whereas N trials resulted in confinement to the empty goalbox for 30 seconds.

At the beginning of pretraining, the rats within each group were randomly assigned a permanent number (1 through 9 for CAD and 10 through 18 for SAC). This sequence was used as the fixed, daily within-group order for running the animals. On each day of runway training Trial 1 was administered to all rats within a group before Trial 2 was administered, and so forth. All daily trials were administered to a particular group before the second group was tested. The order for running groups alternated daily. The entire apparatus was swabbed with a water-dampened sponge and dried with an electric hair dryer after the completion of each trial for each group. Pitt et al. (1973) demonstrated that such procedures are sufficient to remove conspecific R and N odors from the straight runway. Thus, the first animal in each group was always tested in a clean, odor-free apparatus. Visual cues were constant between all groups in the apparatus. Run and goal-approach latencies, stops (cessation of forward movement), and retraces (movement back toward the startbox) were recorded on all trials.

Phase 1 lasted 12 days (96 trials). During Phase 2 (6 days, 48

trials) a wire-mesh (hardware cloth) insert was in place in the run section and goalbox of the runway on R trials for all subjects. Thus, floor texture could be utilized as a discriminative cue during Phase 2. Removal of the wire-mesh insert during Phase 3 (3 days, 24 trials) returned conditions to those experienced during Phase 1.

CHAPTER 3

RESULTS

For each animal, run and goal latencies were recorded for each

trial. To yield speed scores in meters/second I calculated the reciprocals

of the eight daily latencies for each rat and multiplied by the appropriate

metric constant. The latency reciprocals were converted to speed scores,

a more commonly reported measure in this area of research. The

reciprocal transformation also normalizes the distribution and precludes

problems of heterogeneity of variance that may threaten the assumptions

of the analysis of variance (ANOVA) technique. The use of the

appropriate metric constant allows all speeds to be expressed in

meters/second. Prior to graphing, the speed scores for the daily,

eight-trial DA sequence were combined as follows: the first two trials

were averaged to yield an R_1 composite score, the third and fourth trials

were averaged to yield an N_1 composite score, and so forth. Hence, daily

DA performance was reduced to four speeds for each subject: R_1, N_1, R_2,

and N_2. These four speeds were used for graphing and analysis

purposes.

Mean run and goal-approach speeds of Groups SAC and CAD for

the final three days of Phase 1 (the point at which maximal patterning

had been established by Group SAC), Phase 2, and Phase 3 are shown in

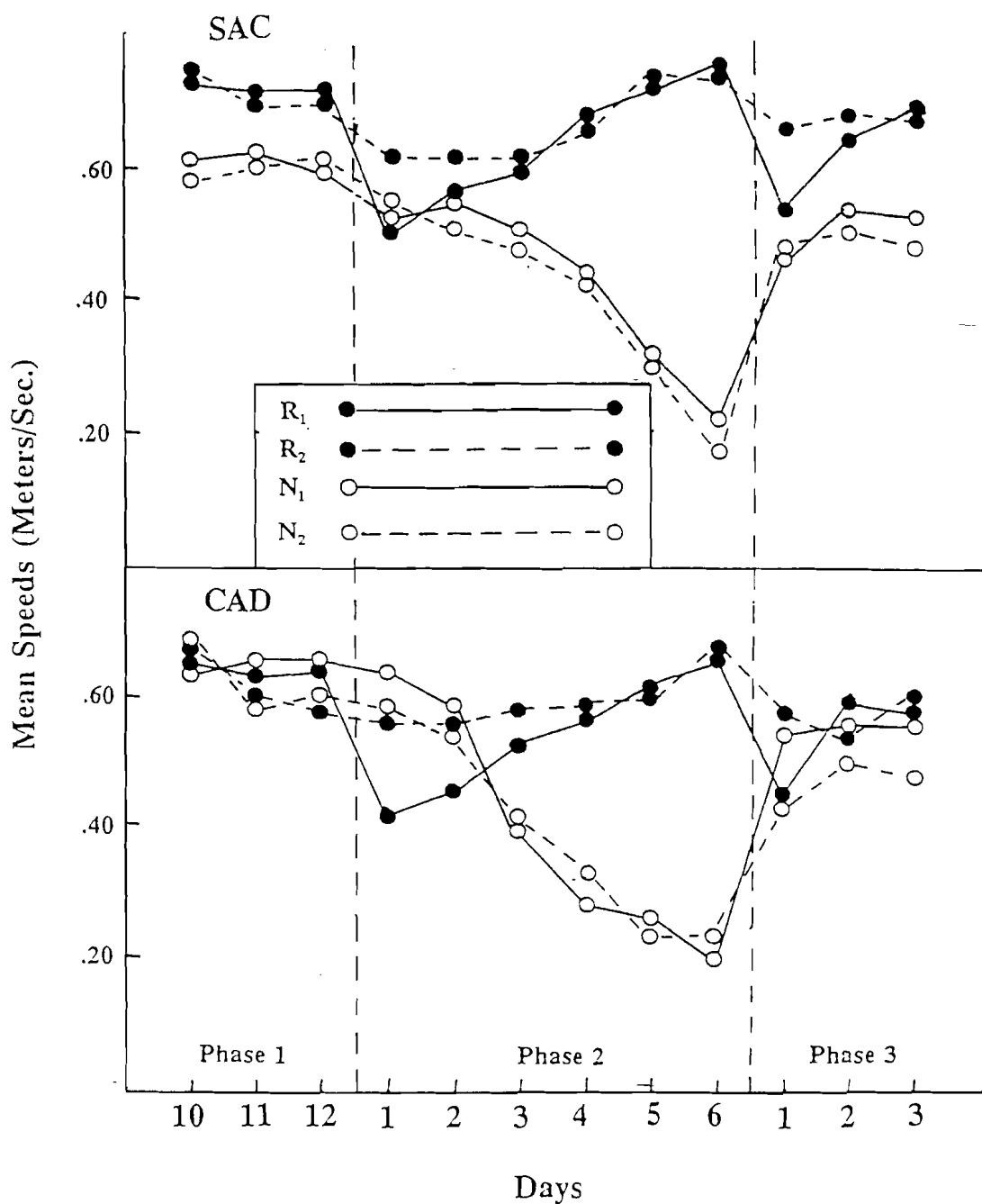Figures 1 and 2, respectively. As the first animal in each group was

Figure 1. Mean reward (R) and nonreward (N) run speeds (meters/seconds) for cadmium-exposed (Group CAD) and non-cadmium exposed (Group SAC) animals during Phases 1-3.
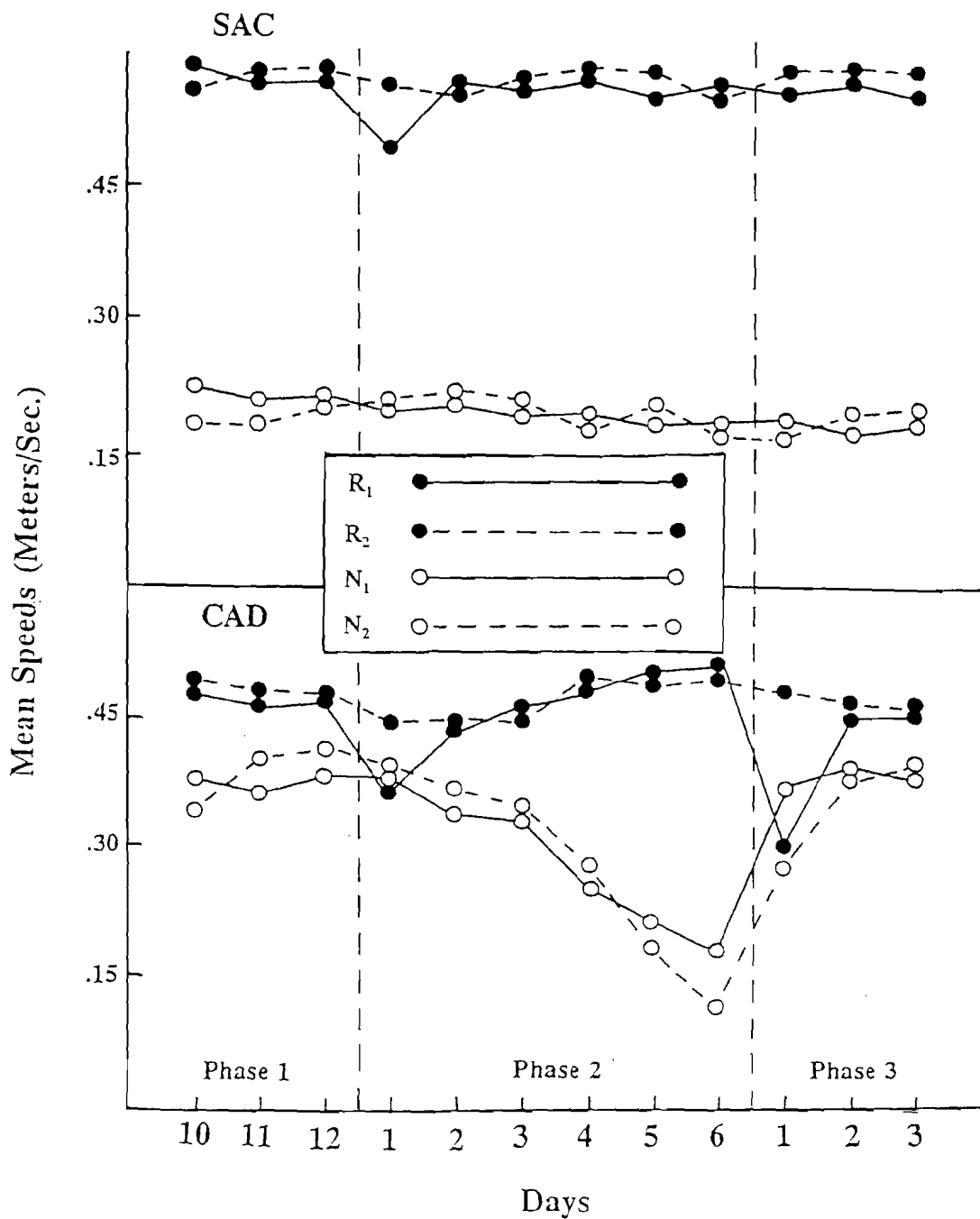
Figure 2. Mean reward (R) and nonreward (N) goal-approach speeds (meters/seconds) for cadmium-exposed (Group CAD) and non-cadmium exposed (Group SAC) animals during Phases 1-3.

always tested in a clean, odor-free apparatus, their data were not used

for graphing and analysis purposes. Visual inspection of the speeds of

these rats indicated that they displayed nondifferential R versus N

responding in both measures during all phases of the experiment.

A separate split-plot ANOVA incorporating groups (CAD vs. SAC) as

a between-subjects factor and days and type of trial (R_1, N_1, R_2, and N_2)

as within-subjects factors was performed on the run and goal-approach

speeds for the last three days of Phase 1, Phase 2, and Phase 3. In all

cases an alpha level of 0.05 was employed to determine statistical

significance.

Phase 1

Run speeds. Upon initial observation Group SAC appeared to

develop rational patterning in the run speed portion of Phase 1. Analysis

of the run-speed data failed to yield any statistically reliable effects.

Goal-approach speeds. Analysis of the Phase 1 goal-approach

speeds yielded significance for the groups, $F(1, 14) = 6.51$, $p < .05$, type of

trial, $F(3, 42) = 3.17$, $p < .05$, and groups by type of trial, $F(3, 42) = 5.17$,

$p < .01$, effects. Subsequent Newman-Keuls tests indicated that

although the R_1 and R_2 speeds of Group SAC did not differ from each

other, they were significantly ($p < .01$) faster than the N_1 and N_2 speeds of

this group. Despite the graphical suggestion (see Figure 2) that Group

CAD had developed appropriate patterning, their R and N speeds did not

significantly (p < .05) faster than the N_1 and N_2 speeds of this group on Days 2 and 3. Other differences were not statistically reliable.

Goal-approach speeds. Analysis of the goal-approach speeds yielded significance for the type of trial, $F_{(3, 42)}$ = 5.06, p < .01, and groups by type of trial, $F_{(3, 42)}$ = 5.57, p < .01, effects. Subsequent Newman-Keuls tests indicated that the R_1 and R_2 speeds of Group SAC were significantly (p < .01) faster than their N_1 and N_2 speeds on all days of Phase 3. No additional significant differences were obtained.

Weight and Cadmium Analysis

Analysis of the weight data was conducted at the inception of food-deprivation, as well as the beginning of Phases 1, 2, and 3, and the end of Phase 3. The results of these analyses failed to yield significant between-groups effects (all Fs < 2.00). Thus, Cd ingestion did not produce a weight differential between the two groups.

Tissue analysis for Cd was conducted 24 hours following the completion of Phase 3. The atomic absorption spectrophotometry procedures described by Nation, Clark, Bourgeois, and Baker (1983) were employed to determine Cd residues in the olfactory bulbs, kidneys, and liver. The results of t tests on olfactory bulbs, $t(16)$ = 3.12, p < .01, kidney, $t(16)$ = 4.33, p < .001, and liver, $t(16)$ = 3.12, p < .01, indicated that the concentration of Cd was significantly greater for Group CAD than Group SAC in all instances. Thus, the present Cd-ingestion

technique successfully created groups that differed in the amount of Cd present in the olfactory bulb and other tissues.

CHAPTER 4

DISCUSSION

Group SAC's ability to develop patterned responding in a DA straight runway task supports previous studies (Davis, 1970; Ludvigson & Sytsma 1967; McHose & Ludvigson, 1966; Morrison & Ludvigson, 1970; Prytula et al., 1973) which demonstrate the conspecific olfactory control of straight runway performance. Also in agreement with these studies, Group SAC developed the strongest patterning in the goal measure. The goal measure is the point at which subjects would be expected to exude odors signaling the receipt or omission of reward most strongly (e.g., Davis, Prytula, & Voorhees, 1979). The odor hypothesis also receives support from the finding that the initial subjects in each group failed to display rational patterning during any phase of the experiment. Because the apparatus was wiped clean before the beginning of each new trial for a group, no odors for the first subject should have been available to utilize as a discriminative cue.

One major purpose of this study was to investigate the effects of Cd on odor-based DA runway responding. A comparison of the Phase 1 performance of Groups SAC and CAD indicates that Cd exposure resulted in a significant decrease of patterned responding in the goal measure by Group CAD. The CAD animals, unlike the SAC animals, also failed to display any indication of patterning in the run measure. The

fact that Group CAD was unable to learn an olfactory-based discrimination supports the contention that Cd exposure can affect olfactory ability.

In Phase 2, the addition of the wire-mesh runway floor resulted in the acquisition of patterned responding by Group CAD in both the run and goal measures. Group SAC developed appropriate patterning in the run measure, while maintaining such responding in the goal measure. Thus, Cd exposure did not interfere with the animals' ability to master the DA pattern when olfaction was not a salient cue.

The removal of the wire-mesh runway floor during Phase 3 of the experiment resulted in immediate disruption of the appropriate responding in the run measure by both Groups CAD and SAC, and the elimination of goal-measure patterning in Group CAD. These results also support the contention that the wire-mesh floor served as an effective discriminative stimulus. Group SAC seemed to regain some degree of appropriate run-measure responding on the final 2 days of Phase 3; Group CAD did not.

Goal-measure performance of Group SAC was unaffected by removal of the wire-mesh floor (i.e., Phase 3). Thus, subject generated odors probably did not continue to be the prominent discriminative stimuli used by these subjects as they approached the goal during all phases of the experiment.

In addition to the behavioral differences between Group CAD and SAC, the histological analyses provided additional support for the damaging effects of Cd on olfactory ability. Significantly greater amounts of Cd were concentrated in the olfactory bulbs of Group CAD than in the olfactory bulbs of Group SAC.

Contrary to the present results, Hastings (1990) reported that rats did not display anosmia even though they had been chronically exposed to aerosol Cd for 20 weeks and had a build up of Cd in the olfactory bulbs and epithelia. A possible explanation for this discrepant data is the route of administration of the Cd. Hastings (1990) utilized an aerosol form of Cd while Cd was ingested orally in this experiment. These two different routes of administration may have resulted in differing amounts of damage to the olfactory bulbs. On the other hand, the Cd-exposure procedure used in the present experiment may not have entirely eliminated olfactory ability in Group CAD. The CAD animals appeared to display some, albeit nonsignificant, odor based patterning in the goal measure during Phase 1 and 3.

In conclusion, the present study not only poses some possible questions for further research in this area but also adds to the existing research dealing with effects of Cd on olfactory abilities in animals. Olfactory ability is affected by Cd ingestion and hence will affect odor based DA runway performance. However, additional research is needed

to determine if Cd exposure can completely eliminate olfactory ability.

Additional research is also needed to determine if Cd exposure is effective in eliminating non-subject-generated olfactory cues. For example, one wonders if a natural odor, such as the odor of peppermint, could be utilized as a discriminative cue by Cd-treated animals. If Cd-treated animals were unable to use such natural odors as discriminative cues, the generality of the present results would be extended.

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Lay Corper
Signature of Graduate Office Staff Member

September 12, 1991
Date Received