DEVELOPMENT OF STEREOTYPY IN DEER MICE (*PEROMYSCUS MANICULATUS BAIRDI*): EFFECTS OF ENVIRONMENTAL ENRICHMENT AND ROLE OF STRIATAL DOPAMINE

By

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Stereotypies are patterns of motor behavior which are repetitive, excessive, topographically invariant and which lack any obvious function or purpose. One particular condition associated with stereotypic behavior has been environmental restriction as evidenced by the development of stereotyped behaviors in zoo and farm animals. We have observed deer mice (*Peromyscus maniculatus bairdi*) to exhibit high rates of stereotyped behavior when housed under standard laboratory conditions. To assess the development of stereotyped behaviors and to test the hypothesis that these behaviors are associated with environmental restriction, deer mice were housed in either standard laboratory cages or larger enriched cages and behavior was tracked over a 17-week period. The number of animals exhibiting stereotyped behaviors was higher in standard cages than in enriched cages, although this difference did not reach statistical significance. Standard-caged deer mice, however, engaged in stereotyped behaviors at a higher rate when compared to

animals in enriched caging. Deer mice raised in enriched cages developed stereotypy at a significantly slower rate than did deer mice housed in standard cages. There was a significant effect of litter, but no effect of gender, on the rate of development of stereotypy. Deer mice raised in standard cages developed higher rates of repetitive jumping, and mice raised in enriched cages developed higher rates of patterned running.

No differences were found in the density of either striatal D_1 or D_2 dopamine receptors as a function of rearing condition or as a function of whether the animals developed stereotypy. In addition, no differences were observed in the concentration of dopamine or its metabolites in deer mice which developed stereotypy when compared to those deer mice which did not develop stereotypy, nor was there a difference across the two housing conditions. These results provide one of the first descriptions of the development of stereotypies and demonstrate the importance of environmental conditions in the genesis of stereotypy.

CHAPTER 1
BACKGROUND AND SIGNIFICANCE

Introduction

Stereotypies are sequences of motor behavior that are repetitive, topographically invariant, often rhythmical and apparently purposeless (Berkson, 1967; Dantzer, 1986; Lewis & Baumeister, 1982). Stereotypy has been considered an important feature of psychopathology and is also associated with a variety of neurological and developmental disorders. Stereotyped behaviors were described in schizophrenic patients dating back to the writings of Kraeplin and Bleuler in the early 1900s prior to the introduction of antipsychotic medication (Rogers, 1992; Jones, 1965). Neurological disorders, such as basal ganglia lesions, Tourette syndrome, and Rett syndrome, have also been associated with stereotypy (Shulman, Sanchez-Ramos, & Weiner, 1996). Stereotypies are frequently observed in individuals with mental retardation and other developmental disabilities and are a defining feature of autistic disorder (Berkson, 1983; Lewis, Gluck, Bodfish, Beauchamp, & Mailman, 1996; Baumeister & Forehand, 1973; Bodfish, Crawford, Powell, Parker, Golden, & Lewis, 1995). The repetitive behaviors observed in developmentally disabled populations, which include body rocking, head rolling, and often self-injurious behaviors, interfere with the acquisition of adaptive skills and are often refractory to treatment. Despite the high occurrence of repetitive behaviors in

developmentally disabled populations, little is known about the pathophysiology and treatment of these behavior disorders.

Stereotypic behaviors can also be observed across a wide variety of environmental contexts in a large number of animal species (Mason, 1991). Stereotypies associated with environmental conditions linked to situations of frustration and conflict are referred to as displacement activities by ethologists (e.g., Duncan & Wood-Gush, 1972) and adjunctive or schedule-induced behaviors by investigators studying operant behavior (Falk, 1971). Stereotypies in both humans and animals have been documented to result from abnormal rearing conditions including early social or maternal deprivation (e.g., Berkson, 1967; Harlow, Dodsworth, & Harlow, 1965). Stereotypic behaviors reliably occur in rhesus monkeys exposed to total social isolation for the first nine months of life (Harlow et al., 1965) and often appear following hand-rearing of gorillas (Meder, 1989). These animals engage in body rocking, self-huddling, and self-biting, which appear strikingly similar to stereotypies displayed by individuals with mental retardation and autism (e.g., Berkson, 1967; Harlow et al., 1965). Finally, there is a large literature documenting stereotypies in animals that experience environmental restriction including confinement and movement restraint (Heidiger, 1934; Levy, 1944; Meyer-Holzapfel, 1968).

Conditions Associated with Stereotyped Behavior

Stereotyped behaviors which appear in zoo and farm animals are thought to result from conditions of environmental restriction and are a major animal welfare concern for veterinarians and animal caretakers (Lawrence & Rushen, 1993). Animals raised in zoos, in particular foraging animals such as polar bears, frequently exhibit high rates of route

tracing which can resemble the pattern of a figure eight or pacing back and forth (Meyer-Holzapfel, 1968). Domestication of animals for food production has commonly resulted in the development of abnormal repetitive behaviors. For example, stereotyped eye rolling often develops as a consequence of housing veal calves in restrictive stalls (Fraser & Broom, 1990), whereas, tethering pregnant sows has been associated with the development of chain chewing and stereotyped licking behaviors (Cronin & Wiepkema, 1984).

In the laboratory several species exhibit cage stereotypies whether being raised in captivity or caught in the wild (for review see Lewis & Baumeister, 1982). For example, trapped bank voles (*Clethrionomys glareolus*) develop stereotyped jumping, backwards somersaulting, and patterned running when housed in standard rodent cages (Ödberg, 1986). The stereotypies exhibited by bank voles appear pathological as their duration is excessive and these behaviors often interfere with species-specific behaviors such as pup retrieval (e.g., performing stereotypy with pups in mouth) (Sorensen, 1987). Although it is commonly assumed that these stereotypies are a response to environmental restriction, few empirical studies have established this relationship. The few studies that are available have been conducted with bank voles. When housed under enriched conditions (e.g. larger cage size, addition of nest materials, hiding places, twigs on which to climb), fewer bank voles (12%) developed stereotypy compared to bank voles housed in standard cages (70%) (Sorensen, 1987).

Environmentally-induced stereotypies are thought to reflect a narrowing of the primary behavioral reaction to the particular environmental context (Dantzer, 1986). For example, sequences of exploratory behavior may become repeated with the animal's

behavioral repertoire becoming successively narrowed. The stereotyped behaviors are thought to become successively less dependent on the environmental context that originally elicited the behavioral pattern and increasingly more self-directed (Mason, 1993; Dantzer, 1986). For example, piglets begin to engage in non-nutritive oral behaviors after being denied the opportunity to suck (Fry, Sharman, & Stephens, 1981).

During particular stages of development (e.g., during periods of synaptogenesis) animals might be more susceptible to the detrimental effects of restricted environments. Stereotyped body rocking appears relatively early (ca. 29 days of age) in the behavioral repertoire of chimpanzees raised in isolation with a stationary surrogate mother but is not observed in chimpanzees raised in isolation with a moving surrogate mother (Mason & Berkson, 1975). As suggested in this model, understanding the expression of stereotyped behavior during ontogeny may provide insight into the underlying pathogenesis (e.g. movement restraint, neurological insult, stress) of the stereotyped behavior. Charting the developmental time course of stereotypies will help us characterize the deer mice model and allow for future investigations into the neurobiological factors associated with the development of repetitive behaviors in these animals. Understanding the role of environmental variables in the induction and prevention of stereotyped behavior and how these influences are mediated by the CNS is important for designing and assessing behavioral and/or pharmacological interventions.

Neurobiological Basis of Stereotyped Behavior

Drug-Induced Stereotypy

Investigations of the role of the CNS in the expression of stereotyped behaviors have generally relied on models of drug-induced stereotypy (Lewis & Baumeister, 1982). The impetus for investigation of the ability of a wide variety of compounds (e.g. stimulants, opiates, methylxanthines) to elicit stereotyped behaviors came from clinical observations. Highly stereotyped sequences of behavior (e.g., repeating the same phrase, repeatedly assembling and disassembling objects, repetitive sorting of the contents of a handbag) have all been reported in individuals abusing psychostimulants such as amphetamine (Ellinwood, 1967; Rylander, 1971). As these individuals also exhibited some of the features of schizophrenia, animal studies on drug-induced stereotypy and its blockade proliferated. It is now well established that stereotyped patterns of behavior can be induced in a number of mammalian species following administration of dopamine agonists and drugs that alter nigrostriatal dopamine function (Randrup & Munkvad, 1967; Fog, 1972; Lewis et al., 1996; Cooper & Dourish, 1990). Furthermore, stereotypies can also be induced in rodents and non-human primates by direct-acting dopamine agonists such as apomorphine or the administration of the dopamine precursor L-DOPA (Fog, 1972; Waddington, Molloy, O'Boyle, & Pugh, 1990).

Dopamine or dopamine agonists injected directly into the striatum induce stereotyped behaviors in rats (e.g., Ernst & Smelik, 1966). Studies on the role of dopamine in stereotyped behavior suggest a particularly important role for the nigro-striatal dopamine pathway in the mediation of stereotypy. Dopamine neurons originating

in the substantia nigra synapse on both GABA cells and cholinergic interneurons in the striatum which in turn synapse on GABA cells projecting back to dopamine-containing neurons in the substantia nigra (Groves, Wilson, Young, & Rebec, 1975; Côté & Crutcher, 1991). Induction of stereotyped behavior by application of GABA agonists to the substantia nigra pars reticulata supports the importance of the nigrostriatal circuitry and its output pathways (Scheel-Kruger, Arnt, Braestrup, Christensen, Cools, & Magelund, 1978). Dopamine receptor antagonists such as haloperidol are effective in blocking dopamine agonist-induced stereotypy (Ridley, Baker, & Scraggs, 1979). Amphetamine-induced stereotypy can be blocked by inhibiting the synthesis of dopamine using α-methyl-p-tyrosine or destroying dopamine-containing neurons with the neurotoxicant 6-hydroxydopamine (6-OHDA) (Stolk & Rech, 1970; Creese & Iversen, 1973). On the other hand, after 6-hydroxydopamine lesions of the dopamine pathway, animals become supersensitive to direct-acting dopamine agonists such as apomorphine. Rats treated neonatally with 6-hydroxydopamine appear to be even more sensitive to apomorphine, exhibiting intense stereotyped and self-injurious behavior (Creese & Iversen, 1973; Ungerstedt, 1971).

Non-Drug-Induced Stereotypy

As this literature suggests, the role of the dopamine system, particularly the nigrostriatal dopaminergic system, in the mediation of drug-induced stereotyped behaviors is well established (Lewis & Baumeister, 1982; Cooper & Dourish, 1990). Whether the same neurobiological pathways are involved in spontaneous stereotypies (e.g., those associated with conditions of environmental restriction) remains an interesting question. Studies of drug-induced stereotypy typically reveal little about the environmental factors

influencing the development of the behavior and the corresponding CNS changes. Although the literature on stereotypies associated with environmental restriction in zoo and farm animals is rich in description, information on the neurobiology of such repetitive behaviors is lacking (Dantzer, 1986). Neurobiological data from animal models of spontaneous stereotypy may provide us with insight into effective treatment of stereotyped and self-injurious behaviors in individuals with mental retardation and autism. The role of dopamine in the mediation of spontaneous stereotypy has been examined in the past. As early as the 1870's, the German scientist Feser injected cows and sheep with the recently discovered compound apomorphine and observed behaviors similar to those displayed by cattle with "licking sickness" and wool biting in sheep (Sharman, 1978). Unaware of the mechanism of action of apomorphine, Feser predicted that the same areas of the brain affected by apomorphine were involved in the repetitive behaviors observed in these farm animals (Sharman, 1978).

Rhesus monkeys which developed stereotypy following total and partial social isolation early in development showed decreased tyrosine hydroxylase immunoreactivity in the striatum and substantia nigra (Martin, Spicer, Lewis, Gluck, & Cork, 1991). These monkeys also show an increased behavioral sensitivity to an acute dose of apomorphine, suggestive of dopamine receptor supersensitivity (Lewis, Gluck, Beauchamp, Keresztury, & Mailman, 1990). The development of repetitive oral behaviors in early weaned piglets has been associated with decreases in HVA and DOPAC, the major metabolites of dopamine, in the putamen and nucleus accumbens (Fry, Sharman, & Stephens, 1981; Sharman, Mann, Fry, Banna, & Stephens, 1982) and increases in D_2 dopamine receptors in the caudate nucleus (Sharman, Mann, Fry, Banna, & Stephens, 1982). In our own work

with individuals who have mental retardation, stereotyped behavior has been associated with decreases in spontaneous blink rate (Bodfish, Powell, Golden, & Lewis, 1995) and plasma HVA concentrations (Lewis, Bodfish, Powell, Wiest, Darling, & Golden, 1996), suggesting hypodopaminergic function.

Studies examining captivity-induced stereotypies of bank voles have suggested an important role for dopamine and opiate systems in the mediation of these repetitive behaviors. Naltrexone, an opiate receptor antagonist, effectively reduced jumping early in development, but was less effective in reducing stereotyped jumping in older animals. Conversely, haloperidol, a dopamine receptor antagonist, was preferentially effective in reducing stereotyped jumping in older animals independent of a decrease in overall activity (Kennes, Ödberg, Bouquet, & De Rycke, 1988). Cronin, Wiepkema, & van Ree, (1986) reported a positive correlation between length of time (weeks) since the development of stereotypy and the time to suppression of stereotypy following naloxone in sows. This decrease in stereotyped behavior was also observed independent of an effect on exploratory behavior. These observations are important as they point to potentially different neurobiological mechanisms mediating newly developing stereotypies (e.g., opioid peptides) vs. stereotypies well established in the repertoire of the animal (e.g., dopamine). Stereotyped jumping in bank voles was decreased by α-methyl-para-tyrosine, an inhibitor of tyrosine hydroxylase, and increased by L-DOPA, the precursor to dopamine (Ödberg, Kennes, De Rycke, & Bouquet, 1987). These drug effects were not solely due to a generalized effect on motor activity as both the drug treatments failed to effect other activities. The dopamine-β-hydroxylase (DBH) inhibitor fusaric acid had no significant

effects on stereotyped behavior in these animals, suggesting the importance of dopamine but not norepinephrine (Ödberg et al., 1987).

When placed on fixed schedules of reinforcement, animals often develop stereotypies termed adjunctive, or schedule-induced, behaviors (Palya & Zacny, 1980; Falk, 1971). A frequently observed consequence of maintaining rats on fixed schedules of food presentation either with or without behavioral contingencies is excessive water drinking, or schedule-induced polydipsia. Selective cytotoxic lesions of the nucleus accumbens using 6-OHDA prevent the acquisition of schedule-induced polydipsia (Robbins & Koob, 1980). In addition, amphetamine and methylphenidate have been shown to attenuate SIP (e.g., Wayner, Mintz, Jolicoeur, & Rondeau, 1979), and neither icv corticotropin-releasing factor (CRF) nor the antagonist α-helical CRF appeared to have a selective effect on SIP (Cole & Koob, 1994).

Spontaneous Stereotypy in Deer Mice

We have been investigating the use of a rodent model of spontaneous stereotypy. Deer mice (*Peromyscus maniculatus bairdi*), when housed under standard laboratory conditions, develop high rates of spontaneous stereotyped motor behavior (Baumgardner, Ward, & Dewsbury, 1980). The current study was designed to characterize the specific forms of stereotyped behavior displayed by deer mice, describe the developmental trajectory for the stereotyped behaviors, and determine the upper and lower age limits for the initial expression of these behaviors. In order to test the hypothesis that the stereotyped behavior observed in deer mice housed in standard laboratory conditions was due to environmental restriction, a series of observations to assess the effects of

environmental enrichment on stereotypy and track the development of stereotypies in animals housed in standard and enriched cages was conducted. It was hypothesized that stereotyped behavior was associated with decreased concentrations of dopamine and its metabolites and an increase in dopamine receptors in the corpus striatum.

CHAPTER 2
MATERIALS AND METHODS

Subjects

Deer mice (*Peromyscus maniculatus bairdi*) were housed in a standard colony room kept at 24° C and maintained on a 16/8 hour light/dark cycle, with lights off at 9:30 am. At the time of weaning (23 days of age), deer mice were randomly assigned to either standard (n=16) or enriched (n=15) caging. Standard caging involved either two or three same sex mice in a standard laboratory mouse cage (29 x 18 x 13 cm) with bedding on the cage floor. Rodent chow and water were located on the cage top available and available ad lib. Four cages contained three animals and two cages contained only two animals. The discrepancy in number of animals per cage was due to an unequal number of males and females and the death of one animal. Enriched caging involved housing three same sex mice in a larger cage (51 x 41 x 22 cm) equipped with a running wheel, habit trails, small enclosures for nesting or hiding, nesting material, and sunflower seeds inside the cage. Rodent chow and water were located on the cage top and available ad lib. The objects within the cage were changed and rearranged weekly. A commercially available blonde hair dye was applied to the animals' fur every four weeks to individually identify the mice in a given cage. A second cohort of deer mice (n = 17) was housed in the same manner as described above in both standard (n = 9) and enriched (n = 8) cages. These animals were included in the analysis of dopamine receptors and monoamine concentrations in striatum.

Observational Procedures

Behavioral observations were conducted twice daily at approximately 10:30 a.m. and 2:30 p. m. every other day (approximately three times per week) for 17 weeks. Each cage was observed for five minutes at each of the two time periods. Each five minute observation period was divided into five second intervals. During each five-second scoring interval, the occurrence of specific topographies of stereotyped behavior was recorded for individual animals. From preliminary observations of the animals, three distinct topographies of stereotyped behaviors were observed and operationally defined: jumping, backward somersaulting, and route tracing or patterned running. Similar behavior patterns have been observed in captive bank voles (Sorensen, 1987). To be considered a stereotypy, the behavior had to occur more than once within the five second interval. Inter-rater agreement across topographies of stereotyped behavior as computed using Cohen's kappa averaged 0.83 (SD = 0.15). The second cohort of animals was observed in a similar manner, but only for two weeks before being killed. These animals were not included in the analysis of behavioral data as they were only used for analysis of monoamines and dopamine receptors.

Homogenate Radioligand Binding

At the end of the seventeen week period, animals were killed by cervical dislocation followed by decapitation and brains were rapidly removed, snap frozen in isopentane, and stored at -80^{0}C until time of assay. Estimates of the density of D_1 and D_2 dopamine receptor sites in the corpus striatum (caudate nucleus and putamen) were determined in animals in both standard and enriched caging. At the time of assay,

individual striata were homogenized in a volume of ice cold 50 mM HEPES buffer pH 7.4 (4°C), using Teflon-glass homogenizers, to equal a concentration of approximately 1.0 mg wet weight/ml. At this point a 300 ul aliquot of homogenate was removed for HPLC analysis. The remaining tissue was centrifuged at 27,000 g for 10 min, the supernatant discarded, and the pellet resuspended in 5 ml ice cold buffer and centrifuged again. The final pellet was suspended at a concentration of approximately 1.0 mg wet weight/ml.

Assay tubes (1 ml final volume) were incubated at 37°C for 20 min. Binding of 1.0 nM ^{3}H-SCH23390 was used to assess the density of D_1 receptors with unlabeled SCH23390 at a concentration of 10 μM to define nonspecific binding. Ketanserine tartrate (500 nM) was used to displace binding of SCH23390 to 5-HT_2 receptors. Binding of 1.0 nM ^{3}H-spiperone was used to determine the density of D_2 receptors with unlabeled domperidone (10 μM) to define nonspecific binding. Ketanserine tartrate (500 nM) was used to displace binding of spiperone to 5-HT_2 receptors. Binding was terminated by filtering with 15 ml ice cold buffer on a Skatron cell harvester (Skatron INC, Sterling, VA) using glass fiber filter mats (Skatron #7034, Sterling, VA). Filters were then allowed to dry and 3.0 ml of Scintiverse E (Fischer Scientific Co., Fair Lawn, NJ) was added. After shaking for 30 minutes, radioactivity was determined on a LKB Rack Beta liquid scintillation counter. Tissue protein levels were estimated using a BCA spectrophotometric assay and microplate reader with absorbance set at 562 nm. Estimates of the density of dopamine receptors was computed at the given concentration of radiolabeled drug used for the two receptor subtypes.

HPLC Analysis of Monoamines and Metabolites

The concentrations of monoamines and metabolites from striata were quantified using an HPLC procedure with electrochemical detection. Differences in specific compounds between specified experimental conditions were determined quantitatively using amperometric detection of the column effluent with a potential of +0.75 V vs. a Ag/AgCl reference electrode. Chromatographic separations were performed using a delta bond stainless steel column (150 mm X 4.6 mm i.d.) packed with 3 μm C^{18} bonded microparticulate silica (Keystone Scientific, INC, Bellafonte, PA). The mobile phase consisted of 95 mM Na_2HPO_4 containing 27 mM citric acid, 0.038% sodium octyl sulfate (SOS), and 13% methanol, with a final pH of 3.4 and a flow rate of 0.80 ml/min.

Standard curves for the quantification of all compounds [dopamine (DA), serotonin (5-HT), homovanillic acid (HVA), dihydroxyphenylacetic acid (DOPAC), and 5-hydroxyindoleacetic acid (5-HIAA)] were prepared by analyzing a series of standard solutions containing a fixed amount of the internal standard 3,4-dihydroxybenzylamine (DHBA) and varying amounts of each compound. The slopes of the standard curves obtained by linear regression were routinely greater than or equal to 0.99.

At the time of the radioligand binding assay, 240 ul of perchloric acid was added to the 300 ul of striatal homogenate. Samples were vortexed, then centrifuged for 10 min at 13,200 rpm, supernatant collected and both supernatant and pellet were stored at -80°C until assay (for HPLC and protein assays, respectively. Supernatant (450 ul) was removed and 50 ul of DHBA (20 ng/ml) was added; the solution was filtered (0.2 mm nylon acrodisc), and 100 ul of the solution was injected onto the column. The concentration of

monoamines and their metabolites in these unknown brain samples were determined from the internalized standard curve and the ratios of the particular compounds to DHBA.

The tissue pellet was sonicated in 500 µl mobile phase buffer using an ultrasonic cell disrupter (Heatsystems, Farmingdale, NY; setting 1) for protein determination. Tissue protein levels were estimated using a BCA spectrophotometric assay and microplate reader with absorbance set at 562 nm.

CHAPTER 3
RESULTS

Development of Stereotypy and Effects of Enrichment

Table 1 lists the topographies and operational definitions of stereotyped behaviors that were observed in deer mice in the current study. All three topographies of stereotypy, which confirmed our preliminary observations, were observed in both standard cages and enriched cages.

Table 1. Stereotyped Behaviors in Deer Mice in Standard and Enriched Caging

Repetitive Jumping	Rearing in one of the four corners of the cage and repeatedly jumping on his/her hind paws
Backward Somersault	A somersault in a backward direction with or without assistance from the cagetop or side
Patterned Running	Repetitive route tracing or circling of the cage in a clear pattern

The percent of animals engaging in stereotyped behavior (collapsing across topographies) observed in each of the two housing conditions over the 17 week period is presented in Figure 1. Animals were judged to have stereotypy in a given week if they engaged in repetitive behavior in greater than 5% of the intervals. As can be seen in Figure 1, animals housed in standard cages developed stereotypies at a faster rate than did animals housed in enriched cages.

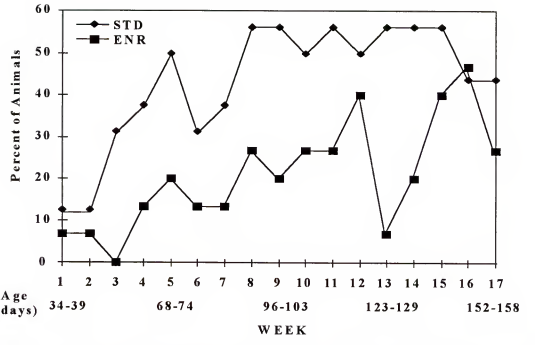

Figure 1. Effects of housing condition on the percent of animals developing stereotypy over the seventeen week experimental period.

In order to test whether environmental condition resulted in a differential rate of development of stereotypy, a variant of logistic regression was used. A generalized estimating equations model was used to determine whether experimental condition, litter and gender affected the development of stereotypy over time (Liang & Zeger, 1986). Animals housed in standard cages developed stereotypy at a significantly faster rate than did animals raised in enriched cages $z = -1.84$, $p = .033$, one-tailed. As we were interested in a preliminary investigation of the relative importance of genetic and / or early environmental experience on the development of stereotypy, the effect of litter on the rate of development of stereotypy was included in the model. There was an overall effect of litter on the rate of development of stereotypy $\chi^2(8) = 20.64$, $p = .0082$. There was no

effect of gender, however, on the rate of development of stereotyped behavior $z = 1.24$, $p = .22$.

In order to compare the number of animals that developed stereotypy in each condition, a stricter criterion was applied. An animal was judged to be stereotypic if the repetitive behavior occurred in greater than 5% of the intervals/week for two consecutive weeks. Although stereotyped behavior was observed in 62.5% (10 of 16) of animals housed in standard cages vs. 46.7% (7 of 15) of animals housed in environmental enrichment cages (Table 2), these proportions were not significantly different (Fisher's exact probability test; one-tailed, $p = .30$).

Table 2. Number of animals developing stereotypies in standard and enriched housing conditions.

	Standard Cages (n=16)	Enriched Cages (n=15)
Overall (all topographies)	10	7
Jumping*	7	0
Backward Somersaulting	3	2
Patterned Running*	1	6

*$p < .05$ (Fisher's exact probability test)

Although the number of animals exhibiting stereotypy was not significantly different between the housing conditions, the stereotyped behaviors exhibited by the two groups were of different forms. Table 2 indicates the number of mice in each condition judged to have developed each topography of stereotypy (jumping, backwards somersaulting, and patterned running).

Significantly more deer mice housed in standard cages (7/16) developed repetitive jumping than did deer mice housed in enriched cages (0/15) (Fisher's exact probability test; two-tailed, $\underline{p} = .007$). Forty percent (6/16) of deer mice housed in enriched cages developed patterned running vs. only 6.3% (1/16) of deer mice housed in standard cages (Fisher's exact probability test; two-tailed, $\underline{p} = .037$). The number of mice developing backwards somersaulting did not differ between the two housing conditions (Fisher's exact probability test; two-tailed, $\underline{p} = 1.0$).

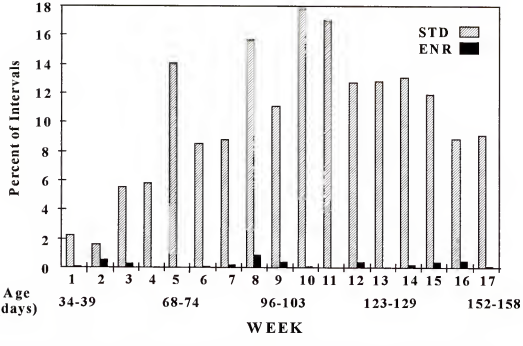

Figure 2. Effects of housing condition (STD = standard cage condition, ENR = enriched cage condition) on the percent of intervals in which repetitive jumping was observed over the seventeen week experimental period.

Deer mice in standard cages developed significantly higher rates of repetitive jumping than did deer mice raised in enriched cages (Figure 2). Repetitive jumping appeared in an average of 10.7 % of intervals ($\underline{SD} = 15.9$) across the seventeen week observation period in the standard cage condition compared to an average of 0.23% of

intervals (SD = 0.38) in the environmental enrichment condition $t(29) = 2.54$, $p < .05$, one-tailed). The great majority of stereotyped behavior in enriched cages manifested itself as patterned running (Figure 3). Deer mice in enriched cages engaged in patterned running in 5.7% of intervals (SD = 11.1) compared to 0.18% of intervals in mice in standard cages (SD = 0.73) $t(29) = 1.98$, $p < .05$, one-tailed.

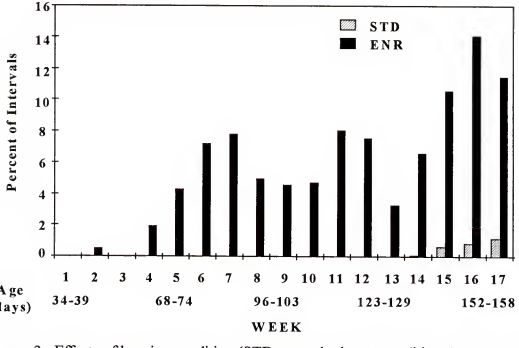

Figure 3. Effects of housing condition (STD = standard cage condition, ENR = enriched cage condition) on the percent of intervals in which patterned running was observed over the seventeen week experimental period.

Although the average percent of intervals in which backward somersaulting was observed was higher in standard cages (4.74%, SD = 10.12) than enriched cages (0.98%, SD = 2.36), this difference was not statistically significant $t(29) = 1.40$; $p = .086$ (Figure 4).

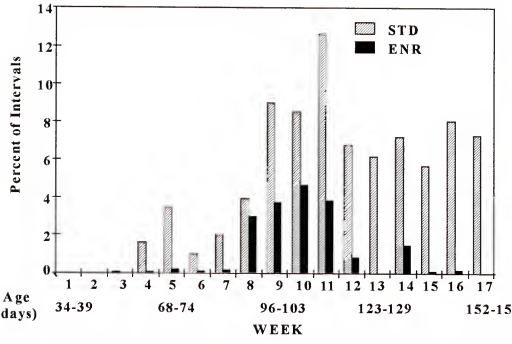

Figure 4. Effects of housing condition (STD = standard cage condition, ENR = enriched cage condition) on the percent of intervals in which backwards somersaulting was observed over the seventeen week experimental period.

Considering that each topography developed in only a subset of animals, further analyses of the data were conducted including only those animals which were judged through the previous criterion to have developed specific topographies. This analysis indicated that deer mice in standard cages engaged in higher rates of backward somersaulting (25.1% of intervals), vs. deer mice in enriched cages engaged in backward somersaulting (6.6% of intervals). Of those animals judged to engage in patterned running, animals in the enriched condition did so at higher rates (13.8% of intervals) than did the one animal in the standard cage condition (2.9% of intervals). Since no animals in enriched caging were judged to have developed repetitive jumping, this comparison is not applicable to the jumping topography. The small sample sizes in this breakdown of the data precluded statistical analysis.

Within the standard cages, there was a different developmental rate for somersaulting and jumping. As seen in Figure 5, stereotyped jumping occurred in a greater percentage of animals housed in standard cages and developed earlier than backward somersaulting. This may relate to the animals' stage of physical development with backward somersaulting requiring greater motor competence (e.g., Berkson, 1968).

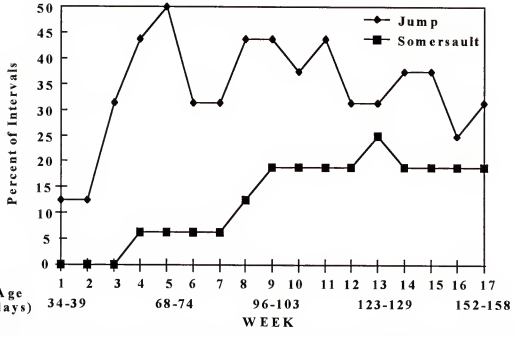

Figure 5. Percent of intervals of jumping and backwards somersaulting in deer mice raised in standard cages over the seventeen week experimental period.

Analysis of Striatal Dopamine and Dopamine Receptors

The effects of stereotypy status (stereotypy/no stereotypy) and housing condition on D_1 and D_2 dopamine receptors and monoamine and monoamine metabolites were analyzed using 2 (housing condition) x 2 (stereotypy status) analyses of variance (ANOVA). Table 3 indicates the binding of [^{3}H]-SCH23390 and [^{3}H]-spiperone to D_1 and D_2 dopamine receptors, respectively, in striata of deer mice with and without stereotypy

for each housing condition. There were no effects of housing condition $F(1,34) = 1.09$, $p = .31$ or stereotypy status $F(1,34) = 1.19$, $p = .28$ on D_1 receptor densities. Similarly, there were no differences in D_2 receptors as a function of housing condition $F(1,34) = .17$, $p = .68$ or stereotypy status $F(1,34) = .47$, $p = .50$. There were also no significant housing condition by stereotypy status interactions for D_1 $F(1,34) = 0$, $p = .99$ or D_2 $F(1,34) = .55$, $p = .46$ dopamine receptors.

Table 3. Density (fmol/ mg protein) of D_1 (^{3}H-SCH23390) and D_2 (^{3}H-Spiperone) dopamine receptors in striatum of deer mice.

Group	N	1.0 nM ^{3}H-SCH23390 (fmol/mg protein)		1.0 nM ^{3}H-Spiperone (fmol/mg protein)	
		Mean	SD	Mean	SD
Stereotypy	22	1005.3	180.9	262.1	122.1
Standard Caging	14	983.8	211.7	276.3	150.8
Enriched Caging	8	1042.9	111.1	237.1	36.7
No stereotypy	16	958.4	145.0	234.9	47.2
Standard Caging	6	920.5	99.6	228.0	31.8
Enriched Caging	10	981.1	167.3	239.1	55.7

Considering the high degree of variability in the percent of intervals in which a given animal engaged in stereotyped behavior, a correlational analysis was performed to determine the relationship between frequency of stereotypy during the last week of observations and the relative density of dopamine receptors. Neither the correlation between D_1 dopamine receptors $r(24) = -.16$, $p = .43$ or D_2 dopamine receptors $r(24) = -$

.24, $p = .23$ and percent of intervals in which stereotyped behavior occurred reached statistical significance.

Table 4. Concentration (ng/ mg protein) of dopamine (DA), 3, 4-dihydroxyphenylacetic acid (DOPAC), DOPAC/DA ratio, homovanillic acid (HVA), serotonin (5-HT) in striatum of deer mice expressed as mean and SD.

Group	N	DA	DOPAC	DOPAC/DA Ratio	HVA	5-HT
Stereotypy	22	134.6 (31.1)	16.9 (5.7)	0.13 (0.03)	9.58 (4.4)	3.3 (1.1)
Standard	14	129.0 (36.6)	16.8 (6.6)	0.13 (0.03)	9.19 (5.1)	3.3 (1.0)
Enriched	8	144.3 (15.8)	17.1 (3.8)	0.12 (0.03)	10.26 (2.9)	3.4 (1.2)
No stereotypy	16	137.2 (27.6)	15.4 (4.3)	0.11 (0.03)	7.84 (2.4)	4.6 (4.2)
Standard	6	138.7 (25.7)	16.2 (4.9)	0.11 (0.04)	6.65 (1.9)	3.26 (1.8)
Enriched	10	136.3 (30.1)	15.0 (4.1)	0.11 (0.03)	8.55 (2.5)	5.5 (5.0)

The concentrations of monoamines and monoamine metabolites in striata are shown in Table 4. The major metabolite of serotonin, 5-hydroxyindolacetic acid (5-HIAA), was undetectable in the striatum. Concentrations of dopamine did not differ between the two housing conditions $F(1,34) = .40$, $p = .53$ or the two stereotypy groups $F(1,34) = .007$, $p = .93$, nor was there a significant housing condition by stereotypy status interaction $F(1,34) = .74$, $p = .40$. There was also no significant effect of housing condition $F(1,34) = .064$, $p = .80$ or stereotypy status $F(1,34) = .56$, $p = .46$ on DOPAC concentrations, nor was there a significant housing condition by stereotypy status interaction $F(1,34) = .20$, $p = .66$. The same pattern of results existed for HVA and serotonin with no differences being apparent as a function of housing condition $F(1,34) =$

1.37, $p = .25$, $F(1,33) = 1.39$, $p = .25$ or stereotypy status $F(1,34) = 2.82$, $p = .10$, $F(1,33) = 1.13$, $p = .30$, respectively. There were also no housing condition by stereotypy status interactions for HVA $F(1,34) = .11$, $p = .75$ or serotonin $F(1,33) = 1.16$, $p = .29$. The concentration of serotonin in one sample was undetectable. Stereotyped behavior during the last week of the observation period was not correlated with concentrations of dopamine $r(24) = -.048$, $p = .82$ or DOPAC $r(24) = -.14$, $p = .5$.

CHAPTER 4
DISCUSSION

The purpose of this study was to characterize the development and expression of stereotyped behavior in deer mice, assess the effects of environmental enrichment on the development of stereotypy, and examine the relationship between dopaminergic function and spontaneous stereotyped behavior. The findings of the current study provide a preliminary description and assessment of the occurrence of stereotypies in this particular colony. They also provide an initial assessment of the development of these behaviors, including differences in the trajectories for different topographies (jumping vs. backward somersaulting). These data suggest that alterations in the environment (e.g., enrichment) have a substantial effect on the type of stereotyped behavior expressed and the time course of its development.

The environmental enrichment procedure used, however, was associated with the development of stereotyped behavior. Stereotyped behavior observed in enriched cages, primarily patterned running, was expressed later in development than the jumping and backward somersaulting observed in standard cages. Thus the degree of enrichment used in the present study was not sufficient to prevent completely the development of stereotyped behavior. Future studies should investigate the effects of larger and/or more complex environments on the development of stereotypy. As suggested by the current study, a significantly larger housing area would be more likely to prevent the development of stereotypy and support the notion that stereotypies observed in deer mice in standard

laboratory cages is associated with environmental restriction. Larger living environments might be particularly important for wild-type muroid rodents such as deer mice that are highly motorically active and maintain a relatively large home range in the wild (estimated range 242 - 3,000 square meters; Wolff, 1989).

Although the stereotyped behaviors that develop in zoo and farm animals have been associated with conditions of environmental restriction, few studies designed to test the environmental restriction hypothesis have been conducted. With the exception of the work with bank voles (Sorensen, 1987; Cooper, Ödberg, & Nicol, 1996), the relationship between cage size and complexity with the development of stereotypy has not been empirically analyzed. Other investigations of the relationship between cage size and stereotypy have focused on changes in the amount of stereotypy performed in relation to changes in cage size in adult animals (Berkson, Mason, & Saxon, 1965; Draper & Bernstein, 1963). In the study by Berkson et al. (1965), chimpanzees were separated from their mothers at birth and raised in small cages during the first 2 1/2 years of life. As adult animals (4-5 years of age), these chimpanzees engaged in more stereotyped behavior when temporarily placed in small enclosures. Similarly, wild-born and laboratory-reared rhesus monkeys (*Macaca mulatta*) display higher rates of stereotyped behavior when placed in small versus large enclosures (Draper & Bernstein, 1963; Paulk, Dienske, & Ribbens, 1977). Both of these studies provide support for the movement restraint hypothesis of stereotypy, but neither of them address the critical environmental components associated with the development of stereotypy. The current data represent one of the first attempts to assess the relationship between environmental variables, such as cage size and complexity, and the development of stereotypy. However, the current study does not provide

information on what key aspects of the environment are critical for the prevention of stereotypy. Analyzing the relative importance of cage size, enrichment objects, and social density may be critical for a better understanding of the features of the environment important in the development or prevention of stereotypy (Lewis & Baumeister, 1982).

Although environmental enrichment did not result in an elimination of stereotypy in deer mice, raising deer mice in enriched cages resulted in the emergence of different topographies of stereotypy which developed at a slower rate than did those in deer mice raised in standard cages. The delayed development of stereotypy in animals raised in enriched cages may be explained by the increased number of motor possibilities for the animals and the greater amount of complexity involved in patterned running, the main topography observed in enriched cages. An interesting and yet unanswered question in the study of stereotypy has been the relative importance of genetic factors associated with the behavior. We were able to assess the effect of litter on the rate of development of stereotypy independent of experimental condition. Interestingly, there was an overall effect of litter on the rate of development of stereotypy. Observation of a litter effect suggests a potentially important role for genetic and/or early environmental factors in the rate of development of stereotyped behaviors. Future studies designed to manipulate such variables as prenatal and postnatal maternal environments (e.g., cross fostering pups between stereotypy and non-stereotypy mothers) may or may not help disentangle the relative importance of genetic and early environmental factors in the development of stereotypy. As suggested by our preliminary observations of this colony of deer mice, males and females developed stereotypy at similar rates. The issue of sex effects on the development of stereotypy has not been addressed in other models of environmental

restriction-induced stereotypy but will be useful in our further characterization of the model and in our investigations of the neurobiology of stereotypy.

The emergence of different topographies between the standard cage condition and the enriched cage condition suggested the importance of environmental constraints associated with the development of repetitive behavior patterns. Stereotyped behaviors are generally thought to develop from the normal behaviors appropriate to the particular environmental context (Dantzer, 1986; Mason, 1991). The fact that patterned running was by far the most prevalent form of stereotypy in the enriched cages may have been due to the physical arrangement of the cages. It should be stressed, however, that there was ample space in the enriched cages for stereotyped jumping (which occurred at a low rate) and a small number of animals did exhibit backward somersaulting in the enriched cages. Thus, the substantial decrease in jumping and somersaulting, by far the most prevalent forms of stereotypy observed in standard cages, was not due to physical impediment of expression of these behaviors.

Considering that jumping and backwards somersaulting are the most prevalent forms of stereotypy in standard cages, it is interesting to compare the rate of these behaviors in only those animals which displayed these two topographies. The average percent of intervals in which jumping occurred was significantly greater in standard cage animals than in enriched cage animals. Comparisons of animals judged to have developed jumping could not be made between the two groups since no animals in the enriched condition met criterion for the development of stereotyped jumping. Comparing all of the animals on percent of intervals in which backward somersaulting occurred did not result in a statistically significant difference between the two groups. Those animals that did engage

in backward somersaulting in the enriched condition, however, did so at a substantially lower rate when compared to animals in the standard cage condition. When all animals in the groups were compared, this difference was masked by the low levels of backwards somersaulting in the two conditions by most of the animals. Therefore, even though the number of animals judged to have developed backward somersaulting did not differ, the average rate of backward somersaulting appeared to be lower in animals raised in enrichment. Statistical analysis of these data could not be performed due to the small sample size.

Our informal observations have suggested that spontaneous stereotypies in standard cages may occur even earlier in development, in some cases prior to weaning. Thus, subsequent studies on the effects of environmental enrichment on the development or prevention of stereotypies will be initiated in younger animals. Importantly, we have observed stereotypy in some mice when they are handled and marked for identification at weaning. Mice in the two environmental conditions were kept with their mothers in standard cages up until the time of weaning. Considering the early development of stereotyped behaviors, it may be important for future studies to control for environmental condition for mothers and their pups prior to weaning. Examining the role of maternal behavior on the development of stereotypy may also be important to the understanding of the developmental trajectory of stereotypy and the early neurobiological changes associated with the development of these behaviors.

To test the hypothesis that stereotypy was associated with changes in dopaminergic function, the concentration of monoamines and their metabolites and the density of dopamine receptors were estimated in the striatum of deer mice with and

without stereotypy. No differences in the concentration of dopamine and its metabolites were observed in deer mice that developed stereotypy compared to deer mice that did not develop stereotypy. Similarly, the density of D_1 and D_2 dopamine receptors did not differ as a function of whether or not animals had developed stereotypy nor did they differ between the two housing conditions. The current study failed to observe the same pattern of a decrease in dopamine metabolite concentration and an increase in dopamine receptor density as that observed in piglets developing non-nutritive oral behavior after being denied the opportunity to suckle (Fry et al., 1981; Sharman et al., 1982). This discrepancy in findings is most likely due to the differences in the conditions associated with the behaviors in the two models and the differences in the behaviors themselves.

The repetitive behaviors of deer mice housed in standard laboratory cages are motor stereotypies developing in animals which are highly motorically active. Previous work on drug-induced stereotypy has suggested the importance of the nigrostriatal dopamine system in the expression of stereotyped behaviors. Stereotypies in these models, although similar to the stereotypies observed in deer mice in terms of being repetitive, are quite different in their topography. For example, administration of high doses of dopamine agonists primarily induce focused sniffing, gnawing, and licking of the cage floor (Cooper & Dourish, 1990). Although not discounting the importance of nigrostriatal dopamine in the mediation of stereotypy in deer mice, it may be critical to examine whether dopamine agonists induce similar behaviors to those observed spontaneously in deer mice. The effects of dopamine agonists on the induction of stereotypy in deer mice which do not exhibit the behavior spontaneously are currently being pursued in our laboratory.

It may also be important to investigate the role of mesolimbic dopamine in the expression of stereotyped behavior, particularly locomotor stereotypies since the nucleus accumbens is an important limbic structure involved in locomotor behavior (Le Moal & Simon, 1991). As Le Moal and Simon (1991) suggest, the long held notion that the stereotypy-inducing effects of stimulant drugs was primarily explained by activation of the dorsal striatum and that these effects could be pulled apart from the locomotor-inducing effects of stimulants as requiring stimulation of the ventral striatum has not been consistently supported. Some investigators have reported that microinjections of d-amphetamine into the nucleus accumbens resulted in increased locomotion without the induction of stereotypy and d-amphetamine injections into the caudate nucleus induced stereotyped behavior, while failing to increase locomotion (Statton & Solomon, 1984). Conversely, intra-accumbens injections of amphetamine have also been reported to induce stereotypy (Annett, Ridley, & Gamble, 1983). The dorsal striatum has been considered an important aspect of sensorimotor integration and the ventral striatum considered to be an important relay station for motivational input from limbic structures. As such, these two areas serve as important filtering and gating mechanisms involved in motor output for limbic and cortical areas (Le Moal & Simon, 1991). Therefore, both brain regions may interact to generate the production of stereotyped behaviors. Indeed, studies on schedule-induced polydipsia have suggested the importance of the nucleus accumbens in the acquisition of these behaviors (Robbins & Koob, 1980).

Most of the dopamine being quantified through our HPLC procedures was dopamine sequestered in nerve terminals, which does not address the possibility of differences in dopamine release in these terminal fields. Future studies should also consider

differences in dopamine release in the striatum and nucleus accumbens in animals which engage in stereotyped behaviors.

Other animal models of stereotyped behavior have observed an association between stereotypy and dopamine receptor supersensitivity. Rhesus monkeys that develop stereotypies following complete social isolation early in development, are behaviorally more sensitive to the effects of dopamine agonists (Lewis et al., 1991). Rats with neurotoxic lesions of the dopamine system using 6-OHDA are more sensitive to the induction of stereotypy following administration of direct-acting dopamine agonists (Ungerstedt, 1971). These observations of behavioral supersensitivity are generally attributed to an upregulation of dopamine receptors in terminal fields of dopamine-producing neurons.

Interestingly, depending upon the route of administration of 6-OHDA, a differential effect on dopamine receptors is observed in the striatum, the major terminal field of dopamine-containing neurons (Mileson, Lewis & Mailman, 1991). With bilateral and intracisternal injections of 6-OHDA, rats showed behavioral supersensitivity after challenge with the dopamine agonist, apomorphine. In this study Mileson et al. (1991) failed to observe an increase in the density of D_1 or D_2 dopamine receptors in animals with either bilateral or intracisternal injections of 6-OHDA but found the predicted increase in D_2 receptors on the lesioned side of animals with unilateral lesions with 6-OHDA. As suggested by the investigators, there could be another mechanism of dopamine receptor supersensitivity accounting for the behavioral effects observed (Mileson et al., 1991). Although the current study did not assess behavioral supersensitivity directly, our hypothesis was that stereotypies in deer mice would be associated with an upregulation of

dopamine receptors. The failure to observe a difference in dopamine receptor number, however, does not rule out the possibility that stereotypy is associated with dopamine receptor supersensitivity. Future studies should investigate other mechanisms of receptor sensitivity such as changes in cAMP or interactions with other neurotransmitter systems. Indeed, Mileson et al. (1991) observed an increased dopamine-stimulated adenylate cyclase response in rats with bilateral 6-OHDA lesions, suggesting an increased sensitivity of D_1 dopamine receptors.

In general the heterogeneous nature of the stereotyped behaviors observed in deer mice and the high degree of variability in both dopamine concentration and dopamine receptor density become a problem for group comparisons. Dopamine receptor density and dopamine and DOPAC concentrations, however, were not correlated with the frequency of stereotypy. The intensive, lengthy observation schedule used in the study did not allow for a large enough sample size to investigate thoroughly the relationship between dopamine function and particular topographies of stereotypy. We are currently conducting an investigation of the effects of a much larger housing area with a larger sample size to increase the magnitude of our overall effect and increase our ability to do subgroup analyses

As Ödberg et al. (1987) suggest, the literature on drug-induced stereotypy has not been very well integrated with the literature on spontaneous stereotypies developing under conditions of environmental restriction. As discussed earlier, such integration would provide a better understanding of the neurobiology of repetitive motor behavior in general. It is thought that the repetitive behaviors displayed in contexts of environmental restriction become increasingly more self-directed and are associated with a decreased ability to

respond adaptively to a changing environment (Dantzer, 1986; Mason, 1991). The same notion of a narrowing of the behavioral repertoire has been the common explanation of the stereotypy-inducing effects of increasing doses of stimulant drugs (Robbins, Mittleman, O'Brien, & Winn, 1990). A similar conceptual framework has been put forth by some investigators studying stereotypy in individuals with mental retardation (Newell, 1996) and typically developing children (Thelen, 1996). Newell argues that repetitive behaviors whether they be dyskinesias or stereotypies represent a "decreased adaptability" of the motor system and that individuals with stereotypies exhibit fewer degrees of freedom in their ability to compensate through postural adjustments (Newell, 1996 p. 133).

Stereotypies often appear during transition stages throughout the motor development of normally developing children (Thelen, 1996). Thelen (1996) proposed that repetitive behavior represents a regression to a more rudimentary level of motor development, oscillation. Thus, during development if an infant is not yet capable of carrying out goal directed behavior, he/she will revert back to the normal pattern of the system which would be oscillation (Thelen, 1996). Similarly, Dantzer argues that stereotypies in animals and humans represent a disruption in normal inhibitory control by higher brain structures (Dantzer, 1986). In classic studies conducted on the effects of environmental enrichment on the development of the CNS, Rosenzweig (1965) described an increase in dendritic arborization and an overall increase in cortical weight in the brains of animals raised in environments of substantially greater surface area and environmental complexity. In the deer mouse model inhibitory control of motor pathways may be disrupted due to housing the animals in the more restrictive standard cages. In relation to stereotypy, an enriched environment may enable higher brain structures to develop more

fully and provide the appropriate inhibitory control over areas of the brain which would otherwise fall into oscillation. The relative importance of descending cortical pathways which provide feedback inhibition of striatal and limbic areas, could potentially be addressed using deer mice as a model of stereotypy. Indeed, 6-OHDA lesions of prefrontal increase DA activity in striatum and nucleus accumbens (Pycock, Carter & Kerwin, 1980). Focusing on a rodent model of spontaneous stereotypy which appears to have a variety of similarities between other spontaneous stereotypies in animals and in humans may provide us with a means to address some of these questions.

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BIOGRAPHICAL SKETCH

The candidate was born at Emory hospital in Atlanta, Georgia, to Clabron and Rick Powell. She has two sisters, Beth and Laura, and two brothers-in-law, Robbie and Jim. She attended Dunwoody High School and then went on to college at the University of North Carolina - Chapel Hill. She graduated from UNC with a degree in psychology with honors. At UNC she conducted research with Drs. Mark Lewis and Louis Gariépy on post-partum aggression in mice from lines selectively bred for aggressive behavior. She then went to work at Western Carolina Center in Morganton, NC, where she began her work on stereotypic movement disorder in individuals with mental retardation with Dr. Lewis and Dr. Jim Bodfish. After traveling for several months both abroad and within the U.S., she packed her bags and headed to Gainesville to begin her studies in psychobiology at the University of Florida. In Gainesville she enjoys sitting on her porch weathering the summer heat, canoeing in the swamps, swimming in the springs, and an occasional bike ride.

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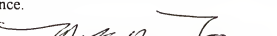

Mark Lewis, Chairman
Professor of Psychology

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Professor of Psychology

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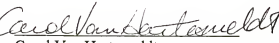

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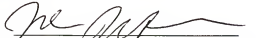

John Petitto
Associate Professor of Neuroscience

This thesis was submitted to the Graduate Faculty of the Department of Psychology in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Master of Science.

August, 1997

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Dean, Graduate School