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Ontogeny of Behavioral Arousal:
Genetic and Pharmacological
Manipulations

Gary Remington

Dissertation presented to
the Faculty of Graduate Studies
of Carleton University
in partial fulfillment of the requirements
for the degree of Doctor of Philosophy in Psychology

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Gary Remington 1977

The undersigned recommend to the Faculty
of Graduate Studies acceptance of the thesis
"The Ontogeny of Behavioral Arousal: Genetic
and Pharmacological Manipulations"

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September, 1977

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I hereby declare that I am sole author of this research. I authorize Carleton University to lend it to other institutions and individuals for the purpose of scholarly research.

Ray J. Remington

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ABSTRACT

A series of six experiments evaluated developmental changes of simple behaviors among six lines of mice selectively bred for differences in locomotor activity. It was observed that general locomotor activity increased in all lines between 15 and 60 days of age. Between the ages of 20-60 days those animals bred for high activity (H_1 and H_2) exhibited higher levels of locomotion than animals bred for low (L_1 and L_2) or control (C_1 and C_2) activity. However, at 15 days postpartum the line differences were not clearly differentiated. In a spontaneous alternation task performance was similarly observed to increase with age, suggesting a developmental gradient for habituation which mimicked that observed for locomotor activity. In contrast, alternation performance was not found to differ between the lines, thus raising the possibility that the line differences were independent of the habituation factor. An analysis of locomotor activity over blocks of trials confirmed this notion. With respect to exploratory behavior, as measured in a head dipping task, the line and age variations closely paralleled the changes observed in locomotor activity. Not only did the High lines exhibit greater exploration than the remaining lines, but the level of exploration was found to increase with age. Of particular note was the fact that the line

differences were not fully expressed until 20 days of age and beyond. Finally, when response inhibition was assessed upon presentation of an air puff it was noted that behavioral suppression was apparent at 20 days and thereafter; however, little effect was seen at 15 days of age. Again these data are consistent with the notion that mechanisms which subserve response inhibition are not fully mature until 20 days of age. Interestingly, when response inhibition was evaluated over a 10 minute period following the last air puff presentation, it was noted that the inhibition observed in the High lines was less marked than it was in either the Low or Control lines.

Taken together, the behavioral experiments suggest, albeit provisionally, that the line differences in locomotor activity might be a reflection of increased exploration on the part of the High lines. Moreover, the developmental changes observed might be attributable, at least in part, to variations in habituation, response inhibition, as well as exploration.

Experiments 5 and 6 evaluated the effects of several dosages of scopolamine and d-amphetamine on locomotor activity and spontaneous alternation/perseveration. It was observed that d-amphetamine treatment increased activity or attenuated the normal decline in activity seen in saline treated mice. While such an effect was apparent at all ages

in the case of d-amphetamine, this was not true of scopolamine. The anticholinergic effectively increased activity or attenuated the decline in activity in all lines at 20 days of age and beyond. However, at 15 days such an effect was apparent only in the High lines and to some degree in the C₁ line. These data imply that the cholinergic system matures earlier in the High lines than it does in the remaining lines. Consequently, at 15 days of age where behavioral inhibition is present in the High lines, owing presumably to the maturity of the cholinergic system, line differences in locomotor activity are not apparent. With cholinergic maturation in the Low and Control lines the response inhibition engendered permitted the expression of the line differences in locomotor activity. This conclusion, it should be noted, is congruent with the non-pharmacological data indicating that line differentiation for exploration and response suppression was not evident at 15 days of age.

Finally, with respect to the drug effects on alternation it was observed that d-amphetamine caused perseveration in all lines and at all ages. Scopolamine, on the other hand, was not found to produce a perseverative tendency, although it effectively decreased levels of alternation. The latter effect was found to be both line and age dependent. In both High lines the reduction in alternation by scopola-

mine was apparent as early as 15 days postpartum, whereas in the Low lines the reduction in alternation was not in evidence until 20 days of age. As in the case of locomotor activity, an intermediate effect was seen in the Control lines. Once again, these data were taken to suggest that the cholinergic system matures earlier in the High lines than it does in the Low lines.

The data were discussed in terms of those factors, both behavioral and neurochemical, which might subserve the line and age differences in arousal. It was suggested that variations in cholinergic and catecholaminergic activity might modify factors such as exploration, response inhibition, attentional and reinforcement mechanisms. As such, these factors deserve further consideration in accounting for age dependent changes in activity and hyperactivity. Finally, it was suggested that the use of strains or lines which differ in various behavioral capacities might effectively be employed as a tool in the evaluation of hyperactive syndromes, although the present investigation was only marginally successful in this respect.

FIGURE CAPTIONS

- Figure 1. Mean transformed ($\sqrt{x + 0.5}$) levels of locomotor activity as a function of Line and Age.
- Figure 2. Mean transformed ($\sqrt{x + 0.5}$) levels of locomotor activity as a function of Line, Age and Trial.
- Figure 3. Mean proportion of alternation responses as a function of Line and Age.
- Figure 4. Mean number of total head dip responses as a function of Line and Age.
- Figure 5. Mean number of non-repetitive head dip responses as a function of Line and Age.
- Figure 6. Mean proportion of head dip responses as a function of Line and Age.
- Figure 7. Mean locomotor activity during inter-air puff intervals as a function of Line, Age and Air Puff over six minute Intervals.
- Figure 8. Mean locomotor activity during the 10 minute post-air puff interval as a function of Line, Age and Air Puff over two minute Intervals.
- Figure 9. Mean locomotor activity during the 10 minute post-air puff interval as a function of Line and Air Puff over two minute Intervals.

Figure 10. Mean transformed ($\sqrt{x + 0.5}$) locomotor activity as a function of Line, Age and Drug over Blocks of five minutes. The various figures represent 15, 20, 25, 30 and 60 day old animals.

Figure 11. Mean proportion of alternation responses as a function of Line, Age and Drug Treatment.

Evidence derived from anatomical and pharmacological studies has indicated that considerable development of the central nervous system (CNS) occurs postnatally (Coyle, 1974; Eiduson, 1971; Himwich, 1973; Jackson, 1931; Kim, Choi, Kim, Chang, Park & Kang, 1970; Moorcroft, 1971). For example, while marked organization and proliferation of neurons takes place prenatally, very rapid growth and development of synaptic junctions occur in cortical and subcortical areas in the rat and mouse brain during the third and fourth postnatal weeks (Aghajanian & Bloom, 1967; Loizou, 1972). In addition, the first three weeks postpartum have been shown to represent particularly rapid periods of dendritic growth in these species, with the rate of maturation declining thereafter (Pscheidt and Himwich, 1966). Similarly, the maturation of various aspects of neurotransmitter systems appears to approximate the sequence of synaptic development, since the storage and release of endogenous chemicals are directly related to presynaptic functioning (Axelrod, 1970). Indeed, several investigators (e.g., Keller, Bartholini & Pletscher, 1973; Lander & Bloom, 1974; Loizou, 1971; Loizou & Salt, 1970) have identified increased levels of brain monoamines in close temporal proximity to the proliferation of axon terminals of monoamine containing neurons. Of course, the precise nature of the growth is species dependent, with precocial organisms, such as the guinea pig (Bennett & Giarman, 1965) and chick

(Pscheidt & Himwich, 1966), demonstrating greater prenatal development than that seen in altricial organisms such as the mouse and rat (Eiduson, 1971).. Similarly, it appears that genetic differences occur with respect to the maturation of different brain pathways despite the fact that the strains in question exhibit comparable gestation periods (Abeelen, 1970, 1974; Diez, Sze & Ginsburg, 1976; Ebel, Hermetet & Mandel, 1973; Oliverio, 1974; Mandel, Ebel, Mack & Kempf, 1974; Tunnickliff, Wimer & Wimer, 1973; Wahlsten, 1974, 1975).

The finding that extensive development occurs in the CNS during the maturational process takes on considerable importance in light of the extensive data associating various behaviors with adequate neurotransmitter functioning (Carlton, 1969; Feigley, 1974; Mabry & Campbell, 1973; Moorcroft, Lytle & Campbell, 1971; Remington & Anisman, 1976). Thus, the development of such behaviors may be seen as reflecting the maturation of appropriate neurochemical system(s). Indeed, recent findings concerning behavior/neurochemical relations have emphasized that behaviors once assumed to be mediated by a single neurotransmitter, are in fact subserved by a balance between several neurochemical systems (see for example reviews by Anisman, 1975; Antelmann & Caggiula, 197 ; Domino & Davis, 1975; Richardson, 1974). Accordingly, the presence of a behavior in an immature organism does not necessarily assure that the associated neurochemical systems are fully

intact. Rather, as maturation advances towards the neurochemical balances representing functional maturity, qualitative changes in the nature of the behavior may be apparent. One such balance system which appears to influence a number of behaviors involves catecholaminergic and cholinergic pathways (cf. Anisman, 1975, 1977; Carlton, 1965, 1969; Mabry & Campbell, 1973), and will be dealt with extensively in later sections. Suffice it to say at this point that the cholinergic system, which appears to have an inhibitory effect on behavior develops more slowly postnatally than the catecholaminergic system which produces behavioral excitation (Anisman, 1975; Campbell & Mabry, 1973; Carlton, 1963, 1969; Feigley, 1974; Moorcroft et al., 1971; Remington and Anisman, 1976). Accordingly, behaviors related to the functioning of these pathways (e.g. locomotor activity) reveal changes which approximate the differential rates at which these transmitters develop. As such, simply recording a given behavior through postnatal development may offer an indirect method for assessing the maturation of those neurochemical systems thought to subserve the behavior in question.

When behaviors are examined following particular drug treatments which are thought to influence certain neurochemical systems, considerably more information is gained with respect to neurochemical/behavior relations, as well as the ontogeny of the neurochemical systems. Increased knowledge concerning neurotransmitters and the enzymes involved in

their synthesis and degradation has led to the development of a variety of pharmacological agents which modify ongoing neurochemical activity via either pre- or post-synaptic action (Anden, Strombom & Svensson, 1973; Carlton, 1962; 1963, 1969; Herman, 1975; Mabry & Campbell, 1973; Marsden & Curzon, 1976; Pijnenburg, Honig, van der Hyden & van Rossum, 1976; Strombom, 1975, 1976). The use of such treatment procedures has been of considerable importance since they have yielded data concerning (a) the neurotransmitters which subserve given behavioral repertoires, (b) differentiation of central and peripheral contributions of these transmitters in mediating the behavior, and (c) the possible interactions between neurochemical systems. Moreover, from the developmental vantage the pharmacologic method may be employed in order to delineate those systems which are functional at a specific time in the maturational process. For example, given that a drug is known to affect behavior in the adult organism, lack of response during development may imply functional immaturity in the related neurochemical system(s). The numerous studies which have incorporated this procedure (see Section III: Ontogeny of Behavior) attest to its importance in linking behavioral development with structural/neurochemical maturation at the central level.

While the present paper rests within the confines of animal research, it would seem propitious if at least some of the implications of developmental neurochemical changes were

discussed. There now exists an abundance of data concerning the human hyperkinetic syndrome which suggests a neurochemical component in this behavioral disorder (see review in Grinspoon & Singer, 1973; Lambert, Windmiller, Sandoval & Moore, 1976; Millichap & Fowler, 1967; Shetty & Chase, 1976; Wender, 1971, 1974). In light of these findings, the information which has been gained from the animal literature regarding neurochemical correlates of development merits consideration for several reasons. First, the rapid neurochemical changes which take place postnatally in the rat and mouse (Coyle, 1974; Coyle & Axelrod, 1972a, b; Coyle & Henry, 1973; Lamprecht & Coyle, 1972; Porcher & Heller, 1972) parallel a period of marked change in ongoing activity, viz: increased activity to approximately three weeks of age, followed by a decline toward adulthood (Campbell & Mabry, 1973; Campbell, Lytle & Fibiger, 1969; Fibiger, Lytle & Campbell, 1970; Mabry & Campbell, 1973; Moorcroft, 1971; Remington & Anisman, 1976). The possibility of this transient period of hyperactivity being modulated by a neurochemical imbalance has, in fact, been supported by numerous pharmacological studies (Campbell et al., 1969; Fibiger et al., 1970; Mabry & Campbell, 1973; Remington & Anisman, 1976). Second it is noteworthy that psychostimulant drugs, such as d-amphetamine, produce the same results in this instance i.e. a decline in activity, as they do in human hyperkinetic syndromes (Remington & Anisman, 1976).

Finally, efforts have been made to formulate an animal model of hyperactivity based on a neurochemical component (Campbell & Randall, 1975; Glick & Milloy, 1973; Hitzemann, Hitzemann, Brace & Loh, 1976; Shaywitz, Yager & Klopfer, 1976). While certain of these models have been criticized on theoretical grounds (see for example Pappas, Ferguson & Saari, 1976), they do suggest that animal data may serve to explain, at least in part, the nature of the human hyperkinetic syndrome.

The following sections of the introduction represent an overview of the various literatures which pertain to behavioral/biochemical correlates during development. Section I deals with the morphological and pharmacological data concerning the ontogeny of monoaminergic and cholinergic pathways. As such, their development will be delineated through the pre- and postnatal stages of development, with emphasis being placed on the first few weeks of maturation after birth.

The contents of Section II concentrate on the neurochemical correlates subserving a number of behaviors, including locomotor activity, reactivity to novel stimuli, exploration, and habituation. An attempt will be made at this point to elucidate the major neurotransmitters involved in each behavior, and to articulate the nature of their role in behavior modulation i.e. response initiation, response suppression, and so on. It is important to realize that in formulations derived from animal models, it is not sufficient to draw

conclusions based on restricted behavioral changes. In particular, it is now well documented that drug effects may vary, owing to what may seem to be subtle variations of the task (Bignami, 1977; Williams, Hamilton & Carlton, 1974, 1975). Indeed, it is necessary to determine the nature of a given treatment across a wide range of behaviors which bear common features. Accordingly, Section III emphasizes the drug profiles (i.e., the similar and dissimilar behavioral changes) accrued when different response outputs are examined.

Sections I and II are presented in order to familiarize the reader with patterns of neurochemical development, and the relation various transmitters have with certain behaviors. With this in mind, Section III is devoted to the development of behavior and the effects of different pharmacological treatments during maturation. The goal of this section is to delineate the parallels between the ontogenetic changes in a given behavior and the drug effects thereon, thereby providing prima facie evidence implicating certain behavioral/neurochemical relations.

If a model for hyperactivity is to be derived from animal research then it is necessary to demonstrate that a particular drug treatment may differentially affect behavior depending on the characteristic response patterns seen in the absence of drug treatments. As indicated previously, one such method is the induction of a hyperactive response via

chemical treatments. An alternative approach is that of using mice which exhibit different response profiles owing either to inbreeding or selective breeding procedures. Section IV presents a limited survey of research concerning genetic and ontogenetic variations in locomotor activity, neurochemical levels and activity, and drug-induced behavioral changes.

The introduction closes with Section V: Models of Hyperkinesis, a topic which necessitates the integration of animal and human data. It should be emphasized, however, that while the notions expounded in this paper may be relevant to the human hyperkinetic syndrome, the present experiments are not meant to promote an analogue for hyperkinesis. At this time, one can only indicate where the animal models bear similarity with the human syndrome. The fact that certain similarities exist has already been indicated, and what remains is to define more explicitly the contributions of the animal models to current formulations regarding the hyperactive syndrome. As might be expected, the emphasis here will be placed on the possible role an animal model may play with respect to the further clarification of biochemical factors in human hyperkinesis.

I. MORPHOLOGICAL DEVELOPMENT:
BIOCHEMICAL AND BEHAVIORAL CORRELATES

As indicated earlier, considerable CNS development in the mouse and rat occurs postnatally (see General Introduction). In light of the degree of neural maturation which occurs in the first few weeks following birth, it would seem reasonable to assume that related neurochemical activity must also reveal marked development during this time period. As such, behaviors which are assumed to be subserved by particular neurochemical systems should reflect the degree of maturation of these systems and their related anatomical structures. In short, an attempt to correlate anatomical, biochemical, and neurophysiological changes with the development of specific behaviors should aid in clarifying the systems involved in a certain behavioral function, and should indicate the contribution of these systems at various postnatal stages (Himwich, 1962, 1973). From a developmental standpoint then, it is not enough to merely postulate that certain neurochemical systems subserve certain behaviors. Rather, the process seems only to start at this point, and requires that further information be gained with respect to (a) the development of neuroanatomical structures related to a given transmitter, (b) developmental changes in levels and activity of the neurotransmitter as well as the substrates and associated enzymes for its meta-

bolism and catabolism, and (c) maturational changes in the specified behavior. It is to points (a) and (b) that the present section is addressed.

Before dealing with the specific development of the monoaminergic and cholinergic neurotransmitter systems, several more general statements should be made concerning the nature of morphological development in the rat and mouse. Unlike the development of the peripheral nervous system, which follows a proximo-distal and cephalo-caudal pattern, numerous studies have indicated agreement with the Jacksonian model of brain organization (Coyle, 1973; Jackson, 1931; Moorcroft, 1971). That is, there exists a caudal-rostral gradient of brain development with the higher (rostral) regions developing more slowly than the lower (caudal) regions (Eiduson, 1971; Kim et al., 1970; Moorcroft, 1971). Moreover, it has been postulated that the caudal-rostral pattern of CNS maturation has a specific influence in the development of ongoing activity due to patterns of neurochemical distribution. Specifically, it has been reported that rostral structures such as the caudate putamen, septum, hippocampus and amygdala are rich in ACh (Bird & Aghajanian, 1976; de Feudis, 1974; Hrdina, 1974; Orderfeld-Nowack, Narkiewicz, Wierieszko & Gradkowska, 1976). Indeed, from studies involving acetylcholinesterase (AChE) staining and choline acetyltransferase (ChAT) activities, a "cholinergic limbic system" has been

postulated, arising from or traversing the septal region and innervating the hippocampus and cerebral cortex (de Feudis, 1974; Lewis & Shute, 1967; Shute & Lewis, 1967). In contrast, more caudal areas such as the pons, medulla, locus coeruleus, and hypothalamus are known to be innervated by noradrenergic and/or dopaminergic pathways (Iversen & Iversen, 1975; Livett, 1973). Areas between these structures, such as the caudate putamen, contain large amounts of both acetylcholine and dopamine (Cooper, Bloom & Roth, 1970).

From a behavioral standpoint, it has been postulated that while central cholinergic mechanisms have an inhibitory effect upon ongoing activity, catecholamines produce an excitatory influence (see for example Anisman, 1975; Carlton, 1963, 1969). Based on these data, the suggestion has been made that the inhibitory cholinergic system may act, either in an additive or synergistic manner, with the excitatory catecholaminergic system (Anisman, 1975; Campbell & Mabry, 1973; Carlton, 1963, 1969; Fiegley, 1974; Moorcroft et al., 1971; Remington & Anisman, 1976). Moreover, the pattern of CNS development is such that the catecholaminergic mechanisms precede the cholinergic system in maturation, with changes in behavior i.e. locomotor activity, reflecting the retarded cholinergic development.

To this point, the discussion of transmitters has been restricted to the development of catecholaminergic and

cholinergic-mediated structures, and the possibility that they may function in some interactive fashion. However, it is noteworthy that other neurochemical systems have been linked to the mediation of behaviors relevant to the present paper. More specifically, it has been hypothesized that serotonin may play an integral role in a number of behaviors, including locomotor activity (Curzon & Marsden, 1975; Geyer, Puerto, Menkes, Segal & Mandell, 1976; Hollister, Breese, Kuhn & Cooper, 1976; Mabry & Campbell, 1973; Marsden & Curzon, 1976; Swonger & Rech, 1972), and reactivity or habituation to a startle response (Aghajanian & Sheard, 1968; Carlton & Advokat, 1973; Swonger, Chambers & Rech, 1970). In terms of regional distribution, 5-HT-containing neurons are located in the nuclei of the raphe system (Iversen & Iversen, 1975), just anterior to the locus coeruleus in the brain stem (cf. Sidman, Angevine & Taber-Pierce, 1971). Within the caudal-rostral framework of CNS development, this system lies between the noradrenergic pathways of the pons-medulla region and the more rostral forebrain cholinergic structures. Behaviorally, it has been demonstrated that serotonin may have an inhibitory effect upon ongoing activity (Geyer et al., 1976; Hollister et al., 1976; Kostowski, Giacalone, Garattini & Valzelli, 1968; Marsden & Curzon, 1976; Swonger & Rech, 1972), and that during ontogenesis the modulating effects of this serotonergic inhibitory system are observed subsequent to catecholaminergic influences (Mabry & Campbell, 1973), but prior to cholinergic

effects (Campbell et al., 1969; Fibiger et al., 1970;

Moorcroft, 1971). Based on the evidence concerning regional distribution of the catecholamines, serotonin, and acetylcholine, it would appear that the sequence of caudal-rostral morphological development supports these behavioral data.

That is, the ontogenesis of behavioral arousal reflects the maturation of catecholaminergic, serotonergic, and cholinergic systems in that particular order, an order which is similarly followed in neuroanatomical/biochemical development.

It is clear from the previous paragraphs that neuroanatomical development traces a clearly defined pattern of maturation, and for the mouse and rat a considerable amount of this growth occurs postnatally. Moreover, it appears that changes occurring in anatomical/biochemical development postnatally can be associated with specific changes in behavior as the organism matures.

II. THE ONTOGENY OF MONOAMINERGIC, CHOLINERGIC, AND SEROTONERGIC SYSTEMS

A. Norepinephrine and dopamine

It has been demonstrated that forebrain innervation of NE terminals originates from cell body groups located in the pons and medulla (cf. Iversen & Iversen, 1975). From the locus coeruleus, a region rich in NE, one branch innervates the cerebellum, while a second bundle of NE fibres (the dorsal tract), travels rostrally into the cortex and hippocampus. In contrast, a ventral tract innervates the hypothalamus, basal forebrain, and parts of the limbic system, merging briefly with dorsal fibres in the medial forebrain bundle. Finally, fibres from the region of the medulla oblongata also descend to the spinal column, terminating in the lateral column.

Two major dopaminergic pathways have been documented in the CNS (Ungerstedt, 1974), and it is noteworthy that these systems lie principally in the midbrain anterior to the NE cell bodies (Iversen & Iversen, 1975). From the zona compacta of the substantia nigra, the nigrostriatal DA system traverses the lateral medial forebrain bundle (MFB) and the hypothalamus, fanning out in the globus pallidus and finally terminating in the nucleus caudatus-putamen i.e. the striatum.

The cell bodies of the mesolimbic DA system originate dorsally and laterally to the interpenduncular nucleus, with axons ascending medial to the substantia nigra and innervating the nucleus accumbens, amygdala, olfactory tubercle, and some areas of the cortex. A third small group of DA cells, located in the arcuate nucleus of the hypothalamus, consists of short axons which terminate in the median eminence.

There is little question that appreciation of neuronal pathways serves a beneficial purpose in elucidating their respective roles in a given behavior. However, it remains that these pathways reflect adult development, with various stages during ontogenesis revealing marked differences in cellular development, as well as neurochemical and enzymatic activity. Indeed, in the mouse and rat there appears to be a considerable amount of change at the cellular level both pre- and postnatally. For example, it has been reported that catecholamine-induced fluorescence in the rat locus coeruleus can be observed as early as 14 days following gestation, while DA neurons appear at 18 days post gestation in the midbrain and early postnatally in the hypothalamus (Coyle, 1974). While these data support the caudal-rostral pattern of development, Loizou (1972) has noted that at birth DA-containing pathways appear more developed than those containing NE or 5-HT. In addition, it seems that terminal proliferation occurs at different rates depending on the brain region under examination.

Specifically, at birth a paucity of NE terminals is observed, although scattered groups of DA terminals may be seen in the caudate nucleus. Norepinephrine terminals attain adult levels of fluorescence and intensity in the pons-medulla by two to three weeks postpartum, and by three to four weeks in more rostral regions. In contrast though, maximum DA terminal fluorescence in the striatum does not occur until four weeks after birth. In addition to showing that central NE levels reach adult values prior to DA (Coyle, 1974; Kellog & Lundborg, 1973; Loizou, 1972; Loizou & Salt, 1970), these data suggest that noradrenergic neurons undergo a more rapid maturational process. Moreover, the lack of maturation in both systems during the first few weeks postnatally has led to the suggestion that the initial low levels of these amines are, in part, due to lack of neuronal development and a subsequent inability to store newly synthesized NE and DA (Karki, Kuntzman & Brodie, 1962; Lanier, Dunn & Hartesveldt, 1976; Loizou & Salt, 1970). More specifically, with neuronal immaturity there is a shortage of synaptic vesicles which are necessary for the storage of neurotransmitters (Lanier et al., 1976). Indeed, it has been hypothesized that the newborn rat possesses only 5% of the presynaptic endings observed in the adult organism (Ganatco, Autilio-Gambetti, Gambetti & Shafer, 1971). Moreover, few of these endings contain synaptic vesicles, as illustrated by the finding that only 10% of rat brain stem synaptosomes contain synaptic vesicles, although this

figure rises to 80-90% in the adult (Hervonen, Kanerva, Fissari & Suurhasko, 1974).

Catecholamine-induced fluorescence is frequently employed to assess degree of axonal and terminal development under the assumption that the presence of a particular transmitter is related to the functional maturity of its related enzymes (see for example Coyle, 1974; Coyle & Henry, 1973; Keller, Bartholini & Pletscher, 1973; Lamprecht & Coyle, 1972). It has been found that distribution of enzymatic activity is directly related to development, migration, and synaptogenesis. Thus, for example, while tyrosine hydroxylase (TH) activity shows an approximate increase of 50% in the pons-medulla from birth to adulthood, its activity levels increase approximately 600% during the same time period in the cerebral cortex (Coyle, 1974; Coyle & Axelrod, 1972a). Similarly, although dopamine- β -hydroxylase (DBH) activity is largely concentrated in the pons-medulla prenatally, this region ultimately represents only 20% of the whole brain activity for this enzyme (Coyle, 1974; Coyle & Axelrod, 1972b). With respect to dopa decarboxylase (DD), the pons-medulla region reveals approximately a twofold increment in activity from birth to adulthood; in contrast, the striatum undergoes over a 700% increase within this interval (Lamprecht & Coyle, 1972). It thus appears that a specific shift in enzymatic activity occurs in the CNS during development; a shift which is directly related to the caudal-rostral pattern of neuroanatomical

development. More specifically, this enzymatic translocation has been interpreted as a transition from caudal regions, concentrated with CA cell bodies, to areas more rostrally which are made up largely of terminals of CA neurons (Coyle & Axelrod, 1972a, b; Lamprecht & Coyle, 1972; Porcher & Heller, 1972). This notion is further substantiated by studies assessing the subcellular distribution of various enzymes. For example, fractionation of the fetal brain shows tyrosine hydroxylase to be concentrated in the supernatant, suggesting that the enzyme is not localized within the terminals. In contrast, TH largely sediments with the synaptosomes in fractionation of the adult brain, supporting the hypothesis that it is localized within the terminals in the mature organism (Coyle, 1972).

It is noteworthy that increased synaptogenesis during development is reflected by several other intracellular activities. For example, Coyle and Axelrod (1971) reported that although the high-affinity uptake system for NE is apparent in homogenates from the whole rat brain at 18 days gestation, the capacity to take up NE undergoes a 100-fold increase before maturation is complete. In addition, it has been shown that the subcellular distribution of ^3H -NE changes during development, with a progressive increment (300-fold between 18 days gestation and adulthood) in the amount of ^3H -NE identified in the synaptosomal fractions (Coyle & Snyder, 1969).

Based on these data, which reveal a simultaneous increment in uptake and synaptosomal ^3H -NE, it has been postulated that uptake may provide a valid indicant of NE terminal outgrowth (Coyle, 1974; Nomura, Naitoh & Segawa, 1976).

To this point, the discussion of NE and DA development has largely been confined to temporal-spatial changes in enzyme/transmitter distribution as a function of neuronal development, i.e. terminal proliferation and so on. However, in addition to this area of study, it is worthwhile reviewing those investigations which assess development of the catecholaminergic systems at a more general level, i.e. changes in regional and whole brain levels during maturation. The primary advantage served by this approach involves the opportunity to assess the sequence of development of the CA pathways through the simultaneous comparison of both enzyme and transmitter levels during pre- and postnatal growth. With respect to developmental changes of brain enzymes, close coordination of the increases between TH, DD, and DBH has been observed both pre- and postnatally (Coyle, 1974; Coyle & Axelrod, 1972a, b; Lamprecht & Coyle, 1972; Porcher & Heller, 1972). However, total activity for NE has been shown to lag behind the development of these enzymes until approximately 35-40 days following birth (Coyle & Axelrod, 1972; Lamprecht & Coyle, 1972). More specifically, at 15 days of gestation levels of DA and NE represent only 2% of adult levels, whereas their respective

biosynthetic enzymes have specific activities of approximately 10% of the adult brain. This has led to the suggestion that the pattern of enzymatic activity during development does not necessarily reflect levels of the related neurotransmitters. That is, it appears that these enzymes are not saturated during the initial stages of morphogenesis, but represent levels well in excess of those required for the synthesis of the existing catecholamines. As previously indicated, it is assumed that the low NE and DA levels are a consequence of the lack of vesicular storage during the early stages of development (Karki et al., 1962; Lamprecht & Coyle, 1972; Loizou & Salt, 1970; Lanier et al., 1976). However, it has been shown that a parallel in enzyme/transmitter development does occur, but is dependent upon the brain region under examination. Indeed, Porcher and Heller (1972) have reported that although catecholamines and their related biosynthetic enzymes develop concurrently in the forebrain, a dissociated pattern of development is apparent in regions of the brain stem. To account for these data, it has been postulated that the more caudal brain stem regions represent an area which supplies both biosynthetic enzymes and amine storage granules. Accordingly, a lack of parallelism in enzyme/transmitter development in these regions may merely indicate the retardation in development of the amine storage vesicles (Anden, Dahlstrom, Fuxe, Larson, Olson & Ungerstedt, 1966; Porcher & Heller, 1972). In contrast, in rostral areas of the brain which constitute primarily a proli-

feration of catecholamine nerve-endings, a simultaneous maturational pattern for both the enzymes and related transmitters is witnessed.

While developmental aspects of DA, NE and their biosynthetic enzymes have been discussed, the maturation of the enzymes responsible for the degradation of these neurochemicals needs to be considered as well. The major enzymes responsible for the metabolic degradation of the catecholamines include monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) (cf. Cooper, Bloom & Roth, 1970). Although MAO is usually considered an intraneuronal enzyme, it occurs in significant quantities extraneuronally (Cooper et al. 1970). In contrast, it has been suggested that COMT's metabolic action is primarily extraneuronal e.g. synaptic cleft (see for example Schildkraut, 1972). In terms of the development of MAO, both biochemical and histochemical evidence support the finding that the enzyme is localized in monoaminergic neurons at the time of birth (Loizou, 1972). Unlike the guinea pig, which is precocial in its development and reveals almost equal levels of brain MAO between birth and adulthood, the rat brain shows considerable increases during the first weeks of postnatal growth. There appears to be a certain degree of conflict with respect to enzyme levels just following birth. Levels of MAO activity in the brain have been reported as low as 15% one week postpartum (Vaccari, Maura, Marchi & Cugara, 1972), or as high

as 29-38% of adult levels at the time of birth (Bennett & Giarman, 1965; Karki, Kuntzman & Brodie, 1962; Kurzepa & Bojanek, 1965; Porcher & Heller, 1972). The finding that the maturation of MAO develops rapidly during the first two weeks postpartum has generally been supported (Bennett & Giarman, 1965; Kurzepa & Bojanek, 1965; Nachmias, 1960), in that adult levels of the enzymes are attained at approximately 15-20 days following birth (Baker, Hoff & Smith, 1974; Porcher & Heller, 1972). It is worthwhile noting that Eiduson (1972) has reported that within these two weeks of maximal increase in brain MAO, peak activity occurs at around 15 days postnatally, a period which parallels the time which is assumed to represent the greatest elevation in catecholaminergic levels (Campbell et al., 1969; Mabry & Campbell, 1973). Congruent with the decline of catecholamines from this stage to weaning, MAO activity appears to follow a similar decrease towards adult levels. It has been shown, however, that MAO activity does not reveal a parallel pattern of development throughout the brain, but rather matures according to distinct regional differences (Baker et al., 1974; Porcher & Heller, 1972; Robinson, 1968). It would appear to be the case that in more caudal regions, such as the pons-medulla, a more rapid maturation in the levels of MAO occurs (Porcher & Heller, 1972), suggesting that this enzyme also follows a caudal-rostral gradient of maturation.

It is unfortunate that virtually nothing has been reported concerning the developmental aspects of COMT activity at a central level. Unquestionably, one factor contributing to this paucity of data stems from the lack of knowledge pertaining to inhibitors specific to COMT. In contrast, the availability of various MAO inhibitors has led to a number of pharmacological studies which have attempted to assess indirectly the development of MAO activity in the brain. These studies will be further elucidated in a section devoted to the influence of drugs during neurotransmitter maturation. Returning to data available on COMT however, a single study has indicated that this enzyme is found at very low levels during the initial stages of postnatal development (Agrawal, Glisson & Himwich, 1966).

B. Acetylcholine (ACh)

The work of Shute and Lewis (1967) offers the most comprehensive description of cholinergic distribution within the CNS. These authors have employed an AChE-staining technique as an indirect method of determining cholinergic pathways throughout the brain. On the basis of this work, it was suggested that the forebrain in the rat is innervated by at least two cholinergic pathways. The first, the dorsal tegmental pathway, stems from the region of the nucleus cuneiformis in the mesencephalic reticular formation and branches in the

tectum, pretectal area, geniculate bodies and thalamus. The second system, or the ventral tegmental pathway, arises from the substantia nigra and ventral tegmental area of the mid-brain and ascends to areas of the basal forebrain; additional cholinergic neurons project from these regions to all areas of the cerebral cortex and olfactory bulb. It must be noted at this point that although there exists a reasonable correlation between ACh, ChAT and AChE in all brain regions (Hrdina, 1974), AChE itself may be found within cell membranes of neurons which are only innervated by cholinergic fibres (Iversen & Iversen, 1975). Thus, for example, noradrenergic cell bodies of the locus coeruleus reveal a substantial staining for AChE, suggesting that this region is innervated by cholinergic fibres. The finding that AChE may appear within the neurons which simply receive cholinergic input indicates that evidence other than that accumulated through AChE-staining procedures should be assessed in order to delineate cholinergic pathways precisely. In a recent review which incorporates studies evaluating ACh levels within the various brain regions via a number of different techniques, Hrdina (1974) noted that areas which reveal the highest ACh values include the hippocampus, striatum and caudate nucleus. It is worth noting, however, that the values recorded show considerable variability depending on the method of sacrifice and the histological technique employed.

In terms of anatomical development, structures which have been associated with high levels of ACh (i.e. hippocampus, striatum and caudate), are located more rostrally in the CNS than regions considered to be rich in NE, e.g. pons-medulla and locus coeruleus. The fact that CNS development occurs in a caudal-rostral pattern need not be reiterated. However, a number of studies have been carried out in order to investigate changes in ACh as well as its related enzymes during maturation. Accordingly, these reports will be reviewed here without emphasis on the pattern of neurochemical development.

In terms of choline, a substrate necessary for the synthesis of ACh, it has been demonstrated that the neonatal brain contains concentrations of this chemical in excess of adult values (Ladinsky, Consolo, Peri & Garattini, 1972), suggesting that more than enough of the substrate is present from birth for the synthesis of ACh. It further appears that acetyl coenzyme A (Acetyl CoA), a second substrate necessary in the synthesis of ACh, occurs in abundance in both the immature and mature organism (Lanier et al., 1976). However, while concentrations of choline may be high from birth, a progressive increase of choline uptake occurs across developmental ages. This increase appears to be directly related to the morphogenesis of given cholinergic pathways. Consider, for example, the corpus striatum which contains both nerve cell bodies and terminals (McGeer, McGeer, Fibiger & Wickson,

1971) and the hippocampus which appears to be largely composed of nerve terminals emanating from the septum (Sorimachi, Miyamoto & Kataoka, 1974). In the corpus striatum a progressive increase in choline uptake from birth to adulthood is noted, while the hippocampus reveals a marked increment up to 10 days, after which a relatively slow increase of uptake is apparent. These data suggest, albeit speculative, that the lag in hippocampal choline uptake development from 10 to 40 days may reflect a period of growth in which synaptogenesis is taking place, thus resulting in slower maturation of the uptake process.

The morphological differences which appear to hold true for the development of choline uptake mechanisms in the maturing brain also seem to apply to the maturation of ChAcT, the enzyme responsible for the metabolism of ACh from AcetylCoA and choline. It is clear that levels of this enzyme are low in the neonatal organism. Ladinsky et al., (1972) reported levels of ChAcT activity in the neonatal rat to be 7% of adult values, while Van den Berg (1974) noted levels in the developing neonate of approximately 20% of those seen in adulthood. Increases in ChAcT concentration not only appear to be integrally involved with developmental age, but also across brain regions. For example, keeping in mind the anatomical differences specified for the corpus striatum and hippocampus, it has been reported that in the former choline uptake and increases

in ChAcT activity progress in a parallel fashion. This is not true of the hippocampal region, however, where levels of ChAcT activity lag behind the developmental increase in choline uptake. It has been suggested that the retardation of the ChAcT increase in the hippocampus represents the time lag required for transmission of this enzyme, via axoplasmic transport, from nerve bodies in the septum to terminals in the hippocampal region (Sorimachi et al., 1974).

Having reviewed the maturational aspects of the substrates and enzymes responsible for the synthesis of ACh, it is necessary to evaluate developmental changes in the transmitter itself, as well as the enzymes involved in its degradation. Little work has been carried out concerning developmental changes. Indeed, in a recent review Lanier et al., (1976) noted the inconsistencies in the small amount of data accumulated to date. Concentrations of whole brain ACh, for example, have been reported to vary from 25% to 57% according to the assay technique employed (the former figure represents the results of a bioassay, and the latter is the product of a chemical assay) (Mann, Pleul & Kewitz, 1971; Welsch & Hyde, 1944). While adult levels of ACh have been reported by 30 days postnatally (Ladinsky et al., 1972), there appears to be distinct regional differences in the pattern of neurotransmitter maturation. Specifically, utilizing a bioassay procedure, Brus, Zelinski and Gupta (1975) noted that in the first weeks of birth, more caudal regions (i.e. pons-medulla) revealed the highest

content of ACh. However, towards the end of the third post-natal week, a rapid increase in more rostral regions such as the midbrain was apparent. It is noteworthy that while areas such as the midbrain and thalamus/hypothalamus began to level off by the third week of life, other regions (pons-medulla and cerebral hemispheres) showed progressive decreases over time, such that their content was significantly below that of the midbrain and thalamus/hypothalamus by 15-18 months.

Finally, there are several points worthy of consideration with respect to AChE, the enzyme responsible for the degradation of ACh. It would appear that the activity of this enzyme is integrally related to the stage of neural development, but regional differences are fairly dramatic. For example, hippocampal levels of AChE seem to be directly related to the degree of intact fibre connections between the medial septum and the hippocampus itself (Mellgren, 1973; Mellgren & Srebro, 1973). Thus, enzyme activity in the hippocampus has been taken as a reflection of septo-hippocampal neural development and the functional maturity of this system. However, Mellgren (1973) indicated that while AChE activity within the hippocampus seems technically differentiated by 22 days postnatally, further increases have been observed thereafter, suggesting that increments in AChE activity may take place after the apparent neural maturation of a system. At the level of the neostriatum, Hattori and McGeer (1973) noted that maximum increases in synaptogenesis occur between 13 and

17 days following birth in the rat, a time period which is similarly marked histochemically by a transition from islands of enzyme activity to a diffuse, homogeneous staining. Further attempts to map AChE development have led Butcher and Hodge (1975) to postulate that the neostriatum is functionally mature by 30 days postpartum, a time which represents even staining for AChE within the caudate putamen.

It is noteworthy that the presence of AChE activity, like other neurotransmitter-related enzymes, appears to follow an intraneuronal shift during the maturational process. Accordingly, although microsomal AChE activity is greater than synaptosomal activity throughout development and adulthood, a shift occurs during the first weeks of development, such that a decrease in microsomal activity and an increase in the synaptosomal fraction is seen (Adbel-Latif, Smith & Ellington, 1970; Lanier et al., 1976). These results have led to the hypothesis that synaptosomal AChE represents "functional AChE", while microsomal AChE reflects previously stored transmitter (cf. Lanier et al., 1976). Further to this point, it has been noted that during development and adulthood, brain AChE is about 100-fold more active than ChACT. While it does appear that AChE matures more rapidly than ChAct, the consistent pattern of increased AChE activity suggests that these enzymes cannot be equally distributed within the various brain regions (Van den Berg, 1974).

C. Serotonin (5-HT)

While the experiments carried out in the present paper do not address themselves specifically to the effects of serotonergic alterations on behavior, there is sufficient evidence to suggest that this neurotransmitter cannot be overlooked in explaining the ontogeny of certain behaviors e.g. motor activity (cf. Mabry & Campbell, 1973). As such, it is worth considering the developmental aspects of the serotonergic system in order to gain some insight into the possible involvement it may have in the establishment and maintenance of the behavior repertoire.

Although the investigation of serotonin has not received the same degree of attention as that devoted to the catecholamines, its distribution within the CNS has been fairly well established. Specifically, it has been demonstrated that serotonergic neurons are located in the nuclei of the raphe system (Cooper et al., 1970), a region situated just anterior to the locus coeruleus in the brain stem (cf. Sidman et al., 1971). A portion of the ascending serotonergic fibres from this system have been shown to traverse the median forebrain bundle, and 5-HT neurons innervate a number of forebrain structures including the hypothalamus, amygdala, hippocampus and cortex. In addition, there exists a system of descending serotonergic fibres from the raphe nuclei which terminate in the spinal cord. More recently, it has been

reported that the ascending fibres of the serotonergic system may be subdivided into two distinct pathways (Geyer, Puerto, Dawsey, Knapp, Billard & Mandell, 1976; Herr & Roth, 1976; Jacobs, Wise & Taylor, 1974). One (the 'mesostriatal') consists of fibres originating in the dorsal regions of the raphe nuclei, and rising to innervate the striatum, thalamus, cortex and hypothalamus. In contrast, the second pathway (the 'mesolimbic') involves serotonergic tracts ascending from the medial raphe and terminating predominantly in the hippocampus and septal nuclei.

With respect to 5-HT metabolism, tryptophan and 5-hydroxytryptophan (5-HTP) represent the two substrates necessary for its formation. The first step in the pathway involves the hydroxylation of tryptophan to 5-HTP, and a number of reports have indicated that neonatal tryptophan levels are in excess of those values recorded for adults (Bourgoin, Faivre-Bauman, Benda, Glowinski & Hamon, 1974; Hoff, Baker & Buda, 1974; Tyce, Flock & Owen, 1964). Five-hydroxytryptophan is, in turn, converted to 5-HT. Interestingly, Howd, Nelson & Lytle (1975) reported fetal and neonatal concentrations of tryptophan in the rat brain to be 200-300% higher than adult levels. In addition, it was found that the administration of l-tryptophan to a pregnant female resulted in elevated tryptophan and 5-HT levels in the fetal brain as early as 15 days postconception. These data led to the hypothesis that serotonergic neurons within the fetal brain have the capacity

to synthesize exogenously administered l-tryptophan, although the neuron appears relatively immature.

While little has been reported concerning developmental changes in 5-HTP (cf. Lanier et al., 1976), there have been attempts to assess its action at the neuronal level during various stages of maturation. For example, using tritiated 5-HTP administration, in conjunction with MK-486 (a peripheral decarboxylase inhibitor), Kellog and Lundborg (1972) assessed changes in the concentrations of ^3H -5HTP, ^3H -5-HT and ^3H -5-hydroxyindoleacetic acid (5-HIAA). The increased ^3H -5HIAA levels, the metabolite of 5-HT, supports the hypothesis that the capacity to synthesize 5-HT from an exogenously administered precursor exists from the time of birth. Given the degree of elevation in ^3H -5HIAA in relation to the low concentrations of ^3H -5HT, it was posited that rapid turnover of serotonin occurs within the brain from birth. Moreover, the decrements in ^3H -5HTP from 1 to 21 days postnatally in the brain, suggests that a substantial increase takes place in levels of peripheral decarboxylase during the early stages of development.

An assessment of the enzymes responsible for the metabolism of 5-HT serves to elucidate further the ontogeny of serotonin neurons. Given that tryptophan hydroxylase has been postulated as the rate-limiting step in 5-HT synthesis (Lanier et al., 1976), its pattern of maturation is particular-

ly relevant to levels of serotonin. In fact, investigations of tryptophan hydroxylase have indicated that its development parallels that of 5-HT (Deguchi & Barchas, 1972). Tryptophan hydroxylase levels appear to mature in the caudal-rostral fashion acknowledged for various other central neurotransmitters and their enzymes. At birth, tryptophan hydroxylase in the brain stem represents 30% of adult levels, with maximum increases occurring between 10 and 20 days postnatally, a time when adult values are reached. In contrast, at birth, tryptophan hydroxylase in the cerebral cortex is only 10% of adult values. Adult levels are not obtained until approximately day 30 postpartum. Similar results have been reported by Hoff, Baker and Buda (1974), with pons-medulla tryptophan hydroxylase showing adult levels by day 7 postnatally, although more rostral regions such as the cortex fail to reach adult values until the fourth week after birth.

Unlike tryptophan hydroxylase, the development of 5-hydroxytryptophan decarboxylase (5-HTPD) fails to parallel that of serotonin. More specifically, 5-HTPD reveals a maximum degree of development prenatally, with levels at birth being approximately 68% of adult values (Bennett & Giarman, 1965; Loizou, 1972; Karki et al., 1962). However, shortly after birth a dramatic decline in the enzyme levels occurs towards day 25, followed in turn by a more gradual increase towards adult values (Bennett & Giarman, 1965). With respect to regional changes, Baker, Hoff & Smith (1973) reported that

5-HTPD development takes place in a caudal-rostral fashion. In contrast to the decreases in 5-HTPD activity reported by Bennett & Giarman (1965) in the rat up to day 25, these authors have indicated that in the mouse, enzyme activity increases in all brain regions after an initial period of decline during the first postnatal week. The most rapid elevations occur in the cerebellum and medulla-pons, with maximum activity being attained by two weeks postpartum. However, areas such as the mesencephalon-diencephalon and cerebral hemispheres reveal a more gradual increase, with adult values reported by four and six weeks, respectively.

The ontogeny of 5-HT itself is not unlike the development of the catecholamines, in that each of these neurotransmitters follow a caudal-rostral pattern of maturation. Histofluorescence studies have indicated that cell bodies which stain for 5-HT increase in density, as well as number, in the neonatal rat with a maximum occurring around two weeks, followed by a gradual decline towards adulthood (Loizou, 1972). Levels of this neurotransmitter at birth have been reported to be approximately 30-40% of adult values (Bennett & Giarman, 1965; Nachmias, 1960; Lair, Tabakoff, Ungar & Alivisatos, 1976), and it appears that it is five to seven weeks postpartum before adult levels are attained (Agrawal, Glisson & Himwich, 1968; Karki et al., 1960). In accounting for the lower neonatal levels of 5-HT, Karki et al. (1962) postulated a deficiency in

the binding or storage mechanisms. Further to this point, it has been supposed that maturational increments in the ability to bind serotonin are directly correlated to synaptogenesis (Haber & Kamano, 1966). An assessment of regional 5-HT concentrations during development reveals a pattern of growth which is markedly different between brain regions. For example, it has been demonstrated that the serotonergic system matures most rapidly in the medulla-pons and mesencephalon-diencephalon regions, with more gradual increases occurring in the cerebral hemispheres. Indeed, by four weeks after birth the former regions reveal over 90% of adult serotonin values, while the hemispheres contain only 67% of adult levels. In line with the neuroanatomical data indicating 5-HT concentration in the raphe nuclei, the greatest levels in 5-HT are consistently found in the medulla-pons and mesencephalon-diencephalon.

Serotonin is degraded via MAO, and 5-hydroxyindoleacetic acid (5-HIAA) represents the primary indoleamine end-product (Baker, Hoff & Smith, 1974). Given that MAO has already been discussed in this paper with respect to catecholamine degradation, it will not be dealt with extensively at this point. Briefly though, the activity of brain MAO in serotonergic metabolism at birth has been shown to approach 30% of adult values (Karki et al., 1962; Nair et al., 1976). Moreover, a rapid increase in MAO activity occurs during the first two weeks after birth, with adult values attained by approxi-

mately 15-20 days of age (Baker et al., 1974; Jourdikian, Tabakoff & Alivisatos, 1975; Nair et al., 1976). Regarding 5-HIAA, a number of studies have demonstrated that shortly after birth, levels of this metabolite are in excess of those seen in the adult (Baker et al., 1974; Kellogg and Lundborg, 1972; Nair et al., 1976), and it is noteworthy that this appears true for virtually all brain regions. Several hypotheses have been forwarded to account for these data, including the possibility of increased 5-HIAA retention in the immature brain (Baker et al., 1974). A second alternative stems from the work involving administration of tritiated 5-HTP at various time intervals during development. Essentially, this work led to the suggestion that during the first weeks of life turnover rate of 5-HT is rapid, resulting in relatively high concentrations of 5-HIAA (Kellogg & Lundborg, 1972). A third possibility is based on data derived from work involving probencid administration. It has been suggested that the mechanisms for 5-HIAA elimination from the brain may vary during ontogenesis (Atack, Bass & Lundborg, 1974). Regardless of the reason for the heightened 5-HIAA, however, it has generally been concluded that the levels of this metabolite during the early stages of postnatal maturation are not a precise indicant of serotonergic development (Baker et al., 1974). The identification and localization of neurotransmitter substances, together with the advent of clinical and experimental drugs, has resulted in increased attention being

given to the analysis of neurochemical/behavioral relations. On the one hand, the psychopharmacological approach has been that of using more and more specific agents in evaluating simple behaviors; on the other hand, sophisticated behavioral analyses have been carried out using a relatively small range of pharmacological manipulations. Only recently, however, has the sophistication of both routes been melded. Needless to say, this has resulted in a more cohesive analysis of the mechanisms which subserve a wide variety of behaviors. To be sure, this applies also to the evaluation of the ontogeny of behavior (see reviews in Anisman & Bignami, 1977; Friedhoff, 1975; Iversen, Iversen & Snyder, 1977).

III. ONTOGENY OF BEHAVIOR

A good deal of the developmental work carried out thus far has been restricted to isolated behaviors e.g., passive avoidance, activity, exploration. This is not particularly surprising given that psychopharmacology in general, and developmental psychopharmacology in particular, are still in the early phases of their development. The purpose of the present investigation was to evaluate a relatively restricted set of behaviors; however, the intent was to assess these in a more or less systematic fashion. Before proceeding in detail with the work, carried out thus far at the developmental level, it seems propitious to describe the nature of these behaviors, and their postulated underlying mechanisms in the adult organism. It should be emphasized at this point that the literature concerning cholinergic and catecholaminergic manipulations at the developmental level is relatively broad. Of course, the present analysis will be limited, given the numerous recent reviews and monographs on the topic (see for example Anisman & Bignami, 1977; Carlton, 1963, 1965, 1969; Groves, Wilson & Boyle, 1974; Friedhoff, 1975; Kokkinidis, 1977; Rutledge, 1974; Swonger & Rech, 1972, 1977).

A. Locomotor Activity

1. The Catecholamines

In order to assess catecholaminergic involvement in locomotor activity, a number of pharmacological techniques have been employed, including chemical lesioning, enzyme inhibition, and a variety of pharmacologic agents which may act either pre- or post-synaptically. Moreover, there has been an increasing interest in dissociating the respective contributions of NE and DA in mediating this behavior.

At a more general level, it has been demonstrated repeatedly that increasing catecholaminergic activity, via agents such as the amphetamines causes an increase in locomotor activity (Cole, 1967; Hollister, Breese & Cooper, 1974; Khalsa & Davis, 1975; Rolinski & Scheel-Kruger, 1973; Thornburg & Moore, 1972). Although there is little question regarding the increased hypermotility seen following amphetamine, it is cautionary to point out that there are, as with most drugs, qualifications to this finding. Indeed, there appears to be a specificity with respect to the isomer used, with evidence suggesting that the d-isomer is substantially more potent than the l-isomer (see for example Maickel, Levine & Quirce, 1974; Taylor & Snyder, 1970). In addition, it has been shown that genetic differences exist in the response to amphetamine (Moisset & Welch, 1973; Remington & Anisman, 1976). Finally, several reports have indicated that the

effects of amphetamine are dose-dependent. In fact, in low doses amphetamines may induce a decrease in locomotor activity, as is the case at some intervals after drug administration (Cole, 1967; Maickel et al., 1974; Vazelli, 1969). Bearing in mind, then, that these qualifications exist, it is worthwhile assessing the amphetamine data in light of other pharmacologic reports investigating the neurochemical substrates of locomotor activity.

The effects of amphetamine administration have been shown to involve increased catecholamine synthesis and release, as well as inhibition of the reuptake process (Raiteri, Bertollini, Angelini & Levi, 1975). Following this line of thought, reduction of catecholamine synthesis should produce decrements in locomotor activity (i.e. antagonism of amphetamine effect). Studies employing such an approach have shown that this is, in fact, the case. The administration of α -methyl-p-tyrosine (AMPT), a drug which inhibits tyrosine hydroxylase (the rate-limiting step in catecholamine synthesis), results in decreased locomotor activity (Ahlenius, 1974; Ahlenius, Anden & Engel, 1973; Gordon & Shellenberger, 1974; Grabowska & Molinecka, 1971; Hollister et al., 1974; Rech, Borys & Moore, 1966). Predictably, this agent antagonizes the amphetamine-induced hypermotility (Carlsson, 1970; Dingle, Owens, Norvich & Sulser, 1967; Hollister et al., 1974). Furthermore, administration of L-dopa, the precursor of DA and NE, effectively counteracts the locomotor decrements seen fol-

lowing AMPT (Ahlenius, 1974; Maj et al., 1971). These results have been taken to suggest that locomotion is integrally related to catecholaminergic activity. Moreover, since synthesis inhibition effectively antagonizes the amphetamine effects, it seems that the behavioral consequences of the latter agent are of an indirect, as opposed to a direct, nature (i.e. receptor stimulation action) (Ahlenius, 1974; Ahlenius et al., 1973; Carlsson, 1970).

That catecholamines are involved in locomotor activity seems well-documented; however, as noted earlier, considerable interest has been shown concerning the respective effects of NE and DA. For example, it has been reported that the locomotor excitation produced by amphetamine is antagonized by 6-OHDA lesions of the substantia nigra, but is unaffected by lesions of the dorsal or ventral noradrenergic pathways (Creese & Iversen, 1973, 1974; 1975a, b; Fibiger, Philips & Zis, 1974; Roberts, Zis & Fibiger, 1975). Based on such data, it would appear that DA is of primary importance in terms of catecholaminergic involvement in locomotor activity. Stressing the importance of the mesolimbic DA system, Pijnenburg et al. (1976) have reported that bilateral administration of DA to the nucleus accumbens results in a significant increase in locomotor activity. Moreover, this hypermotility was antagonized by haloperidol, a specific DA receptor blocker. Further to these findings, it has been shown that apomorphine, a DA receptor stimulant, produces marked in-

creases in locomotor activity (supersensitivity) in animals which previously received 6-OHDA, while DA antagonists, such as pimozide, reverse this effect (Kelly, Miller & Neumeyer, 1976).

While the aforementioned evidence supports a dopaminergic role in locomotor activity, there are data which indicate that NE may also be involved to some degree. For example, Herman (1975) has reported that both NE and DA applied intraventrically increase locomotion. Furthermore, these excitatory effects are attenuated by the administration of various blocking agents, e.g., phenoxybenzamine blocking the NE effect, and pimozide reversing the effects of DA. Additional evidence has revealed that intraventricular administration of NE may also reverse the sedative effects seen following reserpine treatment (Geyer & Segal, 1973). Work involving enzyme inhibition has, by and large, indicated that DA plays a primary role in the amphetamine-induced motor excitation. More specifically, unlike AMPT, inhibition of DBH via U-14,624 (i.e. the synthesis of NE from DA is blocked) does not attenuate the effects of amphetamine (Khalsa & Davis, 1975). Hollister et al. (1974) reported that amphetamine-induced hypermotility in animals pretreated with reserpine may be attenuated with AMPT, but not by U-14,624. Similarly, it has been shown that the L-dopa reversal of decreased locomotor activity following AMPT is not altered when the L-dopa is ad-

ministered in conjunction with FLA-63 (Ahlenius, 1972). Although such findings would suggest that NE is not involved in the locomotor excitation induced by amphetamine, other reports involving DBH inhibitors present contrary results. For example, as mentioned earlier, Khalsa and Davis (1975) have reported a significant decrement in amphetamine-induced hypermotility following a single dose of U-14,624. Additional evidence has indicated that in reserpinised animals, the increase in activity following L-dopa is markedly suppressed, following the administration of FLA-63 (Dolphin, Jenner & Marsden, 1976). Finally, Rolinski and Scheel-Kruger (1973) have noted that amphetamine-induced hyperactivity is completely antagonized by AMPT and partially antagonized by FLA-63, suggesting that both NE and DA mechanisms are involved. Further evidence for a dual involvement stems from data indicating that clonidine, a NE receptor agonist, which produces a small decline in activity (Strombom, 1975, 1976), augments the behavioral excitation seen after apomorphine or metatyrosine (Anden et al., 1973). Summarizing, it would appear that in terms of locomotor activity, the dismissal of NE as a neurochemical factor is, at present, premature. Rather, one might speculate that both NE and DA are involved, with NE possibly augmenting the effects of DA stimulation and thereby increasing locomotor activity (see review in Antelman & Caggiula, 1976).

2. Acetylcholine

Reference has already been made to the numerous studies suggesting that various neurotransmitters, including ACh, may act in some interactive fashion in the modulation of ongoing behavior (see for example Anisman, 1975; Campbell & Mabry, 1973; Campbell, Lytle & Fibiger, 1969; Carlton, 1963, 1969; Feigley, 1974; Moorcroft et al., 1971; Remington & Anisman, 1976). Therefore, although discussion here is primarily restricted to the effects of ACh on locomotor activity, it is important to bear in mind that the various neurochemicals involved in activity may act in some form of balance.

While few data are available concerning the direct effects of ACh on locomotor activity, it has been reported that intraventricular injection of ACh inhibits locomotion, and this effect is abolished by an anticholinergic, atropine (Herman, 1975). For the most part, the literature concerning ACh and its role in locomotor activity is largely composed of studies which involve pharmacologic manipulations in the form of anticholinergic (antimuscarinic) agents i.e. scopolamine, atropine. For example, a number of studies are now available indicating that administration of anticholinergics induces augmentation of locomotor activity (Carlton 1961, 1963, 1965, 1969; Herman, 1975; Payne & Anderson, 1967; Pradhan & Roth, 1968; Remington & Anisman, 1976; Stewart, 1975; Stewart & Blain, 1975), although this effect appears to be related to

dose (Stewart & Blain, 1975), apparatus dimensions (Stewart, 1975), strain (Anisman, Wahlsten & Kokkinidis, 1975; Remington & Anisman, 1976) and previous experience in the test situation (Anisman & Cygan, 1975; Anisman et al., 1976). These effects appear to be mediated centrally, since drugs such as methyl atropine or methyl scopolamine, which pass into the brain rather poorly (Carlton, 1962), fail to induce an increase in motility (Pradhan & Roth, 1968).

One notion advanced to account for the behavioral effects of the anticholinergics, is that the cholinergic system underlies the habituation of nonrewarded behavior (cf. Carlton, 1961, 1962, 1963, 1969). More recently, it has been proposed that the cholinergic system mediates response inhibition (Anisman, 1975; Bignami, 1976; Bignami & Michalek, 1977; Carlton, 1969; Carlton & Markiewicz, 1971). That is, the effect of anticholinergics is one of reducing inhibition associated with the experimental situation, thereby increasing activity. Further reference will be made to this hypothesis in the section devoted to habituation. For the time being, it is sufficient to recognize that the comparable effects of amphetamine and anticholinergics on locomotor activity have been linked to different underlying mechanisms. It has been postulated that the effect of the former agent is excitatory in nature, while that of the latter is one of disinhibition (Anisman, 1975; Anisman & Cygan, 1975; Anisman, et al., 1976; see section on habituation).

Several approaches have been employed in order to elucidate the possible neurochemical interactions involving ACh. The first of these is behaviorally oriented, concentrating on changes in ongoing activity following various pharmacologic treatments. Fibiger, Lynch and Cooper (1971) noted that pilocarpine, a cholinomimetic, produced a period of marked behavioral inhibition, followed in turn by a period of excitation. Administration of scopolamine, prior to pilocarpine treatment eliminated both these effects, while it exacerbated the observed hyperactivity if injected immediately before the excitatory phase. These data were taken to suggest that cholinergic stimulation may result in an adrenergic rebound. Consistent with these results, it has been shown that subthreshold doses of scopolamine potentiate the hypermotility observed following amphetamine, suggesting that catecholaminergic stimulation and cholinergic inhibition may act in some synergistic fashion (Fibiger et al., 1970). Noting that the increased locomotor activity produced by benzotropine, scopolamine or atropine is inhibited by AMPT but not FLA-63, Thornburg and Moore (1973) postulated that the dopaminergic system is involved in locomotor stimulation induced by anticholinergics. Comparable effects have been noted so far as several other behaviors or neurochemical effects are concerned. For example, scopolamine has been shown to antagonize the effects of haloperidol on DA turnover (Anden, 1972; Bowers & Roth, 1972; O'Keefe, Sharman & Vogt, 1970; Westerink

& Korf, 1975), avoidance/escape (Fibiger, Zis & Philips, 1975), stereotypy (see review in Wallach, 1974), and parkinsonism (Bartholini, Stadler & Lloyd, 1973; Lloyd, Stadler & Bartholini, 1973). Predictably, scopolamine augments amphetamine-induced motor activity (Fibiger et al., 1970), in addition to stereotypy (cf. Wallach, 1974; see section on alternation/perseveration for additional work).

More recent availability of related biochemical data has yielded a second source of support for mutual regulation between ACh and other neurotransmitter systems. For example, it has been demonstrated that the enzymes associated with ACh synthesis undergo an increase following injection of catecholamine stimulants such as NE (Ho, Singer & Gershon, 1971), L-dopa (Sethy & Van Woert, 1973) and d-amphetamine (Mandel & Knapp, 1971). Conversely, decreases in catecholamine levels induced by 6-OHDA are reflected in a decrement in ACh-associated enzymes (Benton, Moffat, Rick & Taberner, 1975). Finally, several investigators have postulated that in the striatum, DA acts in an inhibitory fashion on ACh activity (Agid, Guyenet, Javoy, Beaujouan & Glowinski, 1974; Ladinsky, Consolo, Bianchi, Saminin & Ghezzi, 1975; Sethy & Van Woert, 1974). Accordingly, it has been demonstrated that the increased release of ACh following pharmacologic treatments which inhibit DA is, in turn, reversed with DA stimulants (Bartholini et al., 1973; Stadler, Lloyd & Bartholini, 1974; Stadler, Lloyd, Gadea-Ciria & Bartholini, 1973). While

this form of balance does not appear to hold true for limbic structures (Lloyd et al., 1973), its presence in other regions of the brain supports the notion of ACh involvement in mechanisms involving neurochemical balances.

3. Serotonin

Although the attention paid 5-HT is not as extensive as that received by the catecholamines, there is a growing body of evidence suggesting that serotonergic mechanisms contribute in some way to locomotor activity. However, while there is a certain degree of support for 5-HT involvement, the data are at present contradictory in some respects. For example, it has been reported that the administration of parachlorophenylalanine (PCPA), an inhibitor of 5-HT synthesis, produces an increase in activity (Mabry & Campbell, 1973; Marsden & Curzon, 1976), thus suggesting that the serotonergic system may act in an inhibitory fashion with respect to locomotion. In accordance with this line of thought, several investigators have shown that either 5-hydroxytryptophan (5-HTP) (Fibiger & Campbell, 1971; Mabry & Campbell, 1973) or l-tryptophan (Curzon & Marsden, 1975; Marsden & Curzon, 1976) antagonize the inhibitory effects seen following treatment with PCPA. Further support for an inhibitory role for serotonin stems from data indicating that serotonin depletion with p-chloroamphetamine (PCA) produces increased locomotor activity for up to three days following a single injection, while pre-

treatment with a 5-HT uptake inhibitor, Lilly 110140, blocks this effect (Messing, Phebus, Fisher & Lytle, 1976).

On the basis of the aforementioned evidence, one might readily conclude that serotonergic mechanisms are integrally involved in locomotor activity. However, there exists an alternate body of evidence suggesting that this conclusion is premature. One source of discrepancy involves a more recent comparison of serotonergic lesions and drug administration in the form of PCPA (Watanabe & Watanabe, 1975). As pointed out by these authors, earlier studies would have it that midbrain raphe lesions produce an excitation of general behavior, an effect which appears correlated with reductions in 5-HT levels, as well as 5-HIAA (Kostowski, Giacalone, Garattini & Valzelli, 1968, 1969). In contrast to these results, Watanabe and Watanabe (1975) reported a lack of correlation between 5-HT levels and locomotor activity. Indeed, lesions restricted to the median raphe reduced 5-HT levels in the telencephalon to 70%, although no change in locomotor activity was observed. Moreover, administration of PCPA was found to decrease 5-HT content in the diencephalon-midbrain, pons-medulla, and telencephalon, with no subsequent changes in locomotor activity.

Bearing in mind that some question exists concerning the specificity of lesion data (Kostowski et al., 1968, 1969; Watanabe & Watanabe, 1975), there are yet additional data which offer conflicting results with respect to the exact role of

serotonergic pathways in locomotor activity. More specifically, these data are derived from studies assessing changes in activity following the administration of drugs known to increase serotonin levels. Several reports involving such pharmacologic manipulations have indicated that administration of either tryptophan or 5-HTP, in conjunction with a monoamine oxidase inhibitor (MAOI) or an extracerebral decarboxylase inhibitor, increased levels of activity (Grahame-Smith, 1971a, 1971b; Modigh, 1974). Furthermore, these precursors given alone resulted in activity decrements. Based on these data, Modigh (1972, 1974) concluded that the role of 5-HT may vary in its effect upon activity according to the site of action. That is, at the peripheral level 5-HT may act in an inhibitory fashion, while centrally its effect would be excitatory in nature.

There are now a number of reports available suggesting that serotonergic mediation of activity involves some form of interaction with one or more additional neurotransmitter systems. The findings that PCPA exacerbates the hyperactivity observed following amphetamine or immediately after the injection of reserpine, as well as the ability of 5-HTP to antagonize PCPA's effect, led Mabry & Campbell (1973) to postulate that the serotonergic system acts indirectly on activity. Precisely, it was suggested that the interaction is one in which serotonergic pathways exert an inhibitory influence on

catecholamine arousal. Similarly, Green and Harvey (1974) noted that lesions of the medial forebrain bundle, which decreased telencephalic 5-HT levels by 60-84%, markedly enhanced the increased rates of responding induced by amphetamine. By the same token, decrease in serotonin by means of tryptophan-free diets or PCPA have been reported to potentiate amphetamine-induced hypermotility, while L-tryptophan administration antagonizes amphetamine's effect (Hollister, Breese, Kuhn, Cooper & Schanberg, 1976). Along the same lines, there are data indicating that the locomotor stimulation resulting from the administration of apomorphine, a DA receptor stimulating agent, is exacerbated following lesions of the mid-brain raphe area, or after injection of PCA (Grabowska & Michaluk, 1974). In contrast to these results, however, Marsden & Curzon (1976) noted that while a DA receptor antagonist, pimozide, reversed d-amphetamine's stimulatory effects, this was not the case with PCPA-induced hypermotility. Finally, Foldes and Costa (1975) reported that L-tryptophan may induce a period of hyperactivity, an effect which is antagonized by 6-OHDA lesions. However, it is noteworthy that the tryptophan metabolite, tryptamine, also elicited a state of increased activity, a phenomenon which was antagonized by AMPT, reserpine and PCPA. These data suggest that the metabolites of 5-HT may, at least in part, be responsible for the mediation of the hyperactive response observed here; moreover, it would appear that this effect is the result of the meta-

bolites' action on catecholaminergic neurons.

Returning to the lesion data, it has become increasingly more apparent that two factors are of utmost importance in considering the overall behavioral and biochemical alterations, namely site of action (Jacobs, Wise & Taylor, 1974, 1975; Jacobs, Trimbach, Eubanks & Trulson, 1975), and lesioning technique (Hole, Fuxe & Jonsson, 1976; Lorens, Gölberg, Hole, Kolater & Srebro, 1976). Indeed, differences between studies on the basis of these factors may serve to account for, at least in part, the discrepancies seen in the lesioning data. For example, Watanabe and Watanabe (1975) recorded changes in telencephalic 5-HT content ranging from 0 to greater than 50% according to whether the lesion i) was located between the median and dorsal raphe nuclei (0%), ii) was localized in the median raphe nucleus (30%), or iii) included both the median and dorsal raphe nuclei (>50%). Further to this point, it has been reported that while both dorsal or lateral raphe lesions selectively reduce tryptophan hydroxylase in various brain regions, their effects on several behavioral measures, including activity, are negligible (Geyer, Puerto, Menkes, Segal & Mandell, 1976). However, these same authors demonstrated that median raphe lesions resulted in hyperactivity within a novel environment, as well as a potentiation of amphetamine-induced locomotor stimulation. In agreement with these results, several studies by Jacobs and his associ-

ates support the notion that the precise location of the lesion is integrally involved with subsequent behavioral changes. More specifically, although median and dorsal raphé lesions both reduce 5-HT levels, only the former increases open field activity (Jacobs et al., 1974, 1975a, 1975b). It ~~was~~ demonstrated by these authors that although both types of lesions resulted in comparable changes in 5-HT in cerebral cortex, striatum and hypothalamus, differential responses in hippocampal 5-HT were recorded. These data were taken to suggest that this latter structure is of primary importance in the mediation of activity (Jacobs et al., 1974). Moreover, ablation of the anterodorsal hippocampus has been shown to block the synergistic effects raphé lesions may have on activity following administration of PCPA (Jacobs et al., 1975b). Finally, the fact that lesions of the median raphé potentiate both amphetamine- and scopolamine-induced locomotor stimulation (Jacobs et al., 1975b) suggests that interactions other than serotonergic/catecholaminergic may play a role in locomotor activity i.e. serotonergic/cholinergic.

In contrast to the data presented by Jacobs and his associates, more recent reports have failed to verify the importance of the hippocampus in the mediation of activity. Specifically, it has been demonstrated that while both electrolytic and 5,7-dihydroxytryptamine (5,7-DHT) produce comparable changes in hippocampal 5-HT, only the former procedure leads to increased activity. These results support the notion

that decreased hippocampal 5-HT is not necessarily a requisite for increased activity; however, it is worthwhile noting that Lorens and his co-workers (1976) have suggested that axonal sprouting following the 5,7-DHT lesions may account for the differential lesion effects.

B. Exploration

Although a distinction between exploratory behavior and locomotor activity may often be overlooked, several investigators have attempted to tease apart these two components of general behavioral arousal (cf. Abeelen, 1974; Berlyne, 1966; File & Wardill, 1975). More specifically, it has been noted that a prominent characteristic in a number of species, including the mouse, is their investigativeness or curiosity, a trait which has been labelled 'neophilia' (Abeelen, 1974). It is noteworthy that the nature of exploratory responses is species-specific, in that rats initially tend to be neophobic (Barnett, 1965; Mitchell, Kirschbaum & Perry, 1975), while mice have been shown to exhibit considerable exploratory tendencies in the presence of novel cues i.e. sniffing, rearing, and leaning against objects (Abeelen, 1974). Moreover, considerable differences have been demonstrated among strains in a given species (Abeelen, 1974). While locomotor activity and exploration are intuitively related, there is some question as to whether their occurrence is parallel within a given

situation (Anisman, et al., 1976). In addition, as might be expected, exploratory behaviors such as rearing appear to be regulated by the mechanisms common to those which subserve general locomotor activity (Lat & Gollova-Hemon, 1969). It is not clear, however, as to what extent there exists congruency between the neurochemical bases for these behaviors, although DA and NE have both been implicated (see for example File, 1976; Hollister et al., 1974; Khalsa & Davis, 1975; Rolinski & Scheel-Kruger, 1973; Strombom, 1975). As such, one should expect similar responses to a variety of related pharmacologic manipulations. Given the possibility that locomotor activity and exploration are independent of one another, it is worthwhile elucidating the mechanisms which underly each of these. Indeed, this distinction becomes particularly important when one considers that in human syndromes characterized by hyperactivity e.g. hyperkinesis, the degree of activity is closely related to the surrounding environment and its novelty (see review of hyperkinetic syndrome in Wender, 1971).

1. Techniques for the Assessment of Exploration

Before evaluating exploration in terms of neurochemical factors, it is worthwhile reviewing those techniques employed to assess exploratory behavior. The exact nature of the methods utilized ranges from calculating the cumulative total of arm-entries in a Y-maze over a given period of time (Strombom, 1975), to recording the rearing activity within a

novel environment (Bresler, Diaz & Ellison, 1976). As might be expected, what is designated as exploratory behavior i.e. rearing, head-poke, is integrally associated with the particular apparatus employed. Moreover, in almost all cases reported, the occurrence of an increase in a specific behavior is frequently at the expense of other behaviors. Indeed, several reports have indicated that a measure of exploration may be obfuscated by a design which unduly biases towards a given behavior (cf. File & Wardill, 1975; Uster, Battig & Nageli, 1976), or employs a measure which appears secondary to (i.e., an artifact of) the explorative-type behavior promoted by the apparatus (Sheldon, 1968). Accordingly, studies have been carried out which concurrently attempt to dissociate various components of ongoing behavior e.g. locomotion versus exploration (Robbins & Iversen, 1973; Ungerstedt, 1974). Similarly, efforts have been made to gain additional information by subcategorizing the particular behavior under investigation. For example, head-poke, as a measure of exploration, has been investigated in terms of frequency, duration, and number of holes investigated (Cooper, 1976; Nolan & Parkes, 1973; File & Wardill, 1975a, b). It is important to bear in mind, then, that reports on exploration may vary markedly with respect to the behavior studied, as well as the assessment procedure employed.

2. Neurochemical Factors in Exploration

i) The Catecholamines

Despite the differences in experimental approach, there is a surprising degree of consistency regarding catecholaminergic involvement in exploratory behavior. Wimer and Fuller (1973) indicated that d-amphetamine may increase, decrease, or have no detectable effect on open field activity, bar pressing for light, and investigation of a changed region of the environment, respectively. It is noteworthy, however, that while these three behaviors were categorized as independent measures of exploration by these authors, others would disagree with this assumption (Robbins & Iversen, 1973). Indeed, open field activity seems more conducive to a measure of general locomotion, and as pointed out earlier, several attempts have been made to dissociate locomotor activity and exploration (Anisman et al., 1976; Robbins & Iversen, 1973; Ungerstedt, 1974). Further to this point, there are numerous investigations which suggest that amphetamine increases locomotion within an open field situation (see previous section on locomotor activity). More recent investigations of catecholaminergic induced changes in exploration have displayed a greater consistency in their findings. Specifically, it has been shown in a variety of tasks (hole-board, modified Berlyne Box, novel environment), that administration of d-amphetamine results in decreased exploration (Bainbridge,

1970; File & Wardill, 1975b; Robbins & Iversen, 1973; Wakeley & O'Sullivan, 1969). Moreover, the decrease in exploration may well be a consequence of increases in horizontal activity (see Bignami, 1977).

It was previously indicated that several experiments favor the hypothesis that dopamine is the catecholamine principally involved in locomotor activity (see for example Creese & Iversen, 1973; 1974; 1975a, b; Fibiger et al., 1974; Roberts et al., 1975). In contrast, the data appear to support a more prominent role for norepinephrine with respect to exploratory behavior. For example, administration of 6-OHDA, which markedly reduces central norepinephrine levels, results in increased rearing in an open field, as well as exaggerated avoidance to novel visual stimulation in light onset and light escape tests (Bresler, Diaz & Ellison, 1976). It has been demonstrated that administration of apomorphine, a dopamine receptor stimulating agent, to bilaterally dopamine denervated animals, completely abolishes head-poking, while horizontal locomotion is greatly increased (Ungerstedt, 1974). Further to these findings, it has been shown that both apomorphine and clonidine, DA and NE agonists respectively, depress exploration in a Y-maze (Strombom, 1975). However, the inhibitory effect of clonidine was markedly more pronounced, suggesting that norepinephrine is of primary importance in exploratory behavior. Finally, while it is

worth noting that other pharmacologic agents have been employed, their contributions to an understanding of the catecholaminergic mechanisms involved in exploration are limited for several reasons. First, the other major source of drug data stems from work with transquillizers and barbiturates (Cooper, 1976; File & Pope, 1974; Nolan & Parkes, 1973), both of which are rather non-specific in their mode of action (Iversen & Iversen, 1975). Second, in certain instances the experimental design is such that generalization to other findings is restricted. For example, File and Pope (1974) reported that chlorpromazine failed to alter exploration in a hole-board task. However, animals were tested in pairs, and while no effect was observed for head-poke responses, differences were noted in the frequency and type of social interaction.

ii) Acetylcholine

The decline in exploratory behavior with repeated exposure to a particular environment represents an inhibition of responses no longer rewarded by the novelty of the environment (Carlton, 1969; cf. Green, Joyce & Summerfield, 1975). In terms of neurochemical mediation, it has been suggested that cholinergic mechanisms are involved in the habituation of emitted responses such as exploration (Carlton, 1963; 1968; 1969; Carlton & Markiewicz, 1971). Given this assumption, it

would be expected that pharmacologic manipulations which block ACh receptors, would attenuate the habituation of exploratory behaviors. Indeed, a number of reports have indicated that cholinergic manipulations may alter overall levels of exploration, as well as its course of habituation. For example, Wakely and O'Sullivan (1969) demonstrated that the anticholinergics, atropine and Ditran (N-ethyl-e-piperidyl phenylcyclopentylglycolate), produce a marked increase in exploration in a head-poke task. Similarly, Green et al. (1975) noted that scopolamine, administered prior to an initial 20-minute exposure to a Y-maze, attenuated the course of habituation seen in control animals during a second exposure one week later. However, within session habituation was not affected during the initial exploration period. In the same vein, it has been reported that scopolamine mitigates habituation in a hole-board task on successive presentations over a four day period. Moreover, the attenuation of habituation has been recorded for both frequency and duration of head-pokes. File (1976) noted that differences between these two patterns of responding are abolished if novel objects are not present beneath the holes of the apparatus. This finding has led to the suggestion that the effect of cholinergic mechanisms on exploration may be directly related to the complexity of the task. In general agreement with such an interpretation, Stewart and his associates (Hughes, Blampied & Stewart, 1975; Stewart & Blain, 1975) and Kokkinidis and Anisman (1976a, b)

have found that the effects of anticholinergics are dependent on the complexity of the environment and prior exposure to the situation.

It is important to keep in mind that as with other drug/behavior relations, there exist strain differences with respect to the role of ACh in exploration. More specifically, there may be inherent differences both within and between strains depending on the behavioral measure under investigation i.e. rearing, leaning, sniffing (Abeelen, 1974; Abeelen, Ellenbroek & Wigman, 1975). In addition, it has been shown that anticholinergics may differentially affect behavior as a function of the strain used. Based on these data, Abeelen (1974) postulated that response to novelty may be mediated by a genotype-dependent mechanism, which may be located within the hippocampus. It should be noted, however, that Anisman (1975) suggested that these strain differences may be more a reflection of differences in locomotor activity than exploration per se.

C. Habituation

The process of habituation simply reflects the waning of responsiveness to repeated or constant stimulation (Peeke & Herz, 1973). While the phenomenon of habituation appears, at first blush, intuitively obvious, it has been subject to repeated investigation owing to several factors. For example,

habituation is a ubiquitous phenomenon which occurs in humans (Gallaway III, 1973; Hill, 1973), invertebrates (Clark, 1965; Eisenstein, 1967; Eisenstein & Peretz, 1970; Lahue, Kokkinidis & Corning, 1975), as well as surgically simplified organisms (Thompson & Spencer, 1966). Indeed, habituation appears even when the responses of a single neuron are recorded, thereby giving rise to theoretical models which attempt to account for response change at the cellular level (see for example the work of Groves & Lynch, 1972; Thompson & Spencer, 1966).

In addition to its ubiquity, it appears that the habituation process is both task- and strain-specific. For example, habituation has been established for a number of behavioral measures, including several varieties of exploratory behavior (Anisman et al., 1976; Carlton, 1968; Grant, 1968; Kokkinidis & Anisman, 1976; Wakely & O'Sullivan, 1969), startle response (Carlton & Advokat, 1973; Groves, Wilson & Boyle, 1974), head raising in pups (File & Plotkin, 1973), and flexor withdrawal reflex (Pearson, 1973). However, while each of these appears to reflect changes typical of the habituation process (cf. Groves & Thompson, 1971; Thompson & Spencer, 1966), precise differences have been documented between behaviors and the nature of their respective habituation curves. Furthermore, considerable attention has been devoted to elucidating the exact nature of these variations, as well as the mechanisms responsible for them. For example, it

seems that rate of habituation is closely associated with stimulus intensity, but this relationship is not a monotonic one (Sokolov, 1960; Thompson & Spencer, 1966). The matter has been further complicated by the notion that habituation represents two distinct processes. More specifically, Groves and Thompson (1970; 1973) postulated that one component of habituation entails a response decrement (habituation), which occurs after repeated stimulation. A second component involves a sensitization or response enhancement phase. It has been suggested that with moderate or intense stimulation, sensitization precedes habituation, while this does not appear to be the case with weak stimulation (Groves & Thompson, 1970).

Since numerous reviews are available concerning habituation and sensitization (see for example Groves & Lynch, 1972; Groves & Thompson, 1970; Sokolov, 1960; Thompson & Spencer, 1966; Thompson, Groves, Teyler & Roemer, 1975), a review of this literature will not be attempted here. However, there are several points which deserve consideration. The ubiquitous nature of habituation has already been pointed out, although there is some question as to the precise nature of the underlying mechanisms. Within a physiological framework, there are at least two models which have attempted to account for the phenomenon of habituation. The first of these was forwarded by Sokolov (1960) and centres around the

orienting response (OR) to repeated stimulus presentation. Briefly, it was noted that for a number of physiological measures i.e. galvanic skin response, eye movement, respiration, and heart beat, a decline in response occurred upon repeated presentation of a given stimulus. In order to account for these findings, Sokolov suggested that certain brain regions, such as the cerebral cortex, are responsible for establishing an imprint which reflects the qualitative and quantitative nature of the stimulus, as well as its temporal characteristics. Moreover, it was postulated that this internal representation of the stimulus is not a permanent imprint, but rather, varies in a continuous fashion in accordance with stimulus change. Thus, with respect to a stimulus such as an auditory tone, variations in pitch, tone or duration may serve to elicit an OR, while repeated presentation of the same stimulus produces a decline in the OR.

An interesting facet of the above model involves the role of stimulus intensity in the process of habituation. In contrast to later models e.g. Thompson and Spencer (1966) which hypothesize an inverse relationship between stimulus intensity and habituation, Sokolov suggested that their interaction is markedly more complex. He indicated that their relation is integrally dependent upon the organism's sensory and pain thresholds. Accordingly, a weak stimulus i.e. one just above the sensory threshold level, is seen as eliciting a stronger OR than slightly more intense stimuli; furthermore,

habituation to the weaker stimulus proceeds in a slower fashion. Finally, stimuli exceeding the pain threshold level often result in an OR which intensifies over repeated presentation of the stimulus, a response which Sokolov considered to represent a defense reaction on the part of the organism.

A second theoretical model of habituation stems largely from work carried out on the hind-limb flexor reflex in the decerebrate spinal cat (Groves & Thompson, 1970; Thompson & Spencer, 1966). It was suggested that habituation involves at least two distinct processes: the first involves a decrement in response to repeated stimulus presentation, or 'habituation', while the second process, termed 'sensitization', refers to a response enhancement which occurs for a transient period in response to strong stimulation. Following initial increase in response during the stimulus presentations, this component peaks and subsequently declines over time. The habituation curve observed for a particular organism represents an interaction of these two processes (Groves & Thompson, 1973; Thompson, Groves, Teyler & Roemer, 1973).

A more intensive investigation of the aforementioned hypotheses has led to several models concerning the exact nature of this dual-process system. For example, in the semi-intact preparation it has been demonstrated that the activity of interneurons between the fifth lumbar segment and the

first sacral segment is correlated with shock-induced flexor twitches. Moreover, an attempt has been made to categorize these neurons according to their pattern of response. Specifically, a group of interneurons has been designated 'Type H', and demonstrates a progressive decrease in activity with repeated stimulation. A second group, or 'Type S', reflects an increase in activity immediately following initial stimulus presentation, followed in turn by a general decline. A third classification of interneurons, 'Type N', reveal no activity alterations in response to stimulation. Given that these systems interact in some fashion to produce the habituation curve (Groves & Thompson, 1970, 1973), an effort has been made to elucidate the physiological structures underlying each of these components. To this end, it has been suggested that the habituation phase involves S-R pathways which offer the most direct route within the CNS, incorporating sensory systems, motor systems, the cerebral cortex, and the frontal cortex. Sensitization has been associated with the organism's general arousal level, and there is some speculation that this system involves the reticular activating system (RAS), in addition to the hypothalamus and various limbic structures (Groves & Thompson, 1973; Groves, Wilson & Boyle, 1974).

As indicated previously, the overall rate of habituation appears to be integrally related to a number of factors,

including various aspects of the stimulus component (intensity, rate of presentation, etc.), as well as the behavior investigated (general activity, startle, and so on). With respect to the latter point, attempts to elucidate the possible role of various neurochemical systems in habituation have indicated that their contribution may vary markedly according to the task employed. For example, while the anticholinergic, scopolamine, disrupts the rate of habituation in an exploratory task (Hughes et al., 1975; Green, Joyce & Summerfield, 1975), within session habituation to a startle response is unaffected by anticholinergics. Without question, there are several alternatives which may be forwarded to account for these data, including differences in type of response (elicited versus emitted). Moreover, change in rate of habituation between various behaviors may simply reflect a drug-induced motorogenic bias i.e. increased horizontal activity at the expense of decreased exploration in, say, a head-poke task (see File & Wardill, 1975). However, the fact remains that the process of habituation may vary significantly across behavioral categories. As such, it is beneficial if more than one task is investigated, particularly if the behaviors studied vary in their origin viz. elicited or emitted responses.

The concern over elicited versus emitted responses raises several questions concerning the pharmacologic basis of habituation. To be more explicit, the possibility arises that

a drug may alter only one phase of the habituation process. For example, if one agrees that a dual-factor process subserves habituation, then it not unlikely that these components are differentially influenced by a particular drug. That is, one drug may alter rate of decline of the habituation component, while showing no observable effects on sensitization. Conversely, a drug may produce an elevated response to an external stimulus complex (i.e. influencing sensitization), without affecting the habituation component per se. Thus, in addition to the need for a variety of tasks in the evaluation of habituation, it is imperative that statements concerning the underlying mechanisms of habituation be carefully qualified with respect to the situation under consideration. To this end, several measures of habituation at the behavioral level are employed in the present investigation. Moreover, pharmacologic manipulations are carried out in several of these experiments in an effort to clarify the possible role various neurochemical systems may play in modulating a particular behavior and its rate of habituation. What follows in this section on habituation is a description of the techniques employed in the present study, as well as a brief overview of those pharmacologic studies which have attempted to clarify the neurochemical mechanisms mediating various forms of behavioral habituation.

1. Techniques for the Assessment of Habituation

i) Spontaneous Alternation

The mechanism involved in spontaneous alternation appears to involve the ability to selectively inhibit responses to non-reinforced stimuli (Bignami, 1967; Carlton, 1969). Accordingly, there is a tendency for animals to select novel cues rather than stimuli to which they have already been exposed. Two tasks which have been repeatedly employed as a measurement of spontaneous alternation involve T- or Y-mazes (Kokkinidis, 1977). It is this latter apparatus which has been incorporated in the present series of experiments, and its use over the T-maze is based on several reasons. First, the design of the T-maze is such that position responding and left/right responding are confounded. That is, a right turn will always lead the animal into one particular compartment, while a turn to the left takes it to the other arm. However, investigation of an organism's behavior in a free running Y-maze serves to clarify this issue, since it may be argued that alternation, which occurs in a free running Y-maze as well as a discrete T-maze, is not based on a simple internal response feedback mechanism viz. alternation of left-right turns. More specifically, if alternation was dependent on such a mechanism, it should not be evident in a Y-maze since the animal would be alternating between two arms only. Rather, the fact that alternation is observed in both

tasks suggests that animals alternate on the basis of position cues instead of a left-right response feedback (Drew, Miller & Baugh, 1973; Swonger & Rech, 1972).

A second major advantage inherent in the use of the Y-maze as a measure of alternation involves the aversive effects of between-trials handling. That is, the design of the Y-maze guarantees that during testing, the animal is presented with a parallel situation regardless of the compartment it occupies. In contrast, the T-maze requires that upon completion of a trial, the animal be removed and returned to the starting compartment. However, the handling of the animals between trials during a testing situation has been challenged, in that Griffiths and Wahlsten (1974) noted that pharmacologically-induced response changes may be modified by a handling process.

ii) General Activity, Exploration, and Reactivity (Startle).

There is little question that a more comprehensive understanding of habituation may be gained if various types of behavior are evaluated. Accordingly, habituation will be evaluated in terms of general activity, exploration and reactivity, as well as spontaneous alternation in the Y-maze.

By incorporating these different tasks, one gains the distinct advantage of assessing various forms of behavior. For example, habituation in a general activity task simply re-

flects horizontal locomotion, while the hole-board apparatus (exploration) involves purposeful and directed response patterns. Finally, the use of an air puff task (reactivity/startle) permits one to dissociate habituation of emitted behaviors (i.e. general activity, exploration) from habituation of an elicited behavior viz. reactivity to an air puff.

2. Neurochemical Factors in Habituation

i) The Catecholamines

The data presently available strongly favor the notion of catecholaminergic involvement in general activity, in that catecholamine stimulants produce increased activity, while catecholamine blockers result in activity decrement (see previous section on locomotor activity). Unfortunately however, data concerning the role of catecholamines in habituation of general activity appear limited. Furthermore, the data which are available suggest that disruption of habituation following administration of catecholaminergic agents, is probably not a consequence of variations in habituation per se. For example, in rats d-amphetamine (5.0 mg/kg) produces an initial increase in locomotor activity, followed subsequently by reduced locomotion. The reduction in activity is accompanied by increased stereotypy (i.e. continuous sniffing, grooming). Later yet, increments in locomotor activity are observed (Lyon & Randrup, 1972). Thus, the second phase of amphetamine's effect, involving the stereotypy, may

be erroneously assumed to represent a period of habituation. A similar pattern of amphetamine-induced locomotor activity has been recorded by Thornburg and Moore (1972), leaving open the possibility that these data might also be accounted for on the basis of the aforementioned explanation. Somewhat at odds, though, is the finding by the same authors that amantadine, a drug which also inhibits NE and DA uptake, reveals the increased locomotor phase but fails to show a subsequent decline. However, since amantadine reveals a slower onset, the question remains as to whether the time limits of the present investigation (two hours) were sufficient to assess adequately its behavioral effects. Further evidence employing a carry-over design suggests that catecholaminergic stimulation with pharmacologic agents such as amphetamine, does not alter habituation in an open field situation (Anisman et al., 1976). Specifically, the suggestion has been made that carry-over of amphetamine effects in a water-lick task reflects heightened locomotor activity in animals previously treated with amphetamine (proactive effects), whereas the effect of the anticholinergic, scopolamine, is one of dishabituation.

In comparing the effects of catecholamine stimulation on general activity as opposed to exploration (head-poke), the argument of a motorogenic bias becomes readily apparent. Indeed, the increase in horizontal activity following d-amphetamine produces an attenuation of the habituation curve

over time. In contrast though, activity such as vertical head-poking has been shown to undergo a decrement following amphetamine administration (Pile & Margill, 1975). These data would suggest that the excitatory influence of catecholaminergic stimulation is not one of general dishabituation at all behavioral levels. Further evidence suggesting that amphetamine's effect is not one of dishabituation stems from its use in spontaneous alternation. More specifically, in a free running Y-maze, alternation behavior occurs at the level of 50-70%. However, administration of either d-amphetamine (3-10 mg/kg) or l-amphetamine (15-45 mg/kg) results in a marked degree of perseveration (Adkins, Packwood & Marshall, 1969; Anisman & Kokkinidis, 1975; Kokkinidis & Anisman, 1976b). This amphetamine-induced perseveration is in contrast with the effects of scopolamine, an agent which reduces alternation to approximately chance levels (Anisman & Kokkinidis, 1975; Kokkinidis & Anisman, 1976a, b). If amphetamine's effect was one of dishabituation, then a decline to chance levels rather than the observed perseveration would be expected. Furthermore, employment of a carry-over design has revealed that d-amphetamine does not produce performance different from that of animals originally tested following saline. That is, on day 2, when animals were tested in the Y-maze without drug treatment, those animals originally administered d-amphetamine revealed a pattern of between-session habituation similar to that of animals given saline on day 1. It would seem that if d-amphetamine's effect was disinhibitory

in nature, then in a non-drug retest situation, animals which received d-amphetamine on day 1 should not reveal the degree of habituation seen in animals initially given saline. Thus, amphetamine's lack of effect in a carry-over design, as well as its perseverative influence immediately following administration, would suggest that amphetamine's influence within the spontaneous alternation paradigm involves a component other than habituation. In addition, numerous other experiments have been carried out to assess possible alternatives which might account for the amphetamine-induced perseveration. To this end, a number of options have been ruled out including a peripheral component (Kokkinidis & Anisman, 1976b), general locomotor excitation (Anisman & Kokkinidis, 1975; Kokkinidis & Anisman, 1976a), or circling (Kokkinidis & Anisman, 1977).

Models postulating catecholamine involvement in habituation have gained considerably from studies involving reactivity to a novel stimulus which is presented periodically over a given period of time. Of course, it must be remembered that this latter task involves elicited, rather than emitted responses on the part of the organism. In any case, there is now considerable evidence to suggest that catecholaminergic mechanisms in habituation are primarily related to a sensitization component. For example, while within session habituation remains unaffected, the amplitude of startle responses is enhanced following administration of either d- or l-amphetamine (Davis, Svensson & Aghajanian, 1975). Conversely,

reports have indicated that AMPT depresses startle amplitude (Sorenson & Davis, 1975). Contrary to these results, however, is the finding that reserpine enhances the first startle response (Fetcher, 1974), although sensitization does not occur with repeated stimulation. Given that both AMPT and reserpine produce catecholamine depletion, one would expect parallel results at the behavioral level. Moreover, the argument of receptor supersensitivity does not appear to account for this discrepancy, in that administration of clonidine, a norepinephrine stimulant, reverses the reserpine effect while apomorphine, a dopamine stimulant, does not. Indeed, these data suggest that norepinephrine is primarily involved in reserpine's influence on startle. It is noteworthy that Kokkinidis and Anisman (1977) have reported consistent results in this respect. More specifically, it was found that both AMPT and FLA-63 served to attenuate the amphetamine-induced exaggeration of the startle reflex, thereby supporting the notion that norepinephrine is integrally involved in the startle situation. In contrast, however, several studies have been reported which would indicate that dopamine is of principal importance in amphetamine-induced changes in startle response. Similar to the results of Kokkinidis and Anisman (1977), Davis and his associates (1975) reported that AMPT reverses amphetamine-induced enhancement of the startle response (Davis et al., 1975). However, these investigators also pointed out that apomorphine produces a sensitization effect similar to

that of amphetamine, while administration of haloperidol antagonizes the apomorphine effects (Davis & Aghajanian, 1976). Together, these data may be taken to support the notion that amphetamine-induced sensitization is primarily mediated by dopaminergic mechanisms (see, however, Kokkinidis & Anisman, 1977).

ii) Acetylcholine

There presently exist a significant amount of data in support of the notion that cholinergic mechanisms are involved in habituation. However, the results vary according to the task investigated, thereby giving rise to a number of hypotheses concerning the exact nature of this involvement. For example, it is well-documented that scopolamine attenuates the course of habituation in an exploratory situation (Hughes et al., 1975; Joyce & Summerfield, 1975; Stewart & Blain, 1975). In accounting for these data, it has been suggested that such disruptions may, in fact, reflect a motorigenic bias (Graf, 1974; Walters & Block, 1969), or possibly involve the novel cue properties which result following introduction of the drug (Overton, 1968; Payne & Anderson, 1967). Confusating the issue somewhat is the finding that the effects following administration of an anticholinergic, vary across dosages depending on the test situation (Hughes et al., 1975). With specific reference to exploration, for example, low doses

of scopolamine decrease rearing activity, locomotion and reactivity to novel stimuli. In contrast, high doses produce decreased responding in the novel stimulus task, although ambulation is increased and horizontal activity is left unaltered (Stewart & Blain, 1975). Taken together, these data suggest that the various tasks are measuring exclusively different behaviors, although the tendency has been to categorically group them under exploratory-type tasks.

Adding yet another factor to the question of cholinergic involvement, are several studies indicating that external stimulus properties are integrally involved in the behavioral responses following cholinergic manipulation. More specifically, in an illumination task (i.e., bar press to produce illumination), it has been reported that animals with septal lesions or injections of scopolamine respond in a fashion similar to controls when response dependent changes in illumination are not employed. In contrast, introduction of such changes produces decreased response rate but increased response duration in both the scopolamine and lesioned groups (Feigley & Hamilton, 1971). Carlton (1969) has reported that animals will bar press for the rewarding value of dim light onset, and that the normal habituation of this response is attenuated following scopolamine treatment. To account for these data, it has been suggested that such experimentally induced disruptions in habituation reflect increasing sensitivity to external cue components following cholinergic manipu-

lation (Feigley & Hamilton, 1971). Further support for this notion stems from work indicating that with scopolamine-treated animals, increased response duration occurs in a hole-board task when novel objects are placed under the holes (File & Wardill, 1975). Similarly, an animal's tendency to enter one arm of a T-maze when novel objects are placed in it, is markedly increased following the administration of scopolamine.

As in the case of catecholaminergic involvement in habituation, the question arises as to whether cholinergic influences simply reflect a motorogenic bias (see for example Graf, 1969; Walters & Block, 1969). Predictably, there has been an effort to clarify this problem, and the use of the Y-maze spontaneous alternation task has, to some extent, resolved this issue. Indeed, it has been reported that habituation, as measured in a Y-maze, is independent of locomotor activity (Anisman, 1975b). Further to this point, Anisman found scopolamine to uniformly disrupt alternation in three strains of mice, although drug-induced differences in locomotor activity were recorded between strains. In terms of the disruption induced by cholinergic manipulations, a number of studies have demonstrated that administration of scopolamine or atropine reduces alternation to approximately chance levels in the Y-maze (Anisman & Kokkinidis, 1975; Douglas & Isaacson, 1966; Drew, Miller & Baugh, 1973; Kokkinidis & Anisman, 1976a, b),

whereas physostigmine increases alternation scores (Anisman, 1975b; Anisman & Kokkinidis, 1975; Kokkinidis, 1976a). Of particular importance is the fact that these changes occurred at dosages which did not influence locomotion (see Anisman & Kokkinidis, 1975; Kokkinidis & Anisman, 1976a). It appears, then, that the blockade of cholinergic activity produces random arm entries, thereby resulting in chance levels of alternation scores.

In addition to the aforementioned findings, the use of several carry-over designs has provided additional evidence that cholinergic mechanisms are involved in habituation. To be more explicit, one such study has demonstrated that scopolamine results in a decrease in alternation, in addition to producing carry-over effects which are reflected in subsequent non-drug testing (Kokkinidis & Anisman, 1976b). More specifically, animals were first tested in a Y-maze following administration of scopolamine or saline. Twenty-four hours later, these same animals were again placed in the Y-maze, but with no drug treatment. Testing on day 2 indicated that those animals previously treated with scopolamine revealed significantly higher levels of alternation than the group which received saline on day 1. Indeed, on day 2 the former group alternated at a level similar to animals not pre-exposed to the Y-maze, suggesting that the scopolamine treatment on day 1 produced a dishabituation effect in animals tested in a non-

drug state 24 hours later.

A second carry-over design involves the use of a water-lick task and again supports the notion that an anticholinergic such as scopolamine may attenuate the course of habituation (Anisman et al., 1976; Carlton, 1969). More specifically, water deprived animals were administered one of several pharmacologic agents, followed thereafter by pre-exposure to the test situation with the water bottle removed. Twenty-four hours later, animals were reintroduced to the test chamber, but in this case a water bottle was present. It is assumed that pre-exposure to the environment serves to antagonize any exploratory tendencies which would compete with the animal's approach to the water bottle on subsequent retesting. In fact, this appears to be the case. Those animals which received saline during initial exposure revealed markedly shorter latencies in approaching the water bottle during retest than animals which received scopolamine or atropine. Indeed, during retest the latter groups responded in a fashion similar to naive saline-treated animals. It has therefore been suggested that administration of an anticholinergic attenuates the course of habituation, such that during reexposure, exploratory tendencies compete with an approach response to the water bottle. It is noteworthy that similar carryover effects have been reported for other behavioral measures. For example, it has been demonstrated that disruption of shuttle avoidance after pre-exposure to the apparatus (latent in-

hibition), is mitigated if scopolamine is administered during the first period of exposure (Oliverio, 1968). Taken together, these data provide strong evidence that disruption in cholinergic activity via varied anticholinergic agents markedly attenuates the course of habituation.

3. Habituation: Developmental Aspects

As reported in earlier sections of this paper, central neurochemical systems demonstrate differential rates of maturation in the developing organism (see introduction, section II). Accordingly, it would seem that developmental studies might offer indirect evidence as to the possible neurochemical mechanisms which modulate habituation. It is somewhat surprising, however, that relatively few studies have been carried out using this approach. Moreover, of those which have been reported, the greatest emphasis has been on the elucidation of cholinergic mechanisms.

Reviewing the limited amount of data available involving catecholaminergic contributions, some speculation has been made as to initial levels of habituation and early development of catecholamine pathways. File and Scott (1976) noted that for spontaneous head-turning to an air puff, the number of trials to reach the habituation criterion progressively increases to day 8. This, in turn, is followed by a decline towards day 20. Based on these data, the suggestion has been made that

the initial lack of habituation observed in the immature organism reflects a period of reticular activating system arousal (File & Scott, 1976), a stage represented biochemically by rapid maturation of norepinephrine and dopamine pathways (Aghajanian & Bloom, 1967; Coyle, 1974; Loizou, 1972). The subsequent increases in habituation tendencies during the second postnatal week may, in contrast, reflect increased development of forebrain inhibitory structures i.e. acetylcholine. It is noteworthy that this model is consistent with the one proposed for spontaneous activity (Fibiger et al., 1970; see introduction, section I). However, the decline in spontaneous activity seen at approximately 15 days postnatally in rats, closely approximates the proposed period of functional maturation for the neurochemical inhibitory systems, acetylcholine (Campbell et al., 1969; Fibiger et al., 1970) and serotonin (Mabry & Campbell, 1974). In contrast though habituation appears to develop progressively from week 2. In accounting for this finding, several possibilities may be entertained. For example, it is possible that the initial onset of habituation tendencies does not require that inhibitory systems be fully mature. Accordingly, habituation may increase in a parallel fashion with cholinergic development until approximately week 3, a time when habituation appears to level off and inhibitory neurochemical pathways (acetylcholine and possibly serotonin) are considered largely developed. A second alternative is that other neurochemical pathways and/or

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physiological factors are involved in the process of habituation, with its development contingent upon their respective patterns of maturation. Moreover, the issue is further confounded by a point made earlier in the section on habituation. Specifically, it was noted that pharmacologic manipulations may produce differential responses in habituation according to the behavior investigated (Stewart & Blain, 1975). Consistent with these results, Williams, Hamilton and Carlton (1975) indicated that the development of habituation in the immature rat varies markedly according to the behavior investigated. That is, habituation of the startle reflex (elicited responses) was not clearly differentiated as a function of age. In contrast, no evidence of habituation of exploration was seen in young animals (15-16 days), although it was readily apparent in the older group (36-39 days). As can be seen then, any effort on the part of developmental studies to elucidate neurochemical factors in habituation, must carefully take into consideration the type of behavior investigated.

Bearing in mind the aforementioned considerations, it is worthwhile evaluating the developmental studies assessing the role of acetylcholine in habituation. As pointed out earlier, it has been demonstrated that the development of habituation progresses in a fashion somewhat parallel to the development of certain neurochemical systems (File & Scott, 1976). That is, animals in the second week postpartum reveal

a failure to habituate in an open field exploratory task (Bronstein, Neiman, Wolkoff & Levine, 1974). However, by the latter stages of week 2, evidence of habituation was observed for the air puff response (File & Scott, 1976), while within-session habituation decrements in exploratory activity were recorded by 21 days postnatally (Bronstein et al., 1974). In terms of neurochemical maturation, it has been reported that the development of habituation occurs during that time period when rapid development of the inhibitory cholinergic system is taking place (Campbell & Spear, 1972; File & Scott, 1976; Williams et al., 1975). Consistent with this line of thought, lesioning of the septum and hippocampus in adult animals produces changes in a number of behaviors (Kohler, 1976; Roberts, Dember & Brodwick, 1962; Williams et al., 1975), including performance in a spontaneous alternation task (Clody & Carlton, 1969; Dalland, 1976; Eggar, Livesey & Dawson, 1973; Stevens & Cowey, 1973; White, 1974). Specifically, the changes result in behavior comparable to that of non-lesioned immature animals, thus supporting the notion that limbic structures, such as the septum and hippocampus, are integrally involved in the modulation of habituation (see Douglas, 1975, for a review). Moreover, given that these anatomical regions are known to be rich in acetylcholine (Bird & Aghajanian, 1976; de Feudis, 1974; Hrdina, 1974; Orderfield-Nowack et al., 1976), these data would suggest that cholinergic mechanisms play an important role in mediating habituation processes.

IV. GENETICS

In previous sections of this paper, it has been repeatedly suggested that a number of behaviors, including spontaneous activity, and exploration, as well as the process of habituation, are mediated by specific neurotransmitter systems. Moreover, a variety of approaches have been adopted in an effort to verify the underlying neurochemical hypotheses. As well as evaluating numerous types of behavior, varied experimental procedures i.e. pharmacologic manipulations, lesioning, have been used in order to assess response changes following alterations in endogenous neurochemical functioning. The entire question of behavioral/biochemical relations has gained yet additional information from developmental studies attempting to offer an indirect approach to the investigation of neurochemical factors subsuming different behaviors. However, there is, in addition, at least one further approach to this area of research, that of genetic analysis. To be sure, this approach represents a relatively recent contribution to the study of behavioral/biochemical relations. Nevertheless, the increasing rise in studies incorporating a genetic approach suggests that considerable data may be gained from such a procedure. Indeed, Jinks and Broadhurst (1974) have emphasized the contribution genetic analyses may offer to a more comprehensive understanding of

behavior. In keeping with this approach, the present section serves as an overview of those genetic studies which provide additional information concerning the possible roles of various neurotransmitter systems in determining specific patterns of behavior viz. locomotor activity, reactivity, exploration, and habituation.

Within the animal literature, a number of genetic studies have focused on genotypic variations in ongoing locomotor activity (see for example DeFries, Hegmann & Halcomb, 1974; Halcomb, Hegmann & DeFries, 1975; Oliverio, 1974). As well as existing reports indicating various strain differences in baseline levels of activity (Anisman, 1975b; Anisman & Kokkinidis, 1975; Anisman, Wahlsten & Kokkinidis, 1975; Moisset & Welch, 1973; Oliverio, 1974; Remington & Anisman, 1976), several more recent studies have described the use of bidirectional selection procedures for the purpose of achieving strain-specific differences in open field activity viz. high, low and control levels (DeFries et al., 1974; Halcomb et al., 1975). While neurochemical data on these latter strains are not yet available, numerous other investigations have supported an association between patterns of activity for a given strain and endogenous neurochemical levels. For example, several investigators (e.g. Abeelen & Strijbosch, 1969; Anisman et al., 1975; Oliverio, Eleftheriou & Bailey, 1973) have suggested that strain variations in

locomotor behavior may be the consequence of the relative balance between levels of acetylcholine and cholinesterase. Support for this contention has been derived from experiments showing that levels of acetylcholinesterase and choline acetyltransferase are lower in active strains of mice, such as C57BL/6, than in relatively inactive strains such as DBA/2 (Ebel, Hermetet & Mandel, 1973; Pryor, Schlesinger & Calhoun, 1966). Predictably, the effectiveness of anticholinergic agents in increasing activity in C57BL/6 mice is much reduced relative to that observed in DBA/2 mice (Abeelen & Strijbosch, 1969; Anisman et al., 1975; Oliverio et al., 1973). It has also been observed that these strains differ in enzymes involved in catecholamine synthesis (Ebel et al., 1973). Moreover, across strains the increase in activity elicited by d-amphetamine is inversely related to baseline levels of activity (Anisman & Cygan, 1975; Oliverio et al., 1973). However, Anisman (1976) indicated that the relationship between baseline activity and response to d-amphetamine is not of a causal nature in these strains.

Further confirmation of these genetic differences stems from pharmacological manipulations during various stages of ontogenesis. More specifically, Remington and Anisman (1976) noted that in three highly inbred strains of mice (A/J, DBA/2J and C57BL/6), d-amphetamine increased activity in all strains at 14 days and 28 days of age, and at 21 days

significantly increased activity in all except the C57BL/6 strain which exhibited the highest baseline activity level. In contrast, increased activity with scopolamine treatment was seen in DBA/2 at 21 days, but not in A and C57BL/6 until 28 days postnatally. It is interesting that at 21 days of age when C57BL/6 mice exhibited maximal levels of activity, the response to amphetamine was at its lowest level and did not reach significance. This finding has considerable appeal in light of the human hyperkinetic response to amphetamine, and will be discussed more extensively in the following section. However, for the time being it is noteworthy that the rate of neurochemical development appears strain-specific, as supported by the finding that scopolamine was effective only in the DBA strain at three weeks postnatally. Taken together with the adult data, these findings suggest that genetic variations in a behavior such as general activity may be modulated by various neurotransmitter systems. Moreover, these strain-specific differences appear to interact with age, in that genetic differences are observed in response to pharmacologic manipulations at various stages during ontogenesis.

Regarding other behaviors of interest in this particular investigation i.e. exploration, reactivity and habituation, there exists a paucity of data concerning genetic differences which may occur during early postnatal development. However, there are a number of studies which would indicate that significant differences between strains are observable for these

behaviors at the adult level. For example, in a novel environment, mice of the C57BL/6 strain exhibit greater levels of rearing (i.e. exploration) than animals of the DBA/2 strain. Further to this point, it has been suggested that genotypic variations in cholinergic mechanisms may account for the behavioral differences (Abeelen, 1974; Abeelen, Ellenbroek & Wigman, 1975). In terms of reactivity to novel stimuli, a lack of data exists concerning strain-specific differences. Paranthetically, marked differences have been reported between the DBA/2 and C57BL/6 strains, but these data are confined to aversively motivated situations (see for example Anisman, 1976; Anisman & Cygan, 1975; Oliverio, 1974).

Finally, the use of different strains has been employed in a spontaneous alternation task for the purpose of evaluating strain-specific patterns of responding following several drug treatments. In particular, Anisman and Kokkinidis (1975) noted that locomotor changes following scopolamine administration vary according to strain (A, DBA/2, or C57BL/6, although spontaneous alternation is equally eliminated. In contrast, d-amphetamine increased locomotor activity and increased perseveration in all strains. Given that these strains are known to differ in baseline levels of activity (Anisman, 1975b; Anisman et al., 1975; Remington & Anisman, 1976), these findings suggest that the effects of scopolamine and d-amphetamine on habituation are independent of locomotor activity. At a

more general level, the use of different strains has served to clarify pharmacologically-induced response changes on several aspects of behavior.

V. HYPERACTIVITY:

EXPERIMENTAL AND CLINICAL IMPLICATIONS

That an abundance of data exists concerning neurochemical factors in behavior is clear from a review of the previous sections in this paper. In addition, an integration of the behavioral/biochemical studies would suggest that the existing findings may be of much more than heuristic value. The contributions of animal data to a better understanding of human behavior have, in fact, been repeatedly demonstrated. More specifically, even a cursory glance of the literature on human psychopathology indicates the presence of numerous animal models which have attempted to clarify the mechanisms underlying patterns of human aberrant behavior (cf. Akiskal & McKinney, 1975; Anisman, 1975; Ljungdahl & Johansson, 1974; Mogilnicka & Braestrup, 1976; Seligman, 1975; Senay, 1966; Takahashi, Tsuchi, Nishiwaki, Nakamura, Tateishi & Nagayama, 1976; Wortman & Brehm, 1975). While these studies have concentrated on behaviors such as depression and schizophrenia, a smaller body of literature has focused on a possible animal analogue for the human hyperkinetic syndrome (Campbell & Randall, 1975, 1977; Glick & Milloy, 1973; Hitzemann, Hitzemann, Brase & Loh, 1976; Shaywitz, Yager & Klopfer, 1976; Wray, 1975). Moreover, these latter animal studies have postulated both behavioral (Campbell & Randall, 1975, 1977) and biochemi-

cal mechanisms (Campbell & Randall, 1975, 1977; Glick & Milloy, 1973; Bitzemann et al., 1976; Shaywitz et al., 1976; Wray, 1975) in an effort to explain the etiology of hyperkinesis.

The value an animal model might serve in understanding human hyperactivity cannot be over-emphasized, particularly in light of the apparent prevalence of this syndrome. For example, severe hyperkinesis as observed in either the home or school setting has been estimated in at least 4% of all school-age children (Weiss, Minde, Douglas, Werry & Sikes, 1967). This behavioral disorder has been referred to by a number of labels, including 'hyperkinetic behavior disorder', 'minimal brain dysfunction (MBD)', and 'hyperactivity' (Arnold, 1973; Grinspoon & Singer, 1973; Wender, 1971). The symptomatology of the syndrome has been noted to include extreme overactivity, distractibility, short attention span, impulsiveness, marked mood fluctuations, and aggression (Eisenberg, 1972). It has recently been argued that this subset of symptoms is reflective of attentional deficits which occur in hyperactive children (Barkley, 1977a,b; Douglas, 1972). The pharmacological and morphological evidence presented earlier on the differential development of the two systems associated with motor activity suggests a possible link between biochemical development and the presence of a hyperkinetic syndrome. For example, the notion of delayed brain maturation is compatible with the empirical observation that hyperkinesis tends to improve with age (Millichap & Fowler, 1967). As such, it may well be the case that in the hyperkinetic child, there exists a retarded development of the cholinergic system, or overactivity of the

catecholamine system. In fact, Wender (1974) has postulated that minimal brain dysfunction ~~not~~ only involves monoamine disturbances, but also genetic factors which may be responsible for these aberrant levels of neurotransmitters.

One particularly interesting finding regarding the hyperkinetic syndrome is that administration of pharmacological agents such as amphetamine or methylphenidate, result in a diminution of hyperactive symptoms (Barkley, 1977a,b; Conners, 1970; Douglas, 1972; Eisenberg, 1971; Millichap, 1968; Tec & Levy, 1971). Several possibilities exist which may account for the observed effects of sympathomimetics in the hyperkinetic child. Specifically, where there exists an imbalance between noradrenergic and cholinergic activity, further increases in catecholamine action may result in a rebound involving yet a second or third system (e.g., acetylcholine and serotonin) which inhibits the catecholamine effects (Anisman, 1975; Swonger & Rech, 1970). Secondly amphetamine may produce end-product-inhibition, thus resulting in decreased synthesis of dopamine and norepinephrine (Cooper *et al.*, 1970). Finally, amphetamine may result in release of catecholamines from storage granules, thereby leaving the organism with reduced levels of functionally effective amines (Welch & Welch, 1970). Such an effect would occur when utilization of amines exceeds total biosynthesis. Several behavioral changes are possible as a consequence of these neurochemical effects. Most obvious, of course, is that the decrease in catecholamines and increase in acetylcholine would result in diminished locomotor activity (Anisman, 1975a). By the same token, it is certainly not unlikely that these motoric changes would be secondary to the increases in attention provided by the catecholaminergic stimulation (cf. Barkley, 1977a,b; Campbell & Randall, 1975, 1977).

Turning again to the animal literature, several findings have been reported which are, in some respects, comparable to that seen in the human hyperkinetic syndrome. Specifically, it is well known that activity increases with amphetamine, and as indicated in the previous section, the extent of the increase is inversely proportional to baseline activity (Anisman *et al.*, 1974; Fuller, 1970; Glick & Malloy, 1973; Moisset & Welch, 1973). Moreover, it has been demonstrated that certain strains of mice exhibit a period of marked hyperactivity/hypereactivity ('popcorn') around 21 days of age. This 'popcorn' stage has been observed in the C57BL/6 strain of mouse (Remington & Anisman, 1976), and has been shown to coincide with increased levels of norepinephrine (Schlesinger & Griek, 1970). However, in other strains of mice (i.e. A and DBA/2), this rise in locomotor activity is not evidenced, and they also exhibit lower levels of norepinephrine during this period of growth. Behaviorally, these latter two strains reveal a significant increase in general activity following amphetamine administration at 21 days, while C57BL/6 animals reveal no such increments (Remington & Anisman, 1976). In accounting for these data, it has been speculated that the 'popcorn' stage may well reflect a time period during ontogenesis in which the noradrenergic and cholinergic systems are at greatest imbalance, thus leading to the observed hyperactivity. It is noteworthy that modulation by a third system e.g. serotonergic, has not been discounted.

(Remington & Anisman, 1976). The fact remains, however, that the results with d-amphetamine are somewhat paradoxical, in that at 21 days the same dose which produces large increases in activity in A/J and DBA/2 mice, fails to do so in the hyperactive C57BL/6 strain.

Taken together, the aforementioned data seem to offer appealing possibilities in terms of an animal model of hyperkinesia. The genetic differences in baseline activity, as well as the 'popcorn' stage in C57BL/6 mice around 3 weeks and the paradoxical effects of amphetamine, all suggest that this phenomenon in animals may, at least to a limited degree, be generalizable to the human disorder. Curiously however, little work has been carried out to date extending these animal data. While the report of Remington and Anisman (1976) offers one such study, its efforts are confined to the investigation of one behavior viz. locomotor activity. To this end, the present experiments represent an attempt to accumulate additional information concerning strain variations in behavior during ontogenesis. In doing this, a number of behavioral measures have been included. For example, as well as a general activity task, a measure of exploratory behavior (hole-board) is incorporated, with the goal of dissociating purposeful, directed responding (exploration) and simple horizontal locomotion. In addition, an effort will be made to accumulate data involving response to a repeated stimulus (air puff). Beyond looking at these findings in terms of strain

differences, the opportunity is available to assess animals exhibiting a transient phase of hyperactivity/hyperreactivity during their third week of postnatal development. The distinct advantage of having these data is obvious when one considers that in human hyperkinesis, hyperreactivity is considered to be a key symptom (see review of symptomatology in Wender, 1971). Finally, habituation will be evaluated in a Y-maze spontaneous alternation task, as well as in the other tasks described viz. general activity, hole-board and air puff. The advantage of including several measures of habituation is twofold in nature. First, it serves to elucidate temporal patterns of responding over a variety of tasks. In turn these data may be assessed with respect to strain-specific differences in levels of activity, thereby offering some insight into the interaction between levels of activity and course of habituation. Second, these data will provide the opportunity to evaluate not only strain-specific differences, but changes in response patterns as a function of several pharmacologic manipulations (catecholaminergic and cholinergic).

In choosing these various measures, the overall goal was one of accumulating scores on a variety of tasks which reflect the development of behavioral arousal during ontogenesis. Further, a number of test intervals are included (15, 20, 25, 30 and 60 days postnatally), in order to span the sequence of maturation from early neonatal growth to adulthood.

As expected, greatest concentration is devoted to the first four weeks of development, when rapid changes in central neurochemical development occur. Accordingly, changes over time in response to a specific task may serve to reflect maturation of those neurochemical systems which modulate a given behavior. Particular interest is focused on that time period (approximately 15-20 days after birth) when periods of marked hyperactivity/hyperreactivity have been observed in various mouse strains.

One additional comment is necessary. The present series of experiments does not employ the use of the inbred strains of mice (A/J, DBA/2 and C57BL/6) used in earlier developmental studies carried out in this laboratory (cf. Remington & Anisman, 1976). The basis of this change stems from the recent development of six mouse lines selected for activity levels: two High, two Low, and two Control lines (DeFries et al., 1974; Halcomb et al., 1975). There is, in fact, a distinct advantage to using these six lines obtained through bilateral selection for activity, rather than the inbred strains used earlier. While C57BL/6 and DBA/2 mice vary in activity (see for example Oliverio, 1974; Remington & Anisman, 1976), this merely reflects a phenotypic difference observable between these strains. Indeed, these strains were not developed with this goal in mind and are known to differ in numerous other respects (cf. Anisman 1975a,b,c,d, 1976).

In contrast, the six lines employed here were developed specifically for differences in activity levels, a characteristic of considerable importance within the present experiments. Moreover, these lines are not inbred, thereby avoiding the problems inherent in the use of inbred strains (DeFries, 1973; DeFries et al., 1974). Accordingly, the experiments reported here are based on the comparison of these six lines, with the underlying knowledge that they represent three distinct variations in open-field activity.

EXPERIMENTS 1-4

Differential maturation of neurochemical systems has been posited in order to account for ontogenetic variations in behavior. For example, slower development of forebrain inhibitory regions relative to hind brain excitatory structures may be responsible for the sequence of behavioral changes seen during postnatal growth (Campbell & Mabry, 1972, 1973; Campbell et al., 1969; Fibiger et al., 1970; Remington & Anisman, 1976).

In addition to the evaluation of ontogenetic differences in behavior, the recent development of six mouse lines which vary in activity levels (De Fries et al., 1974; Halcomb et al., 1975), has presented the opportunity to evaluate developmental changes in animals specifically selected for differences in baseline activity. The use of several distinct behavioral measures in these lines (general activity, reactivity, exploration and habituation) permits the clarification of several issues. First, the question arises as to whether genetic variations in locomotor activity are similarly reflected in a variety of behavioral tasks. That is, there is a need to assess whether animals revealing highest open field activity also demonstrate greater exploration than control and Low lines, or by the same token, more intense and sus-

tained responses to repeated presentation of a novel stimulus (air puff). The incorporation of several measures of habituation should serve to clarify any temporal differences which exist in pattern of responding between these various mouse lines. While it has already been pointed out that in the Y-maze general activity and alternation/perseveration scores are independent of one another (Anisman, 1975b), further information may be gained from the assessment of other forms of behavioral habituation. For example, in a general activity task it is possible that higher activity animals reveal similar patterns of habituation to Low or Control animals, although their response rates remain consistently higher. Alternatively, rate of habituation may vary significantly between the different lines. Moreover, habituation curves may differ in tasks involving elicited (air puff), versus emitted responses. In effect, the use of different tasks may provide some insight as to whether observed differences between lines and between ages reflect differences in habituation on the one hand, or "genuine excitation" or perseverative tendencies on the other. The first four experiments were designed in order to clarify the nature of the behavioral differences which exist between six lines of mice selected for high, low and control activity levels, as well as differences which occur over a period ranging from preweaning to full adulthood.

Method

Experiment 1: General Activity

Subjects.

Subjects were 240 experimentally naive mice represented equally from each of six lines of mice selectively bred for high, low and control levels of open field activity (De Fries et al., 1974; Halcomb et al., 1975). Mice were bred at Carleton University from stock of the twenty-seventh generation (S₂₇) originally procured from the Institute for Behavioral Genetics, University of Colorado, Boulder, Colorado. Females were removed from the mating cages when visibly pregnant (16-18 days) and housed individually. Litters were culled such that not more than 10 mice were housed with the dam. Litters of fewer than 5 mice were not included in the experiment. Offspring were tested at either 15, 20, 25, 30 or 60 days postnatally. For each age, there were six test groups (N=8/cell), with each group representing a particular mouse-line. All test groups consisted of equal numbers of male and female animals. Entire litters were tested on the same day in order to eliminate potential confounds owing to removal of one or more offspring from the breeding cage and thereby affecting the rest of the litter (Wahlsten, 1974).¹ For animals up to 30 days of age, ad libitum access to food, water and maternal parent was available. Similar conditions were available for litters to be tested at 60 days, but in this

case animals were weaned at 25 days of age and housed according to sex.

Apparatus

Six circular cylinders 30 cm in diameter and 30 cm high, consisting of black Plexiglas, were used to measure activity. The roof of the apparatus consisted of two sheets of 2 mm red Plexiglas, thereby reducing light within the chambers. The floor consisted of grey Plexiglas, and six infrared photoelectric cells were mounted 1.5 cm above the floor. These photocells were spaced at 7.8 cm intervals around the circumference forming a 3x3 matrix. If a mouse broke a particular beam, then this cell could not be activated until a second beam was broken, thus precluding movements such as tail rattling and head bobbing from being recorded. The number of photobeams crossed were recorded independently for each cylinder at predetermined intervals.

Procedure

At the appropriate age (15, 20, 25, 30 or 60 days), mice were randomly chosen from the home cage and individually placed in separate holding cages for a 15 minute interval. Each subject was then placed in a test chamber, and photocell counts were printed every 5 minutes over a 50 minute period. In this and all ensuing experiments chambers were cleaned with alcohol after each animal was tested.

Experiment 2: Spontaneous Alternation

Subjects

Subjects consisted of 240 experimentally naive mice, representing the two High, two Low and two Control lines. Mice were tested at the appropriate ages (15, 20, 25, 30 and 60 days of age), with each age consisting of groups from the six lines ($N=8/\text{cell}$). Mice were randomly selected within a given line (S_{27}), and males and females were equally represented in each treatment group. Housing and breeding conditions were identical to that described in Experiment 1.

Apparatus

Two symmetrical black Plexiglas Y-mazes with arms $9.0 \times 6.0 \times 7.0$ cm covered by a clear Plexiglas roof served in alternation testing. The floor of the apparatus consisted of black Plexiglas, and each arm of the Y-maze had two sets of infrared photoelectric relays mounted on the side walls 1 cm above the floor. An arm entry was recorded only if both cells were broken i.e., the animal was required to enter at least halfway down the arm in order that an arm entry be counted.

Procedure

At one of five ages (15, 20, 25, 30 and 60 days postnatally), mice were removed from their individual holding cages

and placed in one arm of the Y-maze. The sequence of arm entries was recorded over a 15 minute period. A response sequence in which animals entered the arm least recently visited was considered an alternation (e.g., a sequence of arm entries in this case would be 1, 2, 3, or 1, 3, 2). Nonalternation was considered to be the case in which animals returned to the compartment they had been, to most recently (e.g., 1, 2, 1, or 1, 3, 1). The proportion of alternation was computed by dividing the number of alternations by the total number of alternations plus nonalternations. Perseveration was defined as animals alternating at levels which were significantly below chance (50% given two choices).

Experiment 3: Exploration

Subjects

Subjects consisted of 240 experimentally naïve mice, selected from the two High, two Low and two Control lines. Mice were randomly chosen from each of the six lines (S₂₇), and each treatment group represented a particular line (N=8/cell). Equal numbers of male and female subjects were used in each group. Housing and breeding conditions were similar to those described in Experiment 1.

Apparatus

Two black Plexiglas hole-boards were used in the

measure of exploration. Each apparatus was mounted on a stand 45 cm high. The floor perimeter measured 22 cm square, with the walls 17.5 cm high. Four holes (2 cm each in diameter) were located in the floor and spaced in a square pattern 6 cm apart, and 6 cm from the nearest walls. Four infrared photocells were located 3 mm below the floor's surface in such a fashion that the beams formed a 2x2 matrix, with two beams intersecting directly below the centre of each hole. A head-poke represented a response whereby the subject broke the photobeam below a given hole.

Procedure

As in the earlier experiments, animals of the appropriate ages (15, 20, 25, 30 or 60 days) were randomly chosen from the home cage and placed in separate holding cages for a 15 minute interval. Each subject was then placed on the centre of the hole-board. The number and location of the head-pokes were recorded over the next 50 minutes.

Experiment 4: Reactivity

Subjects

Four hundred and eighty naive mice were used in this experiment, with equal numbers being chosen from each of the six lines (two High, two Low and two Control). For testing purposes, mice were randomly selected at one of the following ages (15, 20, 25, 30 or 60 days postnatally), with all ages

consisting of a treatment group from each of the six lines (S_{27}) ($n=8/\text{cell}$). Groups were composed of equal numbers of male and female subjects. Conditions for housing and breeding were identical to that described in Experiment 1.

Apparatus

Four of the cylinders described in Experiment 1 were used in Experiment 4 in order to evaluate reactivity to repeated air puffs. However, in two cylinders several modifications were added. In each, the Plexiglas roof was connected by a nipple adapter and plastic tubing to a compressed air tank. The original roofs consisted of two identical sections of red Plexiglas sealed in such a fashion that an air space 2 cm in depth was formed between the top and bottom sections. Eight holes, each of 2 mm diameter, were drilled in the lower section in a fashion which permitted an air puff to strike all areas of the floor with approximately equal intensity.

Procedure

Animals were randomly selected and placed individually holding cages for 15 minutes prior to testing. Four animals were tested at a given time, with two of the four cylinders designed to administer air puff. Activity was recorded at equal intervals for all animals. In the test procedure, animals were permitted to adapt to the apparatus for ten

minutes after which testing commenced. Over a period of three minutes, 18 air puffs, .5 sec in duration at 70 pounds/sq in., were given at 10 sec intervals. Activity was recorded during the 10 second intervals following each air puff. Mice remained in the chambers for 10 additional minutes during which photocell crossings were recorded.

RESULTS AND DISCUSSION

Locomotor Activity (Experiment 1)

The mean number of photocell crossings, as a function of Line and Age are shown in Figure 1. Analysis of variance of photocell crossings revealed a significant Line x Age x Block interaction, $F(180,1890)=1.98$, $p<.001$. Subsequent Newman-Keuls multiple comparisons ($\alpha=.05$) of simple main effects involved in this interaction showed a fairly consistent pattern of responding. In all strains and at all ages, activity was found to decline between the initial and later portions of the session.

With respect to levels of activity at the various ages, it was observed that at 15 days of age, the H_1 line was at first considerably more active than the H_2 , L_1 , L_2 , and C_1 lines, which in turn were more active than the C_2 line. The high activity in H_1 was fairly transient, and as testing progressed the differences between the former five lines was eliminated; however, the activity level of C_2 animals remained relatively low. It is clear that at 15 days of age, the pattern of responding was not entirely consistent with the line variations in adult mice reported by DeFries and his associates (DeFries et al., 1974; Halcomb et al., 1975). At 20 days of age, the pattern of responding differed somewhat from that observed at 15 days and, in fact, paralleled closely the expect-

8
Figure 1. Mean transformed ($\sqrt{x + 0.5}$) levels of locomotor activity as a function of Line and Age.

MEAN TRANSFORMED $\sqrt{X+0.5}$
PHOTOCELL CROSSINGS

ted line differences. As seen in Figure 1, initially both H_1 and H_2 mice were considerably more active than the remaining lines, which did not differ from one another. Later in testing, the differences between the 2 High lines and the C_1 and L_2 lines were diminished, but activity nevertheless remained considerably higher in these lines than in L_1 and C_2 animals. At 25 days of age, this pattern of responding remained consistent, with the exception that the differences between H_2 mice and the Low and Control lines were not apparent after the third block of trials. The H_1 line was considerably more active than the remaining lines throughout testing. A comparable pattern of behavior was apparent at both 30 and 60 days of age, although the differences between H_2 animals and the remaining lines were sustained for a considerably longer period of time.

It appears that both High lines were generally more active than the Control and Low lines. However, the Control lines were not found to differ consistently from the Low lines. Moreover, the high level of locomotor activity seen in H_2 animals was not as consistent as that seen in H_1 . One important point deserves particular emphasis. That is, the distinct line variations in locomotor activity, although apparent at 20-60 days of age, were not fully expressed at 15 days. While the H_1 line was somewhat more active than the remaining lines at this age, this was a fairly transient phenomenon and in

fact, H_2 mice were at times lower in activity levels than some of the remaining lines.

In comparing within lines but across ages, a consistent pattern of responding was observed. Namely, all lines revealed a progressive increase in their levels of activity. It should be noted, however, that the rate of increase between ages was considerably more pronounced in the High lines than in the remaining lines. As seen in Figure 1, in both High lines the increments in activity between 15 and 20 days of age were fairly prominent. In L_1 and L_2 animals however, the rate of increase was somewhat slower and, in fact, decreased in L_2 between 15 and 20 days. In Control lines the behavior again resembled that of the Low lines. However, in the case of C_2 , a marked increase was seen between 15 and 20 days of age. This was probably a reflection of the particularly low levels of activity in the former age.

In evaluating the rate of decline in activity within a session, interesting patterns are apparent both between lines and ages. From 20-60 days postpartum, a monotonic decline in activity was observable in all lines, although as seen in Figure 2, the rate of decline was somewhat slower in H_1 at 25 days of age and to a lesser degree at 30 days, than observed in the remaining lines. At 15 days of age, the typical decline in activity was apparent; however, it is clear that the habituation functions are less consistent at this time. For

Figure 2. Mean transformed ($\sqrt{x + 0.5}$) levels of locomotor activity as a function of Line, Age and Trial.

MEAN $\sqrt{X+0.5}$ PHOTOCELL CROSSINGS

example, in H_2 habituation was entirely absent, while in C_1 mice an initial increase in activity was seen between the first two blocks of trials. It is not clear whether the less consistent occurrence of habituation at 15 days of age was a fortuitous phenomenon, or whether in fact it reflects immaturity of the inhibitory systems, as suggested by other investigators (see Introduction).

Taken together, it is clear that habituation of activity is apparent in all lines. The exception to this pattern occurred at 15 days postnatally, when the typical habituation function was apparent in four of the six lines. These data are consistent with the notion presented by Carlton and his associates (Carlton, 1969; Williams *et al.*, 1975), suggesting that habituation does not occur until maturation of the cholinergic system. This has been shown indirectly to occur at approximately 20-28 days of age in mice (Remington & Anisman, 1976). Thus, pending maturation of the cholinergic system, the predicted line differences at adulthood in terms of general activity, are not apparent. In contrast to the 15 days old performance, consistent habituation was apparent at 20 days. In fact, adult-like behavior was seen in all lines.

The fact that line differences in activity and habituation were not clearly apparent at 15 days of age suggests that the mechanisms involved in habituation might, to some degree, account for the line variations in locomotor activity observed

at later ages. That is, one might argue that the retarded rate of habituation is responsible for the line differences in activity. Such an argument, however, probably does not entirely account for the observed variations, since in older animals the line differences in activity were seen even during the first block of five minutes, when little habituation should have occurred. It is possible, though, that considerable habituation occurs during this five minute period, thus permitting line differences to become apparent at this time. This possibility needs to be further considered by examining smaller, more discrete units of time i.e., 30 seconds or one minute. However, to coin some critics, this would be comparable to counting angels on the head of a pin. An accurate count, however, might be worthwhile.

Spontaneous Alternation (Experiment 2)

The mean proportion of alternation responses, as a function of Line and Age, are shown in Figure 3. Analysis of variance of individual alternation scores yielded a significant Line x Age interaction, $F(20,210)=2.07$, $p<.01$. Subsequent Newman-Keuls* multiple comparisons ($\alpha=.05$) across ages indicated a surprising lack of variance between the lines tested. In contrast to the marked between line differences in locomotor activity seen in Experiment 1, spontaneous alternation was not found to differ consistently between lines. Those between line differences which were observed during ontogenesis were largely a function of the consistently low alternation scores exhibited by the H_2 line during development. While no statistically significant differences between lines were observed at 15 days of age, alternation scores for H_2 mice at 20 days of age were significantly below those recorded for the L_1 , L_2 , and C_2 lines. Differences were again obtained at 30 days of age, where the H_2 line exhibited lower alternation scores than the C_2 group. The only other notable difference at 30 days of age involved the L_1 line, which alternated significantly below C_1 animals. At adulthood, alternation in the H_2 line was again significantly below that of the H_1 and C_1 groups.

In terms of ontogenetic changes in alternation within each of the lines, the present data are consistent with earlier

Figure 3. Mean proportion of alternation responses as
a function of Line and Age.

MEAN PERCENT ALTERNATION

60

50

40

15

20

25

30

60

AGE

H₁ ●—●
H₂ ○—○
C₁ ■—■
C₂ □—□
L₁ ▲—▲
L₂ △—△

studies suggesting that younger animals reveal weaker alternation tendencies than other animals (Egger, 1973a,b; Egger et al., 1973). Specifically, while all lines revealed alternation scores about chance levels at 15 days of age, they all exhibited a fairly uniform increase in alternation behavior over successive ages. However, only in the L_1 and C_1 lines was this increase statistically significant. In the remaining lines, the age dependent increase approached, but did not reach statistical significance ($p < .1$). It is noteworthy, however, that in L_1 animals, the high alternation was not consistent in that a drop in alternation occurred at 25 and 30 days of age.

χ^2 analyses were carried out for the total group alternation scores to determine whether alternation differed from chance levels. In contrast to earlier reports (Egger, 1973a,b; Egger et al., 1973), consistent perseveration was not apparent in young animals. That is, at 15 days of age only the C_1 line revealed alternation scores significantly below chance $\chi^2(1)=4.58$, $p < .05$. In sharp contrast, alternation scores significantly exceeded chance in this same line at 25, 30 and 60 days of age, $\chi^2s(1)=18.68$, 23.66, 23.44, $p < .05$. The H_2 mice remained the only line to reveal alternation scores significantly below chance during later ages, with scores below chance being observed at 20 and 25 days postnatally, $\chi^2s(1)=43.75$, 45.13, $p < .05$. In all lines except H_2 , there

appeared to be some tendency towards alternation scores above chance at the later ages. For example, alternation scores for the H_1 line were significantly above chance at both 30 and 60 days postpartum, $\chi^2(1)=56.04$, $p<.05$. Similarly, alternation exceeding chance was observed in the L_1 line at 20 and 60 days of age, $\chi^2(1)=6.04$, 7.26 , $p<.05$, in the L_2 line at 20 and 30 days, $\chi^2(1)=7.18$, 10.16 , $p<.05$, and finally, at 20 and 60 days postnatally in the C_2 line, $\chi^2(1)=10.28$, 11.62 , $p<.05$.

If spontaneous alternation is a valid indicant of habituation, as has been repeatedly suggested (Anisman & Santi, 1977; Bignami, 1976, 1977; Carlton, 1969) then several permissible conclusions are possible with respect to Experiments 1 and 2. First, the fact that lines demonstrated comparable alternation levels, but differed in terms of levels of activity, suggests that locomotor activity and spontaneous alternation are independent of one another (see also extensive discussions in Anisman, 1975b; Anisman & Kokkinidis, 1976; Kokkinidis & Anisman, 1976a). Moreover, the line differences in activity cannot be solely attributed to differential rates of habituation. Of course, the habituation factor cannot be entirely dismissed, in that habituation may interact with other factors in determining activity differences. With respect to ontogenetic differences, it is interesting that alternation behavior roughly paralleled activity changes. That is, both behaviors were found to increase in a monotonic fashion. Indeed, at 15

days of age the line differences in activity did not take on the adult pattern, and at the same age chance alternation was prevalent in all lines. Given the extensive literature implicating cholinergic mechanisms in habituation, and particularly cholinergic effects in alternation (see Introduction), it is not unreasonable to assume that the absence of a mature cholinergic system may play a role in subserving the development changes in these behaviors. As previously discussed in the introduction, this conclusion is supported not only by behavioral/pharmacological data, but by neurochemical data as well.

Exploration (Experiment 3)

While total number of head dips is the most common measure of exploration in a hole-board task (see discussion in File & Wardill, 1975a,b), it fails to distinguish adequately between exploration per se and other related behaviors. For example, high rates of responding may, on the one hand, reflect a pattern of random responding or, on the other hand, may simply represent successive head dips at a particular hole (i.e. response perseveration). Accordingly, in order to dissociate the precise nature of responding in this task, several analyses were carried out. The first of these addressed itself to the data involving total number of head dips over the duration of the test interval. In contrast, the second analysis selectively evaluated total number of non-repetitive head dips. That is, if a sequence of responding occurred in which an animal remained at the same hole, all but the first response were discarded. An additional response was not recorded until the animal moved to a different hole. Again, if a sequence of responding was noted at this hole, only the first head poke was considered. Finally, it remains necessary to determine whether a given set of conditions results in a greater proportion of alternation between holes than some other set of conditions. Accordingly, the third analysis represented a between treatments comparison based on a ratio of the number of head pokes in different holes divided by the total number

of head pokes. This analysis, it will be recalled, is essentially identical to that employed in Experiment 2 to determine alternation/perseveration behavior.

Figure 4 represents the mean number of head dips for each line at the various test ages. An overview of the ontogenetic pattern of development in each line indicated that regardless of baseline levels of activity (see Experiment 1), maturation of head poking appeared to increase in a roughly monotonic fashion in all lines, $F(4,210)=77.68$, $p<.001$. This finding is in line with other behavioral tasks employed in the present series of experiments (i.e. locomotor activity), suggesting that exploration is likewise dependent on maturational factors. Not surprisingly, the analysis of variance revealed that the lines differed with respect to the number of head pokes, $F(5,210)=27.58$, $p<.001$. More specifically, H_1 and H_2 lines exhibited a greater number of head dips than the remaining lines, and L_1 , L_2 and C_1 mice made more head dips than C_2 . In addition to the main effects, the analysis of variance of the head dip responses yielded a significant Line x Age interaction, $F(20,210)=4.25$, $p<.001$. Subsequent Newman-Keuls multiple comparisons ($\alpha=.05$) on the simple main effects involved in this interaction indicated that although the lines did not differ from one another at 15 days of age, this was not the case as maturation progressed. By 20 days postnatally, indications of response variations as a function of line became in-

Figure 4. Mean number of total head dip responses as a function of Line and Age.

MEAN NUMBER OF HEAD DIPS (TOTAL)

creasingly more apparent, with the H_1 group demonstrating levels of head dipping significantly higher than both Control lines, as well as the H_2 group. At 25 days of age, the 2 High lines exhibited markedly greater head dipping than either the Control or Low lines. In addition, both the C_1 and L_1 lines showed significantly more head dip responses than either the L_2 or C_2 lines. Interestingly, while it has already been pointed out that number of head dips appears to increase throughout development in all lines, the 25 day test interval seemed to reflect a transient period of hyperresponding in the 2 High lines. As in the 20 day old animals, performance exceeded that of the remaining lines. The hyperactivity seen at 25 days in H_1 and H_2 was, however, not sustained, and a substantial reduction in head dips was apparent at 30 days in H_1 and H_2 . At this age, the H_1 , L_1 and C_1 lines exhibited head dipping at a higher level than the C_2 group, with H_1 animals also revealing higher rates of head dipping than the L_2 line. By 60 days of age, an increase in response rate was apparent in the H_1 line, resulting in it being significantly higher than all other lines. The generally low rate of responding in C_2 animals continued to be apparent at this test interval, being exceeded by the H_2 , L_1 and C_1 lines as well as the H_1 line.

As indicated earlier, a second analysis of variance was carried out on the number of non-repetitive head dips. As in

the case of locomotor activity, it was observed that lines differed significantly with respect to the number of different head dips, $F(5,210)=41.33$, $p<.001$. That is, both High lines revealed a greater number of responses than all other lines, with the Low and C_1 lines also showing higher rates than animals of the C_2 line. In addition, the analysis of variance indicated a significant Line $\times$ Age interaction, $F(20,210)=7.13$, $p<.001$. Moreover, inspection of Figure 5, which represents the mean number of non-repetitive head dips for the six lines throughout development, reveals that as in the case of total head dips, this measure followed a fairly progressive increase for all lines, $F(4,210)=62.46$, $p<.001$. Again, a pattern of hyperresponding was apparent in the 2 High lines at 25 days of age, although such a dramatic increase at this time interval was not observed in Low and Control groups. One further point of particular interest is the variation in response levels between lines which occurred as early as 15 days of age. While Newman-Keuls multiple comparisons ($\alpha=.05$) indicated that the differences at this age were not statistically significant, inspection of Figure 5 reveals that responding in the two High lines exceeded, to some degree, responding in either the Low or Control animals. In contrast, such differences between lines were not observable at this early age when total number of head dips was considered (see Figure 4). By 20 days of age, the H_1 line demonstrated a significantly higher number of different head dips than all other lines. At

Figure 5. Mean number of non-repetitive head dip responses as a function of Line and Age.

MEAN NUMBER OF HEAD DIPS
(NON-REPETITIVE)

250

150

50

15

20

25

30

60

AGE

25 days postnatally, the hyperresponding of the 2 High lines was readily apparent, with both lines significantly higher than the Low and Control groups. As with the first analysis, though, differences were somewhat reduced by day 30, when the High lines revealed pronounced reductions in the number of responses to different holes. At this age, the H_1 line was significantly higher than the H_2 , L_2 and C_2 groups, with C_1 animals also higher than animals of the C_2 line. By 60 days of age, differences between the High, and the Low and Control animals were again more apparent. Specifically, the H_1 line was significantly higher than all other lines. In accordance with these results, the H_2 line was higher than C_2 , as well as both Low lines. Finally, relatively high levels of responding were observable in the C_1 line by day 60, with this group showing significantly more responses to different holes, than C_1 , L_1 and L_2 animals.

Related to the two aforementioned measures is an assessment of proportion of responding, or more specifically, the number of non-repetitive responses divided by the total number of responses. Such a measure permits the assessment of overall response patterns; for example, numerous head dips may reflect an extensive level of exploratory-type behavior at all holes, or conversely, may simply reflect continued responding of a perseverative nature at one particular hole. Proportions of responding, as a function of Line and Age, are depicted in

Figure 6. As in the case of the first two measures, a significant difference was found between lines, $F(5,210)=19.71$, $p<.001$. More precisely, H_1 and H_2 lines showed distinctly higher proportion values than Low and Control lines. Moreover, L_1 and C_2 animals were higher than L_2 mice, which in turn demonstrated proportion values above the C_1 line. As with the previous measures, performance was found to vary across ages, in that the proportion of responses decreased progressively from 15 to 60 days, $F(4,210)=6.59$, $p<.001$. In addition to these main effects, analysis of variance yielded a significant Line x Age interaction, $F(20,210)=2.61$, $p<.001$. While no significant variations between lines were observed at 15 days of age in so far as total number of head dips was concerned, Newman-Keuls multiple comparisons ($\alpha=.05$) indicated distinct differences in terms of proportion of responses. More specifically, at 15 days postnatally, the L_1 line was significantly lower than all other groups with respect to the latter measure. Generally speaking, this type of trend persisted throughout ontogenesis. With the exception of 20 and 30 days of age, where groups showed a lack of significant differences, Low and Control animals tended to reveal lower proportions of responding than the high lines. These data suggest that differences in pattern of responding are present between lines even at very early ages, which may not be detected when overall levels of responding are considered. However, the lack of consistency in this respect brings into question the validity of

Figure 6. Mean proportion of head dip responses as a function of Line and Age.

MEAN PROPORTION OF HEAD DIPS

this measure. In particular, at 20 days of age, C_1 animals demonstrated a markedly lower score than its C_2 counterpart. Moreover, Low lines were not found to differ from the remaining lines. By 25 days postnatally, both Low lines, as well as the C_1 group, were significantly below the High lines. In addition, the L_1 line was markedly below the proportion score for C_1 mice. Significantly lower scores were again observed in the Low groups at 60 days, with L_1 and L_2 animals significantly below H_1 , H_2 and C_2 animals. Moreover, the L_1 line was also considerably lower than the C_1 group.

In considering between age changes for each line, a fairly interesting behavioral pattern was observed. In all lines, the proportion score was found to decrease with age i.e. animals tended to exhibit greater frequency of successive head dips into the same hole. The exception to this was in the L_1 line, in which this pattern was broken at 15 days of age when the proportion of head dips was lower than that apparent at 20 days postpartum. It will be recognized that this is in direct contrast to alternation behavior in the Y-maze task, in which the tendency to explore novel arms increases with age. Of course, the method of evaluation is distinctly different in the two tasks. That is, in the Y-maze a perseverative response means a return to the compartment visited two trials earlier, whereas perseveration in the hole board reflects a head dip into the same hole as the previous trial.

It is clear that the perseverative tendency is likely independent of general locomotor activity, in that the most active lines exhibited the least perseverative tendencies. A clearly defined explanation for the developmental changes in head dip pattern is not available. However, one possibility is that with increasing age, the progressive increase in total number of head dips results in habituation of the exploratory tendency, and consequently animals tend to dip more often into the same hole. In young animals, in which habituation does not occur, as often as not they tend to visit different holes. Taking this argument one step further, this would imply that the high level of head dip alternation seen in the High lines is due to a deficit of habituation in tasks involving a motor component. Thus, as in the case of locomotor activity, the slowest decrease in habituation is observed in the High lines, resulting in successive dips in different holes. At the same time, however, it should be recognized that when the spontaneous alternation task is considered, differences in habituation are not observed between lines. A firm resolution between the spontaneous alternation experiment, and the activity and head dip experiments cannot be offered. It should be borne in mind, however, that whereas the alternation task is primarily stimulus bound, the latter two tasks are not. In fact, it has been documented that the pattern of head dipping will vary depending on whether stimulus objects are placed beneath the hole board. As such it may be of value to assess

ontogenetic differences in head dip given the presence versus absence of novel stimulus objects. Pending such an evaluation, the aforementioned conclusions can be considered highly provisional.

Summarizing, in addition to the differences between lines which have already been observed in other behaviors, viz. locomotor activity (see also DeFries et al., 1974; Halcomb et al., 1975), it seems that variations exist with respect to levels of exploration, as measured by total number of head dips in a hole board task. While differences were observed throughout development, they were particularly prevalent at the 25 day test interval, during which time the 2 High lines exhibited a transient phase of hyperresponding. By 60 days of age, differences between lines were somewhat attenuated, although the H_1 group continued to reveal markedly higher numbers of responses than the other lines. In accordance with the data gathered on activity, differences appeared greatest when comparisons were drawn between the High lines and the remaining Low and Control groups. In contrast, the Low and Control lines appeared somewhat more congruent in their levels of responding.

An interesting addition to the present findings on exploration stems from an attempt to dissociate the patterns of responding exhibited by each line in the hole board task. Indeed, when total number of different holes investigated (non-repetitive head dips) was considered, rather than simply a to-

tal of all holes, it was noted that further differences could be discerned among the 6 lines. For example, at 20 days of age, the H_1 line was considerably higher in the number of different holes visited than L_1 and L_2 mice. In contrast, no such differences were recorded when total number of head pokes was used as the method of evaluation. It is noteworthy that the use of this second form of analysis served to emphasize many of the between line differences seen in terms of total head dips, particularly the differences observed between the 2 High lines, and Low and Control groups. At a more general level, the latter analysis supported the notion that H_1 and H_2 animals tend to visit a significantly higher number of different holes than Low and Control animals.

Finally, in terms of proportion of responding it was noted that during ontogenesis Low animals in particular, and Control animals to a lesser degree, revealed markedly lower scores than either of the High lines. Again, it does not seem that these differences simply mirror variations in total amounts of responding. Evaluation of the adult values for example, revealed that L_1 and L_2 animals did not differ from H_2 animals in number of head dips. However, in terms of proportion of responding, both Low lines were significantly below the H_2 group. It would seem that while lines may demonstrate similar levels of responding, distinct differences in patterns of responding may be present.

Given the parallel between locomotor activity and head dipping behavior, both between ages and lines, it may well be the case that the increased level of activity across ages, as well as in the High lines, may be a reflection of the conjoint influence of increased exploration and deficits in habituation. As previously indicated, the argument that head dipping is simply an artifact of heightened activity does not account for the data. For example, the proportion measure of head dips, which is independent of level of activity, confirms the line differences in head dipping. Similarly, at 15 days of age, where pronounced differences were not apparent with respect to activity, differences were recognizable in terms of the pattern of head dipping exhibited.

Air Puff (Experiment 4)

The mean number of photocell counts during the inter-puff intervals for each group are shown in Figure 7 collapsed over blocks of 6 trials. Although the Line x Age x Air Puff interaction was statistically significant, $F(20,540)=2.14$, $p<.01$, these factors did not interact with blocks of trials, $F(40,1080)=1.35$, $p=.076$. Nevertheless, certain Newman-Keuls multiple comparisons ($\alpha=.05$) were carried out on the four-way interaction since specific predictions had been made (Winer, 1962, p.208). As in Experiment 1, a progressive increase in activity was observed in all lines among animals not exposed to the air puff. Moreover, whereas between line differences were not apparent at 15 days of age, the H_1 line exhibited locomotor activity greater than that of the remaining lines between 20 and 60 days of age. The exception to this pattern was in the L_2 line, which revealed levels of activity comparable to that of the 2 High lines at 60 days postnatally.

With respect to the effects of air puff, it was found that at 15 days of age air puff generally had negligible effects on behavior, although in C_1 animals a decline in activity was observed. By 20 days postnatally, the air puff elicited a decrement in motor activity in all lines. Interestingly, in the two Low lines the decrease was not apparent until the second block of trials, whereas in the remaining lines it was apparent from the first block of trials on. At the

Figure 7. Mean locomotor activity during inter-air puff intervals as a function of Line, Age and Air Puff over six minute Intervals. Note: solid lines represent animals exposed to air puff, dashed lines indicate animals not exposed to air puff.

remaining ages, the air puff induced decrease in activity was apparent during the first block of trials in all lines except H_1 and L_1 (60 days). Evaluation of Figure 7 also indicates that the extent of the decrement was most pronounced in the H_1 line from 20-30 days. However, this likely reflects the fact that the Low and Control lines not exposed to the air puff were less active than the High lines, thereby precluding full expression of the response suppression. Clearly, these data parallel those of the previous experiments, showing that response suppression does not occur prior to 20 days of age. These data are also consistent with earlier reports in rats showing deficits in response suppression in aversive situations among young animals (Feigley, 1974). Inasmuch as the High lines exhibited response suppression which equalled or exceeded that of the remaining lines, it cannot be argued that the heightened arousal, defined as increased activity or exploration, was a consequence of deficits in response inhibition engendered by relatively strong, novel stimuli.

The analysis of variance of activity during the 10 min post-air puff session revealed a significant Age x Puff x Trials interaction, $F(16, 2160) = 2.59$, $p < .001$ (Figure 8). Newman-Keuls multiple comparisons ($\alpha = .05$) revealed that activity levels in animals both exposed and not exposed to the air puff, increased with age. However, this increase was somewhat more dramatic between 15 and 20 days of age in animals not exposed to the air

Figure 8. Mean locomotor activity during the 10 minute post-air puff interval as a function of Line, Age and Air Puff over two minute Intervals.

- Note: solid lines represent animals previously exposed to air puff, dashed lines indicate animals not exposed to air puff.

AGE

60

30

25

20

15

MEAN PHOTOCELL CROSSINGS

BLOCKS OF TWO MINUTES

puff. It seems that at these ages, as well as at 25 and 30 days of age, approximately four minutes were required before activity levels in air puff animals matched that of animals not exposed to the air puff. Quite unexpectedly, the air puff did not seem to affect the activity observed in 60 day old animals. Given the absence of a cholinergic inhibitory system at 15 days of age, it would have been expected that little suppression would have occurred, much as was the case during the inter-air puff intervals, while at 60 days the air puff might have had a large effect. The fact that suppression was apparent at 15 days of age is somewhat paradoxical, not only on the basis of the theoretical model proposed, but also because little suppression was observed at this age during the inter-air puff interval. Given these anomalous findings, it is difficult to draw firm conclusions pertaining to maturation of systems responsible for behavioral inhibition. It is possible that the immediate response i.e. that which occurred during the inter-air puff interval, and the delayed response i.e. that following the air puff session, are mediated by different mechanisms. However, at this time there are few data which support such a notion from a developmental vantage. Nevertheless, Anisman and Cygan (1975) have argued that activity and reactivity are subserved by different mechanisms, the former being dopamine mediated and the latter being mediated by norepinephrine. Moreover, a role for acetylcholine with respect to behavioral inhibition has been postulated by a large number of authors. As

such, in considering activity following exposure to strong stimuli, complex interactions between neurotransmitters cannot be overlooked. In effect, differential maturation of the mechanisms subserving the long- and short-term consequences may be a viable possibility.

In addition to the Age x Air Puff x Trial interaction, the analysis of variance yielded a Line x Age x Air Puff interaction which approached statistical significance, $F(20,540)=1.45$, $p=.058$. Newman-Keuls multiple comparisons ($\alpha=.05$) of the simple main effects involved in this interaction, indicated that in H_1 animals air puff produced some retardation in activity, but this was restricted to the 30 day old group. In H_2 , a small degree of inhibition was produced by the air puff which was restricted to 15 and 20 day old animals. In the Low lines, air puff did not seem to affect activity particularly, although in 60 day old L_1 animals there was some degree of response inhibition. Finally, Control animals were unaffected by the air puff treatment. It seems that at none of the ages did air puff result in differential behavioral suppression as a function of the line. Indeed, it is not clear whether any of the observed differences were fortuitous, although this is not unlikely given that they arise in a fairly unpredictable arrangement.

Finally, the analysis of variance was also found to yield a significant Line x Air Puff x Trial interaction,

$F(20,2160)=1.76$, $p<.05$ (see Figure 9). Newman-Keuls multiple comparisons ($\alpha=.05$) revealed the H_1 line to be generally more active than the remaining lines, which in turn did not differ significantly from one another. In all lines air puff was found to induce some degree of behavioral suppression which diminished over the 10 minute post-air puff session. In H_1 , the air puff induced suppression was apparent only during the first two minute block, while in H_2 mice the suppression prevailed for four minutes, and in the remaining lines for approximately six minutes. It seems that the degree of suppression witnessed in the High lines was considerably more transient than it was in the remaining lines. As such, it might be the case that the heightened activity in the High lines may be related to factors involving mechanisms which subserve the long-term suppression induced by strong stimuli. It will be recalled that the short-term effect of air puff i.e. that seen during the inter-air puff interval, was not observed to differentially occur in the six lines, which leads again to the possibility of different mechanisms being involved in the shorter and longer term suppressive qualities of strong stimuli.

Figure 9. Mean locomotor activity during the 10 minute post-air puff interval as a function of Line and Air Puff over two minute Intervals.

Experiments 5 and 6

A number of reports have indicated that both catecholaminergic and cholinergic mechanisms are involved in behavioral arousal (see General Introduction). Moreover, it has been postulated that changing patterns of behavior during maturation may reflect the differential rates of development in central structures associated with these neurochemical systems. Of particular interest to the present investigation is the suggestion that excitatory catecholaminergic structures precede the development of inhibitory cholinergic forebrain structures (Campbell & Mabry, 1972, 1973; Campbell et al., 1969; Fibiger et al., 1970; Remington & Anisman, 1976). While the exact rate of maturation has been shown to be species specific (Fibiger et al., 1970; Remington & Anisman, 1976), the fact remains that changes in ongoing behavior have been associated with the maturation of cholinergic pathways. Indeed, a general decline in activity (Campbell & Mabry, 1972, 1973; Fibiger et al., 1970; Remington & Anisman, 1976), as

well as the onset of habituation tendencies (Bronstein et al., 1974; File & Scott, 1976) have been linked with cholinergic development. It is noteworthy that prior to the apparent development of cholinergic inhibitory mechanisms, animals reveal marked increments in behavioral arousal, a pattern of development which possibly reflects increased catecholaminergic maturation. In fact, it has been recognized that various strains of mice manifest a transient phase of hyperactivity/hyperreactivity at approximately 20 days of age. Indirect evidence for a lack of cholinergic development at this time stems from the finding that anticholinergics, such as scopolamine, are without effect before and during this period of maturation. In contrast, administration of scopolamine produces marked behavioral effects at later ages (Remington & Anisman, 1976). A second point of interest involves the somewhat paradoxical effects of amphetamine during this popcorn stage. More specifically, these latter authors noted that at 21 days of age, when C57BL/6 mice exhibit maximal levels of activity, the response to amphetamine was at its lowest level. As pointed out earlier, this finding has considerable appeal in light of amphetamine's effect in human hyperkinesis.

Based on the aforementioned data, it would seem reasonable to assume that the lines of mice in the present experiments may serve to further elucidate the possible role of catecholaminergic and cholinergic mechanisms in the development

of various patterns of behavior. Of particular appeal is the preliminary evidence suggesting that while these lines vary in levels of locomotor activity, they all appear to exhibit a transient period of hyperactivity/hyperreactivity early in development (approximately 20 days of age). Several questions become readily apparent. For example, are differences in activity between strains related, at least in part, to differences in catecholaminergic and cholinergic involvement? If this were the case, one would expect that pharmacologic manipulations would produce differential responses between strains, according to whether the drug's action is catecholaminergic- or cholinergic-related. Further to this point, the question arises as to rate of development in these neurochemical systems across the various lines of mice. Again, one would expect that such differences may be reflected in response patterns to pharmacologically-induced catecholaminergic or cholinergic changes. Finally, there is the question concerning effects of a catecholaminergic stimulant, such as amphetamine on behavior during the popcorn stage in these lines. Given that the lines of mice used here were selected for differences in baseline levels of locomotor activity, one might expect response to amphetamine inversely related to levels of activity. Moreover, it is possible that amphetamine's paradoxical effect during the popcorn stage is most pronounced in those lines of mice exhibiting highest activity levels, i.e., in H_1 or H_2 .

The purpose of the next two experiments was one of indirectly assessing the role of catecholaminergic and cholinergic factors in the six lines of mice during various phases of development. To this end, the pharmacologic manipulations employed here include the administration of various dosages of amphetamine, a catecholaminergic stimulant, or scopolamine, a cholinergic receptor blocker. From a developmental standpoint, their use may elucidate the rate of maturation of catecholaminergic and cholinergic pathways in a number of mouse lines. In addition, the differences in activity levels between these lines provide the opportunity to evaluate the effects of these agents in animals selectively bred for high and low activity. Unfortunately, it was not within the confines of the present investigation to assess the effects of catecholaminergic and cholinergic manipulations on all the behaviors evaluated in Experiments 1-4. However, it is possible to evaluate the effects of such pharmacologic manipulations on both locomotor activity and spontaneous alternation. These two tasks have been chosen on the basis of the numerous reports suggesting that catecholaminergic and cholinergic mechanisms are integrally involved in both general activity and habituation (see introductory section, Locomotor Activity and Habituation). Keeping these data in mind, the purpose of Experiments 5 and 6 was to elucidate the role of these neurochemical systems in six lines of mice selectively bred for differences in ongoing levels of activity.

Experiment 5: General Activity - Catecholamipergic and Cholinergic Manipulations

Subjects and Apparatus

Subjects were 1680 experimentally naive mice, with each of the six lines (two High, two Low and two Control of generations S₂₇ and S₂₈) equally represented in the various treatment conditions and ages (15, 20, 25, 30 or 60 days of age). All groups had equal numbers of male and female subjects. Animals were housed and bred in the same conditions as described in Experiment 1.

Procedure

At the appropriate age (15, 20, 25, 30 or 60 days), mice were removed from their home cage, randomly assigned to seven groups (n=8/cell), and given intraperitoneal (i.p.) injections of d-amphetamine sulphate (1, 3 or 5 mg/kg), scopolamine hydrobromide (0.5, 1 or 2 mg/kg), or physiological saline (2 ml/kg). Mice were placed in a holding cage for a 15 minute period, after which they were placed in the test chamber for 50 minutes. During this time, activity was recorded at five minute intervals.

Experiment 6: Spontaneous Alternation - Catecholaminergic and Cholinergic Manipulations

Subjects and Apparatus

Subjects consisted of 1200 experimentally naive mice, equally representing the 6 lines of mice (2 High, 2 Low and 2 Control), and the 5 test ages (15, 20, 25, 30 and 60 days of age). There were equal numbers of male and female subjects in each group, and breeding and housing conditions were identical to Experiment 1.

Procedure

At the appropriate age (15, 20, 25, 30 or 60 days), mice were randomly chosen from their home cages and assigned to one of five drug treatment groups ($n=8/\text{cell}$). Subjects were administered i.p. injections of either d-amphetamine sulphate (3.0 or 5.0 mg/kg), scopolamine hydrobromide (1.0 or 2.0 mg/kg), or physiological saline (2.0 mg/kg). The dosages of d-amphetamine and scopolamine employed in this experiment were based on those dosages which produced optimal behavioral effects in the general activity situation (Experiment 5). Following injection, mice were placed in individual holding cages, and tested 15 minutes later as described in Experiment 2.

RESULTS AND DISCUSSION

Locomotor Activity: Pharmacological Manipulations (Experiment 5)

Analysis of variance of the photocell crossings yielded a significant Line x Drug x Age x Blocks interaction, $F(1080,13230)=1.41$, $p<.001$. Since comparisons between ages were not considered a valid procedure owing to interpretational difficulties (see Introduction), the Line x Drug x Block interaction was independently evaluated across ages.

Figure 10 shows mean number of photocell crossings for each line as a function of age, drug and blocks of trials. Newman-Keuls multiple comparisons ($\alpha=.05$) between saline treated animals indicated that generally speaking, activity increased with age in all lines, although some fluctuations within this pattern were apparent. At 15 days of age, performance did not differ among the lines, although activity of the C_1 line was somewhat lower than that of the remaining lines. At 20 days of age, an increase in activity was noticeable in all but the L_1 line; however, the increment was more marked in the H_1 and H_2 lines. Indeed, levels of activity in H_1 exceeded that of the Low and Control lines while performance of H_2 mice exceeded that of L_1 and C_2 animals. This pattern is precisely that observed in the initial experiment on locomotor activity (Experiment 1). At 25 days of age, a small decline in activity was apparent in both High lines, whereas activity increased in the remaining lines. This unexpected decrease

Figure 10. Mean transformed ($\sqrt{x + 0.5}$) locomotor activity as a function of Line, Age and Drug over Blocks of five minutes. The various figures represent 15, 20, 25, 30 and 60 day old animals, respectively. Note: saline (- - - -); d-amphetamine, 1.0 mg/kg (O—O); d-amphetamine, 3.0 mg/kg (□—□); d-amphetamine, 5.0 mg/kg (Δ—Δ); scopolamine, 0.5 mg/kg (●—●); scopolamine, 1.0 mg/kg (■—■); scopolamine, 2.0 mg/kg (▲—▲).

MEAN $\sqrt{X+0.5}$ PHOTOCELL CROSSINGS

25 DAYS

60 DAYS

MEAN $\sqrt{X+0.5}$ PHOTOCELL CROSSINGS

in activity resulted in the elimination of between line differences at this particular age. At 30 days postnatally, the burst of activity seen in the Low lines at 20 days was not apparent and, in fact, activity levels in these lines decreased. As a result, activity in the H_1 line exceeded that of the Low lines. Performance in the Control lines was intermediate to that of the High and Low lines, and did not differ from either significantly. Finally, at 60 days of age levels of activity were again found to increase and although the levels of activity observed in the H_1 line exceeded that seen in the Low groups, the difference was not significant. Generally speaking, the between line differences noted in Experiment 1 were apparent in the present experiment; however, these differences were attenuated and at some ages, i.e. 60 days, were absent.

In considering the effects of the pharmacological treatments, each of the lines will be considered at successive ages, and between line comparisons will be made where appropriate. One caveat is in order here; namely, owing to the complexity of the results and the often observed variations in the most effective drug dosages, the data will be described in general terms, with particular reference to Figure 9. Furthermore, the reader is encouraged to inspect Table 5a, Appendix B for mean values, as well as differences necessary for significance employing Newman-Keuls multiple comparisons. In addi-

tion to the analysis of variance of the photocell crossings, an analysis of variance was carried out on the change in activity within each group relative to the level of activity seen during the first block of trials (activity block 1/activity block 1 plus 2, and so on). Since this analysis proved to be largely redundant with the analysis of photocell crossings, description of the proportional changes observed will be limited to elaboration of the mean photocell crossings. Again, the reader is directed to Table 5b of Appendix A and Appendix B for the source table and means for these data.

With respect to the performance of H_1 mice at 15 days postnatally, d-amphetamine resulted in an increase in activity which was apparent specifically during the latter blocks of trials. As seen in Figure 10, although the drug did not increase activity above that seen in saline animals early in testing, the drug effectively attenuated the normal decline in motility observed over blocks of trials. Scopolamine was also found to result in an increment in activity during the later blocks of trials, at least in the 0.5 and 2.0 mg/kg dosages. Interestingly however, the drug treatments resulted in a retardation of locomotor activity early in testing. This particular finding is not unique in the literature, and in fact, has been reported from this (Anisman, 1976, Anisman & Cygan, 1975; Anisman *et al.*, 1975b, 1976), as well as other laboratories (Oliverio, Eleftheriou & Bailey, 1973). The source for this

type of effect is not immediately apparent, although several suggestions have been offered. Oliverio et al. have proposed a single major gene responsible for the short-term effects of scopolamine. Anisman (1976), however, has criticized this view and indicated that the effects of scopolamine are not of an excitatory nature per se, but rather one of disinhibition. That is, scopolamine eliminates motor suppression which results from factors such as habituation, response inhibition induced by stressors, and so on. At 20 days of age, d-amphetamine was not found to elicit a pronounced increase in locomotor activity, although a definite trend in this direction was apparent. Scopolamine, likewise, was not found to increase locomotor activity and indeed, reduced habituation to a degree. It may well be the case that the particularly high levels of activity seen in 20 day old H₁ animals precluded drug effects from being observed. At 25 days of age, d-amphetamine in the H₁ line produced a very pronounced increase in motility which was maintained throughout the test session. Scopolamine similarly increased activity, and contrary to the position maintained by Anisman and Cygan (1975), this effect was apparent during the first block of trials, a time at which habituation should not have occurred. It should be borne in mind, however, that as previously indicated the unusually low level of activity seen at this particular age in H₁ animals and the very pronounced drug effects may have been a consequence of the in-

hibition present at this age. The effects of the drug treatments observed at 25 days of age were maintained at 30 and 60 days as well. This was the case not only with respect to the general excitation due to the drug, but also in terms of the fact that the decrement in activity seen in non-drugged animals i.e. habituation, was attenuated.

The performance of mice in the H_2 line paralleled, in many ways, that seen in H_1 , although as indicated earlier, the H_1 line was initially found to be somewhat more active than its counterpart. In the H_2 animals, d-amphetamine produced a very profound increase in activity at 15 days of age. Indeed, this effect was apparent during the first block of trials. Regarding scopolamine, the 2.0 mg/kg dosage resulted in behavioral disinhibition i.e. the decrease in activity seen in saline animals was attenuated. As seen in Figure 8, activity during the later blocks of trials was increased by the two lower dosages of scopolamine. Moreover, evaluation of Table 5a, Appendix B, clearly indicates a marked decrease in activity in saline treated animals, whereas activity in scopolamine treated mice, if anything, increased over trials. While this clearly suggests a disinhibitory effect, the possibility needs to be considered that peak drug effects are not obtained until some 30-40 minutes following the commencement of testing. At 20 days of age, d-amphetamine not only attenuated the course of habituation, but induced behavioral excitation as early as

the first block of trials. This effect, it will be recalled, differs from that seen in H_1 , where minimal effects of d-amphetamine were detectable. In the case of scopolamine, an initial retardation of activity was apparent. However, as in the case of H_1 mice, the drug effectively attenuated habituation (see Table 5a, Appendix 3), and yielded elevated activity levels relative to saline controls. At 25, 30 and 60 days postpartum, both scopolamine and d-amphetamine increased activity, although the effectiveness of these treatments was dose-dependent. As seen in Table 5a, Appendix B, the course of decline in activity was minimized, though habituation was clearly apparent at these ages.

Turning to the performance of the Low lines, d-amphetamine was not found to produce behavioral excitation in L_1 at 15 days of age. This is in direct contrast to the effects observed in the High lines. Moreover, while scopolamine produced a decline in activity early in testing, a recovery of locomotor activity was not apparent and performance of saline treated animals exceeded that of scopolamine animals throughout testing. By 20 days of age, both d-amphetamine and scopolamine produced marked increments in locomotion as well as dishabituation, and this effect was maintained at all subsequent ages. The performance of L_2 mice showed several variations from the L_1 line. At 15 days postnatally, a pronounced d-amphetamine excitation was apparent, and while scopolamine

elicited motor retardation, this effect was not nearly as marked as in L_1 . As in the case of L_1 though, d-amphetamine increased activity in 20 day old animals of the L_2 line; however, scopolamine was ineffective in this respect. It should be emphasized that once again, scopolamine did produce a dishabituation effect. From 25-60 days of age, both drugs increased activity and attenuated the decline observed in the absence of the drug treatment. Moreover, the effect of the drug treatments was directly related to the age of testing.

Finally, in considering the Control lines it must be noted from the outset that for all ages, the performance of these lines was not intermediate between High and Low lines, but rather tended to resemble the Low animals. At 15 days of age, d-amphetamine engendered activity increases in both the C_1 and C_2 lines, while scopolamine reduced activity in C_2 throughout testing, and had an initially retarding effect in C_1 . As in the case of the remaining lines, activity in scopolamine treated C_1 animals increased over blocks of trials and by 40 minutes into the test session, exceeded saline values. At 20 days postnatally, d-amphetamine augmented activity in both Control lines as early as the first block of trials, while the effect of scopolamine was primarily one of attenuating the between blocks decrease in activity. As in the High and Low lines, both scopolamine and d-amphetamine effectively increased activity at 25 days of age and beyond, and not surprisingly,

these drug effects were most apparent later in testing.

Inasmuch as 15 days of age is the age believed to reflect the period during which the cholinergic system is immature, the pharmacological effects observed at this age will be summarized separately from the effects seen at other ages. If a lack of behavioral differences between lines was due to the fact that the cholinergic system was immature at this time interval, then no increase in activity should have been apparent in any of the lines with respect to scopolamine treatment. The fact that some degree of response disinhibition was apparent in H_1 animals suggests a certain degree of maturation in the cholinergic system of this line at 15 days. It is difficult to ascertain why scopolamine attenuated levels of activity throughout testing in the remaining lines. The possibility exists that (a) the drug treatment elicits a compensatory response, resulting in response inhibition (Anisman, 1975b), (b) the Low lines maintain particular genes which lead to the paradoxical scopolamine effects (Oliverio et al., 1973) although this is unlikely given that these lines are not inbred, (c) since the lines exhibited a limited amount of response inhibition, scopolamine has the usual effect of decreasing, rather than increasing activity (Bignami & Michalek, 1977), or finally, (d) the drug may have toxic effects which, in the particular dosages employed, are effective only in Low and Control lines. With respect to the effects of d-amphetamine, be-

havioral excitation, or at least reduction in the course of habituation, was observed in all but the L_1 line. Indeed, even in this line some degree of response disinhibition was apparent, albeit this was not significant. These data would suggest maturity of those mechanisms which mediate the amphetamine effect i.e. dopaminergic and possibly noradrenergic as well.

With respect to the performance seen at 20 days and beyond, it is clear that the drug effects were not particularly surprising. In particular, both drugs effectively increased locomotor activity and/or attenuated the course of decline in locomotor activity ordinarily observed. As such, both the catecholaminergic and cholinergic systems reach maturity by 20 days in all lines. It is important to note that these data, while consistent with the results observed in rats (see Introduction), are at odds with previous mouse studies (Remington & Anisman, 1976). Specifically, while the catecholaminergic system was found to mature early, it was concluded that maturation of the cholinergic system did not occur until approximately 21-28 days postpartum. Moreover, in the most active inbred strain employed by Remington and Anisman i.e. C57BL/6, d-amphetamine was found to increase activity in all ages except the 21 day test interval, during which this particular strain exhibited the highest level of activity. As such, it would seem at first blush that the C57BL/6 strain might be more ade-

quately employed in the evaluation of the effects of retarded cholinergic development and further, as a potential model for human hyperkinesis. This notwithstanding, it is clear that some differences between lines were observed with respect to cholinergic development. The implications such developmental differences in cholinergic maturation have with respect to behavioral arousal will be detailed in the General Discussion.

Spontaneous Alternation: Pharmacological Manipulations
(Experiment 6)

The mean proportion of alternations, as a function of line, age and drug, are shown in Figure 11. The analysis of variance of the alternation scores yielded a significant main effect for Drug, $F(4,1050)=59.59$, $p<.01$, in addition to a significant Line x Age interaction, $F(20,1050)=1.77$, $p<.05$. With respect to the Drug main effect, Newman-Keuls multiple comparisons ($\alpha=.05$) indicated that both the scopolamine and d-amphetamine treated groups alternated at levels significantly below saline controls. Moreover, it was observed that those animals treated with d-amphetamine alternated at levels significantly lower than mice which received either dosage of scopolamine. With respect to the Line x Age interaction, Newman-Keuls multiple comparisons indicated that at 15 days of age, the C_1 group revealed alternation values significantly below that observed at 25 and 30 days postnatally. In none of the other lines was alternation found to increase with development. In terms of between-line differences, the only significant effect was that at 60 days postpartum L_2 mice alternated significantly below mice of the H_1 line. While a significant Line x Age x Drug interaction was not observed, inspection of Figure 11 indicates several points of interest with respect to the present investigation. As mentioned earlier, the data of the present study are consistent with numerous other reports

Figure 11. Mean proportion of alternation responses as a function of Line, Age and Drug Treatment.

Note: saline (- - - -); d-amphetamine, 3.0 mg/kg (O—O); d-amphetamine, 5.0 mg/kg (Δ — Δ); scopolamine, 0.5 mg/kg ($\bullet$ — $\bullet$); scopolamine, 2.0 mg/kg ($\blacktriangle$ — $\blacktriangle$).

(Adkins et al., 1969; Anisman & Kokkinidis, 1975; Kokkinidis & Anisman, 1976a,b,1977), in that administration of an indirect catecholaminergic stimulant, such as d-amphetamine, resulted in a significant decrement in alternation responding i.e. perseveration. The fact that this effect was observed at the earliest test interval (15 days) supports the morphological and biochemical evidence indicating that catecholaminergic pathways are well-developed by this point in maturation (see Introduction, Section I). It is noteworthy that although the amphetamine effect in L_1 at 15 days of age was relatively small in the locomotor activity task, a very pronounced effect was observed in the alternation task. Indeed, in contrasting the two behaviors, it is apparent that a more marked effect on alternation was induced by scopolamine in all six lines, supporting the notion (Anisman & Kokkinidis, 1975), that alternation/perseveration may be a more sensitive index of drug effects than locomotor activity. With reference to administration of scopolamine, the present findings involving the 60 day old animals verified earlier reports showing that scopolamine reduced levels of alternation (see for example Anisman & Kokkinidis, 1975; Douglas & Isaacson, 1966; Kokkinidis & Anisman, 1976a,b, 1977). That is, in those lines which revealed alternation levels above chance (e.g. H_1 , C_1 , C_2), treatment with this pharmacologic agent reduced alternation to approximately chance levels. Administration of scopolamine to those lines which alternated at approximately chance in the non-drug state (e.g., H_2 , L_1 , L_2).

resulted in decreases in alternation responding, although these decreases appeared to rest within the range of chance levels ($50\% \pm 10\%$). From a developmental standpoint, the present findings concerning the scopolamine effects were somewhat less clear than those seen with d-amphetamine. Inspection of Figure 11 indicates that the effect of scopolamine was minimal at 15 days of age in both Low lines. Paradoxically, in both High lines the scopolamine effect was apparent at this age, while in Controls the effect was intermediate. These findings may be taken as indirect evidence that while the cholinergic system is not fully mature by 15 days in Low lines, it appears to be functional in both H_1 and H_2 mice, and possibly in Control lines as well. It should be underlined that the behavioral effects observed in the alternation task closely paralleled those seen in locomotor activity. That is, at 15 days of age scopolamine was also found to increase activity, at least later in testing, in the H_1 and H_2 lines. In both Low lines, as well as C_2 , the drug was virtually without effect, while in C_1 animals some degree of dishabituation was observed. Interestingly, although responsiveness to scopolamine in Low and Control lines appeared to undergo a small, but observable, increment over development, such was not the case for the High lines. It is obvious that these data deserve further consideration in light of other behaviors investigated in the present experiments, and therefore will be subject to further review in the General Discussion.

χ^2 analyses were carried out for the total group alternation scores to determine whether alternation differed from chance levels. In terms of the saline groups, the results were inconsistent with previously reported data (see for example Egger, 1973a,b; Egger et al., 1973), in that perseveration was not apparent in the younger groups. Indeed, in the present experiment all lines were found to reveal alternation scores at chance levels during the first test interval (15 days of age), with the exception of the C₂ group which alternated significantly above chance $\chi^2(1)=9.16$, $p<.05$. If any indications of perseverative responding were apparent at younger ages, they occurred in the High lines. Specifically, as in Experiment 2, H₁ and H₂ animals revealed scores below chance at 20 days postnatally. The precise mechanisms which might account for this finding will be discussed in further detail in the discussion. However, for the purpose of the present experiment, it is sufficient to recognize that the results were fairly consistent with those of Experiment 2. All but the 2 High lines alternated at chance levels at 20 days postpartum. By 25 days of age, the saline groups for all lines were alternating at chance levels and by 30 days, the tendency to alternate at levels above chance became increasingly more apparent. More precisely, levels above chance were recorded for H₂, L₂ and both Control lines. This trend persisted into adulthood, with H₁ animals and both Control groups alternating significantly above chance by 60 days of age.

With respect to catecholaminergic manipulations, the present experiment is in strong agreement with those studies indicating that d-amphetamine produces alternation behavior significantly below chance i.e. perseveration (Anisman & Kokkinidis, 1975; Kokkinidis & Anisman, 1976a,b, 1977). Further to this point, investigation of ontogenetic variations in response to d-amphetamine administration indicated support for the notion that the catecholaminergic system develops relatively early during the maturational process (see Introduction, Section I). Moreover, this pattern appears to hold true for all lines employed in the present investigation. Specifically, in all lines and ages except for the H₂ group at 60 days, the lower dose of d-amphetamine (3.0 mg/kg) elicited alternation scores significantly below chance (see Table 2, Appendix C). While the effects of d-amphetamine (5.0 mg/kg) were slightly less general during the earlier ages, they were nevertheless readily apparent. At 15 days of age, the higher dose of d-amphetamine produced alternation scores significantly below chance in all but the L₂ group. The only other exceptions occurred at 25 days of age, when the L₂ group, as well as L₁ and H₁ mice, alternated at chance levels (see Table 2, Appendix C). It should be pointed out, however, that in the four exceptions observed, ratios of responding were in the direction of perseveration, although statistical significance was not reached. A cursory examination of Table 2, Appendix C, indicates that in all other lines and ages, d-amphetamine (5.0 mg/kg) resulted

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in alternation scores significantly below chance. Together, these data provide strong evidence that an indirect catecholaminergic stimulant, such as d-amphetamine, produces perseverative responding in a spontaneous alternation task, and that this effect is prevalent from early postnatally (e.g. 15 days) to adulthood.

It is of interest that the effects of cholinergic manipulations i.e., scopolamine, were somewhat less clear than catecholaminergic-induced alterations. However, it is generally the case that the present findings offer indirect support for the various morphological, biochemical and behavioral studies discussed earlier. (see Introduction, Sections I and II) Specifically, at a central level, the cholinergic system develops at a later time period than the catecholaminergic pathways. For example, while the effect of d-amphetamine was prominent as early as 15 days of age, this was not the case for scopolamine treatment. In point of fact, only the two High lines revealed a pronounced response to anticholinergic administration during the earliest test interval, and similarly the drug effect on locomotor activity was most pronounced in these lines as well. At this time, scopolamine (0.5 mg/kg) significantly reduced alternation in H₁ and H₂ animals to less than chance levels, $\chi^2(1)=31.76, 23.34; p<.05$. In contrast, the higher dosage of scopolamine (2.0 mg/kg) failed to elicit significant changes in responding at 15 days of age. When considered with

the locomotor activity data of Experiment 5, it seems that in the High lines cholinergic maturation occurs earlier than it does in the Low and Control lines. These findings, however, will be discussed in further detail in later sections of this paper. By 20 days postpartum, the effect of scopolamine treatment was somewhat more apparent, with scopolamine at both 0.5 and 2.0 mg/kg significantly reducing alternation scores in the H_1 and H_2 lines, $\chi^2s(1)=26.08, 49.40, 45.64, 10.30; p<.05$. Of particular note is the finding that while the effects of the anticholinergic became more identifiable by 20 days postpartum, there were some inconsistencies in terms of the more effective dosage.

The results obtained at 25 days of age were comparable to those seen at 20 days; in that the effect of scopolamine was apparent across each of the three sets of bilaterally selected lines. More specifically, as seen in Table 2, Appendix C, scopolamine in the higher dosage in H_1 , and both dosages in H_2 , elicited perseveration, $\chi^2s(1)=44.27, 38.69, 46.27; p<.05$. In C_1 and C_2 , the lower and both dosages, respectively, induced perseveration, $\chi^2s(1)=59.96, 41.38, 38.00; p<.05$. Finally, in L_2 mice the higher dosage elicited a perseverative effect, $\chi^2(1)=56.26, p<.05$, while in L_1 the value obtained with the lower dosage approached significance. By 30 days of age, the effectiveness of scopolamine with respect to the High lines was somewhat attenuated, with only the H_2 line's alternation

scores reduced below chance with the two dosages of scopolamine, $\chi^2s(1)=30.26, 11.48; p<.05$. The remaining anticholinergic effects stemmed from the administration of scopolamine in the 0.5 mg/kg dosage, which significantly reduced alternation scores in L_1 and C_1 animals, $\chi^2s(1)=11.88, 93.30; p<.05$, while increasing the scores for L_2 animals, $\chi^2(1)=6.66, p<.05$. The reduced effects of scopolamine observed in High animals were again observed at 60 days of age. Indeed, the only significant effect was seen with scopolamine (0.5 mg/kg), which significantly reduced alternation scores in H_2 mice, $\chi^2(1)=20.14, p<.05$. Low levels of alternation continued to remain apparent in Low and Control lines. In the lower dosage (0.5 mg/kg), scopolamine reduced alternation scores in L_1, L_2 and C_2 animals to below chance levels, $\chi^2s(1)=16.94, 5.22, 11.98; p<.05$. At 2.0 mg/kg, scopolamine also reduced alternation scores to below chance in the L_2 line, $\chi^2(1)=7.70, p<.05$.

While the aforementioned data appear, at first glance, relatively ambiguous, several points deserve pursuit. First, while the effects of scopolamine appeared in the High lines at 15 days of age, this was not the case for Low and Control groups. These data suggest that in H_1 and H_2 mice, the central cholinergic system is more advanced at 15 days of age than it is in mice of the Low and Control lines. Adding yet more information to the present study are the findings that indicate responsiveness to scopolamine increased in Low and Control ani-

mals during later ages. In sharp contrast, anticholinergic effects in the High lines, particularly H₁, appeared somewhat attenuated at 25 days and beyond. Finally, although the direction of scopolamine induced changes was consistent in the two High lines i.e. decreased, alternation performance in the Low and Control lines was often inconsistent. Whether this finding is linked to the fact that saline controls in the present study do not uniformly alternate at above chance levels, remains subject to further discussion. Indeed, earlier studies which investigated the effects of scopolamine on spontaneous alternation (see for example Anisman & Kokkinidis, 1975; Kokkinidis & Anisman, 1976a,b,1977) employed strains exhibiting control levels of alternation significantly above chance. Generally speaking, however, the results here support the notion that while scopolamine does not reduce alternation to the perseverative levels indicative of d-amphetamine, it does reduce overall levels of alternation responding. These results will be re-examined in the General Discussion, with specific implications drawn regarding effects on habituation, as compared to drug-induced changes of a perseverative nature.

GENERAL DISCUSSION

In considering the results of the present investigation, the non-pharmacological experiments will be evaluated first, followed thereafter by a discussion of the relationship between behavioral differences in the non-drug state, and those seen after treatment with effects of scopolamine or d-amphetamine. In accordance with earlier work carried out by DeFries and his associates (DeFries et al., 1974; Halcomb et al., 1975), the High lines were found to be more active than the remaining lines when tested at adulthood. However, the Control lines were not found to be intermediate between the High and Low lines, but rather tended to resemble the behavior of the Low lines. It is particularly important to note that those line differences in activity which were obtained, became apparent as early as 20 days postpartum and were maintained thereafter. However, at 15 days of age when neither the cholinergic nor serotonergic systems are thought to be mature (Campbell & Mabry, 1973; Campbell et al., 1969; Feigley, 1974; Mabry & Campbell, 1973; Moorcroft et al., 1971), the line differences were not detectable. In the past, such data have been taken to suggest lack of development of those mechanisms responsible for inhibition and indeed, several authors (Williams et al., 1975) have postulated that at this age habituation of emitted responses does not take place. In accordance with such a view, spontaneous alternation was

found to be directly related to age of testing. However, the lines did not exhibit differences in levels of alternation, suggesting that while variations in activity across development might be related to habituation, the line differences in activity are probably independent of habituation rates. Indeed, when habituation is examined within the locomotor task, it is clear that the Low, Control and High lines demonstrate roughly comparable decrements in activity over a 50 minute session. If, in fact, the spontaneous alternation task is an adequate measure of habituation and is independent of differences in baseline levels of locomotor activity (cf. Anisman, 1975; Anisman & Kokkinidis, 1975; Kokkinidis & Anisman, 1976a,b), then some other aspect of the animal's repertoire, which might be related to habituation, might account for the line differences.

As indicated in the introduction, exploratory behavior and habituation are intricately related, but may be subserved by different mechanisms. That is, although habituation should not progress when exploration levels are high, this does not necessarily imply that habituation will take place given low levels of exploration. Indeed, in considering the line differences in exploration, as measured in the hole board task, it is clear that the High lines exhibited exploratory behavior well in excess of that demonstrated in the remaining lines. As in the case of locomotor activity, these line differences were not apparent at 15 days of age, but with few exceptions became

increasingly more apparent across development. This, paranthetically, was observed with respect to total number of head pokes, as well as number of non-repetitive head pokes. In fact, the High lines tended to exhibit greater alternation of holes visited.

In terms of response inhibition induced by an air puff, a fairly consistent pattern of development is apparent. That is, during the inter-air puff interval, response suppression was observed at 20 days and beyond, while at 15 days suppression was negligible. These data are in accord with the notion that inhibition, or rather the mechanisms that subserve inhibition elicited by strong stimuli, are not mature at 15 days postpartum.

When the results of the nonpharmacological experiments are considered together, several permissible formulations can be deduced. One caveat needs to be emphasized however. That is, owing to the complexity of the paradigms employed, as well as the fact that on numerous occasions the parallel between the two High lines was lost, these considerations can at best be considered highly provisional.

The fact that activity increased in a monotonic fashion across ages in all lines is inconsistent with numerous studies in rats showing peak activity between 15 and 20 days of age. Since most experiments do not consider variations in size of the organism across ages, as well as maturational differences

in terms of musculature and sensory systems, the pattern of locomotor activity seen in the present investigation is not theoretically embarrassing. Indeed, one might question the validity of evaluating developmental differences using tasks which are, or may be, unduly influenced by the maturation of peripheral systems. Differential development of musculature and sensory systems notwithstanding, it is of particular interest that the line variations clearly seen in adult animals are only vaguely present, if at all, at 15 days of age. These findings would suggest that the mechanism(s) responsible for the line differences are not yet matured at 15 days. Given the overwhelming amount of data indicating involvement of acetylcholine in locomotor activity (see reviews in Anisman, 1975; Bignami, 1976, 1977; Carlton, 1969), as well as the fact that the cholinergic system is relatively immature until 3 weeks postpartum, it is a reasonable assumption that this neurotransmitter plays a prominent role in the line and age differences in locomotor activity observed in the present investigation.

Inasmuch as the line differences were not observed in alternation behavior suggests that this behavior and locomotor activity are independent of one another. That is, locomotor activity probably does not influence alternation performance and further, these behaviors are regulated by different though, as previously mentioned, possibly overlapping mechanisms. The

fact that alternation increases with age in all lines suggests that habituation processes mature with ontogeny. Yet, the absence of line differences in this behavior precludes the possibility that the activity differences in lines is a reflection of differential rates of habituation.

When the remarkable parallel between exploration and locomotor activity is considered, it seems that the exploratory factor may better explain the developmental and line differences in ambulation. That is, with increasing age, the exploratory tendency becomes more prevalent. Similarly, the High lines tend to generate a higher level of exploration than the remaining lines. In effect, the suggestion here is that the High lines, owing to a greater explorative tendency, also exhibit greater levels of activity. One might argue the converse; namely, the exploration is an artifact of heightened levels of activity. This possibility, however, is weakened by the fact that animals of the High lines tended to explore both the same hole and different holes more frequently than the remaining lines in adulthood. More importantly, at 15 days of age, where total head dips and total non-repetitive head dips did not indicate differences between lines, H_1 and H_2 mice exhibited a somewhat greater alternation of dipping responses. It is our contention that the alternation measure is likely a more valid index of exploration than total number of head dips.

The notion that exploratory differences might account for developmental variations in locomotor activity has recently received support from pharmacological studies. For example, Young, Ervin and Smith (1976) noted that developmental changes in response to 6-OHDA could not be attributed to emotionality factors or response suppression induced by novel stimuli. These authors suggested that the drug effects were more appropriately assigned to changes in exploratory behavior related to damage to forebrain catecholaminergic terminals. In the same fashion, Campbell and Randall (1975, 1977) have shown that the effect of amphetamine in immature rodents is largely dependent on stimulus factors viz., in this case, the presence or absence of the maternal parent or littermates. It may well be the case that the effect of amphetamine on exploratory behavior acts in compliance with the particular needs of an organism at a given age. That is, in the presence of the maternal parent amphetamine increases selective attention, thereby assuring that the young organism does not wander far off. However, in the absence of the maternal parent innervation of noradrenergic neurons, in this case via amphetamine, increases the exploratory tendency, thus maximizing the probability of the necessary parent being located. In effect, the action of amphetamine is twofold: namely, increasing attention given biologically significant stimuli or at least stimuli of importance given a particular environmental

array, and second, increasing exploratory tendencies in the absence of these stimulus arrangements (see Barkley, 1977a, b).

Summarizing, it appears that behaviors related to response inhibition i.e. habituation and response suppression due to air puff, are not manifested at 15 days of age. Given that these behaviors have been linked repeatedly to cholinergic mechanisms (Anisman, 1975; Bignami, 1977; Bignami & Michalek, 1977; Carlton, 1969; Carlton & Markiewicz, 1971, 1973), it is likely that the absence of these behaviors is due to the immaturity of the cholinergic system. Such a conclusion was previously arrived at by numerous investigators evaluating not only locomotor activity (Campbell et al., 1969; Feigley, 1974; Moorcroft et al., 1974; Remington & Anisman, 1976), but spontaneous alternation (Egger, 1973a,b; Egger et al., 1973), and passive avoidance (Feigley, 1974). In contrast to behaviors involving response inhibition, it seems that exploration, at least as measured by alternation of head dip responses, is apparent at 15 days of age. Since this behavior has been linked to noradrenergic mechanisms (Bresler et al., 1976; Strombom, 1975) which presumably mature relatively early, this finding is not altogether surprising. It is also noteworthy that the results of the present investigation provide prima facie evidence suggesting that the noradrenergic system might also play some role in the line differences observed in locomotor activity. That

is, the High lines tended to exhibit greater levels of head dip responses, but did not differ from the remaining lines in those behaviors involving an inhibitory component.

Turning at this point to the pharmacological effects observed, one critical consideration must be borne in mind. Most investigations concerning developmental changes in response to scopolamine have considered level of activity as the dependent measure (see for example Campbell et al., 1969; Carlton, 1961, 1963, 1969; Herman, 1975; Payne & Anderson, 1967; Remington & Anisman, 1976; Stewart, 1975), although as previously indicated, of course, passive avoidance (Feigley, 1974), and spontaneous alternation have been considered as well (Anisman & Kokkinidis, 1975; Douglas & Isaacson, 1966; Kokkinidis & Anisman, 1976a,b, 1977; Leaton & Utell, 1970). It is inaccurate to assume that the lack of change in total activity reflects immaturity of the cholinergic system, even when a wide series of dosages are employed. To be sure, it has been demonstrated on numerous occasions that scopolamine will affect inhibition or habituation without producing a concomitant change in locomotor activity. For example, scopolamine is frequently observed to decrease activity shortly after drug administration, but to attenuate the typical decline in locomotion seen in non-drugged animals (Anisman, 1975b; Anisman & Cygan, 1975). By the same token, a dosage which does not influence locomotor activity, may engender a very large and long lasting effect once inhibition is elicited e.g., by stressors

(Anisman, 1976; Anisman & Cygan, 1975). It seems that the effect of scopolamine is one of disinhibition or dishabituation, as opposed to genuine response excitation as is probably the case with d-amphetamine. Accordingly, in considering the results of the pharmacological experiments, locomotor activity will also be discussed in terms of temporal changes in response patterns.

In accordance with numerous other investigations, scopolamine failed to increase activity in any of the lines at 15 days of age. While this might have been taken as evidence of a totally immature cholinergic system, certain aspects of the present data would argue otherwise. Namely, in both High lines, and particularly H₂, the effect of scopolamine became increasingly more accentuated as testing continued. Whereas scopolamine initially decreased locomotor activity, this was not the case later in testing. Not only was activity not observed to decrease, as was the case in saline treated animals, but it in fact increased, resulting in saline animals revealing lower activity levels late in testing. Some evidence of this phenomenon was apparent in C₁ animals as well, although the effect here was considerably less pronounced. In the case of d-amphetamine, increased activity in all lines was demonstrated at 15 days of age, albeit the increase in L₁ was relatively small. Inasmuch as dopamine is thought to mediate the locomotor stimulant actions of d-amphetamine (Carlsson, 1970; Creese & Iversen, 1972, 1974; 1975a; Kelly & Iversen, 1976;

Roberts et al., 1975; Rolinski & Scheel-Kruger, 1973), it is highly likely that the dopaminergic system is mature in all lines at 15 days postpartum. Moreover, given the effect of scopolamine in H_1 and H_2 mice at this age, it would seem that some degree of maturity of the cholinergic system should be considered. These conclusions are largely verified by the drug effects on spontaneous alternation. More explicitly, d-amphetamine successfully elicited the perseverative tendency in all lines at 15 days of age, as was the case for later ages. In both High lines, scopolamine was also found to elicit some degree of perseveration at 15 days postpartum, a time at which alternation occurred at chance levels. In contrast, in the Low lines scopolamine was entirely ineffective at 15 days. Finally, a certain degree of scopolamine effect was apparent in the Control lines, although as seen in Figure 11 a perseverative tendency was not apparent in either Control line at this age. If one assumes that the cholinergic system is relatively more mature at 15 days of age in the H_1 line than the remaining lines, then one is able to postulate the source for the differential levels of activity observed between lines. It will be recalled that the line differences in locomotor activity were not detectable at 15 days of age, although they were at later ages. It may well be the case that mechanisms other than cholinergic are responsible for the line variations in activity in adult animals. However, owing to the early maturation of the cholinergic system, whose role is one of inhibition, the

elevated activity in High lines which otherwise would be apparent, is minimized. Once the cholinergic system is mature in the Low and Control lines, thereby providing inhibition in these lines, the line differences in activity should become apparent. Indeed, at 20 days of age, where pronounced effects on habituation of locomotor activity were apparent in the Low and Control lines, the High lines tended to be more active. This difference became yet more apparent at 25 days of age, which not surprisingly coincided with more marked scopolamine effects in Low and Control mice with respect to both activity and alternation.

The possibility had been considered that the High lines might be employed as a model for human hyperkinesis, particularly at 20 days postnatally when 'popcorn' behavior is typically observed. The fact that d-amphetamine had consistent effects in the High lines throughout development i.e. at no time did amphetamine produce a decrease in activity, argues against such a model as being overly simplistic. At the same time, however, an additional set of factors should be considered. That is, d-amphetamine at all ages, and in fact all lines, produced a perseverative tendency. Kokkinidis and Anisman (1976,a,b, 1977) have shown on numerous occasions that this perseverative tendency deals with stimulus, as opposed to response perseveration. Moreover, it may well be the case that amphetamine influences attentional properties (Campbell &

Randall, 1975, 1977) or some interphase between attentional and reinforcing mechanisms (see Kokkinidis & Anisman, 1977). As such, the effects of amphetamine, at least in the hyperactive child and possibly normal children as well, may be simply one of indirectly affecting habituation by augmenting selective attention to specific sets of stimuli. Such an hypothesis is not a unique one with respect to the hyperactive syndrome in humans (Barkley, 1977a; see reviews in Douglas, 1972; Barkley, 1977b), and certainly deserves further consideration. In addition, however, it should be considered that other neurotransmitters may play a role in this respect. It has, for example, been shown that cholinergic agonists attenuate or at least reduce amphetamine induced perseveration (Kokkinidis & Anisman, 1976a). Similarly, in the present investigation the perseverative effects induced by amphetamine were reduced across ages, albeit this effect was inconsistent in the Low lines. It is not unlikely that with increased maturation of the cholinergic system, the catecholaminergic stimulation elicited by amphetamine was more effectively antagonized. Of course, it is also possible that the developmental differences with respect to the drug treatments were a consequence of changes in the development of the blood-brain barrier i.e. lesser penetration of drug into the brain with increasing age. Such a notion, however, requires further evaluation involving peripherally acting analogues of d-amphetamine.

When the pharmacological experiments are considered together with other reports, several pertinent caveats and conclusions can be derived. First, given that the cholinergic system matures relatively slowly, but also may vary in different lines as well as different strains of mice (Remington & Anisman, 1976), leads to the suggestion that this system plays an integral role in accounting for genetic and ontogenetic differences in several behaviors. While the results of the present investigation do not speak directly to such an issue, it should also be considered that drug effects on catecholaminergic systems might also reflect direct or indirect influences in terms of cholinergic activation. Indeed, such a notion has not only been advanced to account for response to stressors (Anisman, 1975, 1977), and a variety of pathological states (Davis & Janowsky, 1975; Shopsin, Janowsky, Davis & Gershon, 1975; Fann, Lake & McKenzie, 1975), but more recently to the fact that amphetamine may induce decreases, as opposed to increases, in activity as a function of developmental age (Sorenson, Vayer & Goldberg, 1977). Coyle and Campochiaro (1976) have, in fact, demonstrated that drugs which block dopaminergic activity also affect cholinergic activity as well (see also Agid et al., 1974; Ladinsky et al., 1975; Sethy & Van Woert, 1974); however, this change appears to occur once cholinergic neurons in the striatum begin differentiation.

At this point, one might question the value of an animal model for the hyperkinetic syndrome, given that the results of the present investigation were not, to say the least, overly compelling. Nevertheless, such an approach is certainly with some merit, and in fact, has recently been noted as a potentially valuable source of information with respect to the biochemical factors which might underly hyperkinesis (Barkley, 1977b). Animal models have been incorporated as tools in evaluating a variety of human pathological disorders (see for example Akiskal & McKinney, 1975; Anisman, 1975; Ljungdahl & Johansson, 1974; Mogilnicka & Braestrup, 1976; Seligman, 1975; Senay, 1966; Takahashi et al., 1976; Wortman & Brehm, 1975), and these attempts have not been without hazards, misinterpretations, and surprisingly, political overtones (see review in Anisman & Bignami, 1977). At the same time, however, there are numerous instances in which such generalizations have been employed appropriately. The model presented by Campbell and Randall (1975, 1977), for example, is certainly one worthy of consideration. Similarly, the use of the genetic tool has provided models for numerous behavioral differences including exploration (Abeelen, 1974; Abeelen & Schoones, 1977; Abeelen & Strijbosch, 1969; Abeelen et al., 1975), emotionality (Broadhurst, 1975; see reviews in Broadhurst, 1969, 1976), and avoidance behavior (see review in Wahlsten, 1977). There has been some suggestion in the literature, in fact, that the genetic model might also serve in the role of discerning the

mechanisms responsible for hyperkinesis in humans. There is no question that certain of these reports represent oversimplifications (i.e. Coyle, Wender & Lipsky, 1973), while others have provided data which can be considered as only tentative models (i.e. Remington & Anisman, 1976). Nevertheless, it is probably premature to discount such an approach entirely.

¹Since 4 experiments were carried out concurrently, mice from any particular litter were randomly assigned to different tasks. Accordingly, biases which may have been due to between-litter differences were reduced.

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APPENDIX A

Table 1a

Analysis of Variance of the Mean transformed
 $(\sqrt{x+0.5})$ number of Photocell Crossings as a
 function of Line, Age and Trial (Experiment 1)

<u>Between</u>	<u>df</u>	<u>MS</u>	<u>F</u>
Line (L)	5	1091.25	26.09***
Age (A)	4	1707.63	40.82***
L x A	20	121.55	2.91***
S Within Group	210	41.83	
<u>Within</u>			
Trial (T)	9	529.82	126.88***
T x L	45	6.73	1.61**
T x A	36	6.57	1.57*
T x L x A	180	8.29	1.99***
Trial x S Within Group	1890	4.18	

* $p < .05$

** $p < .01$

*** $p < .001$

Table 1b

Analysis of Variance of Percentage Change
in Activity (Trial x/Trial x + Trial 1) as a
function of Line, Age and Trial (Experiment 1)

<u>Between</u>	<u>df</u>	<u>MS</u>	<u>F</u>
Line (L)	5	2659.46	3.56**
Age (A)	4	749.23	1.00
L x A	20	3883.33	5.20***
S Within Group	210	747.28	
Trial (T)	8	2573.14	31.56***
T x L	40	84.98	1.04
T x A	32	77.70	0.95
T x L x A	160	112.12	1.38***
Trial x S Within Group	1680	81.52	

Table 2

Analysis of Variance of Mean Proportion
of Alternation as a function of Line
and Age (Experiment 2)

<u>Between</u>	<u>df</u>	<u>MS</u>	<u>F</u>
Line (L)	5	486.01	7.03***
Age (A)	4	527.79	7.63***
L x A	20	143.06	2.07**
S Within Group	210	69.15	

Table 3a

Analysis of Variance of Mean Number of
Head Dips as a function of Line and
Age (Experiment 3)

<u>Between</u>	<u>df</u>	<u>MS</u>	<u>F</u>
Line (L)	5	1614.2	19.71***
Age (A)	4	539.48	6.59***
L x A	20	213.97	2.61***
S Within Group	239	81.909	

Table 3b

Analysis of Variance of Mean Number of
Non-repetitive Head Dips as a function
of Line and Age (Experiment 3)

<u>Between</u>	<u>df</u>	<u>MS</u>	<u>F</u>
Line (L)	5	87008.0	41.33***
Age (A)	4	131490.0	62.46***
L x A	20	15007.0	7.13***
S Within Group	210	2105.1	

Table 3c

Analysis of Variance of Mean Proportion
of Head Dips as a function of Line
and Age (Experiment 3)

<u>Between</u>	<u>df</u>	<u>MS</u>	<u>F</u>
Line (L)	5	1614.20	19.71***
Age (A)	4	539.48	6.59***
L x A	20	213.97	2.61***
S Within Group	210	81.909	

Table 4a

Analysis of Variance of the Mean
 Number of Photocell Crossings as a
 function of Line, Age, Air Puff and
 Blocks of Trials (Experiment 4)

<u>Between</u>	<u>df</u>	<u>MS</u>	<u>F</u>
Line (L)	5	10.97	14.94***
Age (A)	4	77.65	105.78***
L x A	20	2.63	3.59***
Air Puff (P)	1	204.36	278.39***
L x P	5	1.55	2.11
A x P	4	10.73	14.62***
L x A x P	20	1.28	1.74*
S Within Group	540	0.73	
<u>Within</u>			
Trial (T)	2	1.78	9.11***
L x T	10	0.16	0.84
A x T	8	0.45	2.33*
L x A x T	40	0.26	1.34
P x T	2	3.62	18.57***
L x P x T	10	0.36	1.85*
A x P x T	8	0.18	0.
L x A x P x T	40	0.28	1.45*
Trial x S Within Group	1080	0.20	

Analysis of Variance of the Mean
 Number of Photocell Crossings (Post-Air
 Puff Interval) as a function of Line,
 Age, Air Puff and Blocks of Trials
 (Experiment 4)

	<u>Between</u>	<u>df</u>	<u>MS</u>	<u>F</u>
Line (L)		5	63963.0	28.03***
Age (A)		4	240530.0	105.40***
L x A		20	13089.0	5.74***
Puff (P)		1	21849.0	9.57**
L x P		5	913.27	0.40
A x P		4	690.84	0.30
L x A x P		20	3554.20	1.56
S Within Group		540	2282.10	
	<u>Within</u>			
Trial (T)		4	3008.60	4.65***
L x T		20	564.01	0.87
A x T		16	1915.00	2.96***
L x A x T		80	683.66	1.06
P x T		4	6644.10	10.27***
L x P x T		20	1141.10	1.76*
A x P x T		16	1676.70	2.59***
L x A x P x T		80	616.73	0.95
Trial x S Within Group		2160	647.18	

Table 5a

Analysis of Variance of Mean Transformed
 $(\sqrt{x+0.5})$ Number of Photocell Crossings as a function
 of Line, Age and Drug (Experiment 5)

<u>Between</u>	<u>df</u>	<u>MS</u>	<u>F</u>
Line (L)	5	5284.55	31.70***
Drug (D)	6	10884.40	65.30***
Age (A)	4	44174.92	265.01***
L x D	30	516.08	3.10***
L x A	20	257.82	1.55
D x A	24	1262.85	7.58***
S x D x A	120	218.24	1.31***
S Within Groups	1470	166.69	
Trial (T)	9	1380.69	185.23***
T x L	45	16.65	2.23***
T x D	54	95.07	12.76***
T x A	36	50.89	6.83***
T x L x D	270	11.35	1.52***
T x L x A	180	14.94	2.00***
T x D x A	216	23.95	3.21***
T x D x L x A	1080	10.56	1.42***
Trial x S Within Groups	13230	7.45	

Table 5b

Analysis of Variance of Mean Percentage Change
in Number of Photocell Crossings as a Function
of Line, Age and Drug (Experiment 5)

<u>Between</u>	<u>df</u>	<u>MS</u>	<u>F</u>
Line (L)	5	18988.20	10.45***
Drug (D)	6	51197.33	28.18***
Age (A)	4	55944.25	30.80***
L x D	30	3019.33	1.66*
L x A	20	5273.20	2.90***
D x A	24	4961.83	2.73***
L x D x A	120	3538.52	1.95***
S Within Groups	1470	1816.52	
Trial (T)	8	2460.38	16.76***
T x L	40	315.08	2.15***
T x D	48	882.35	6.01***
T x A	32	1130.66	7.70***
T x L x D	240	224.22	1.53***
T x L x A	160	244.08	1.66***
T x D x A	192	399.78	2.72***
T x L x D x A	960	175.50	
Trial x S Within Groups	11760	146.77	

Table 6

Analysis of Variance of Mean Proportion
of Alternation as a Function of Line, Age
and Drug (Experiment 6)

<u>Between</u>	<u>df</u>	<u>MS</u>	<u>G</u>
Line (L)	5	978.87	3.60**
Age (A)	4	509.63	1.88
S x A	20	480.41	1.77*
Drug (D)	4	16191.00	59.59***
S x D	20	351.95	1.30
A x D	16	188.79	0.69
S x A x D	80	243.82	0.90
S Within Groups	1050	271.69	

APPENDIX B

Table 1a

Mean Transformed ($\sqrt{x + 0.5}$) Number of Photocell Crossings
($\pm$ S.E.M.) as a Function of Line and Age (Experiment 1)

<u>Line</u>	<u>Age (Days)</u>			
	<u>15</u>	<u>20</u>	<u>25</u>	<u>30</u>
H_1	11.51	14.22	16.19	16.36
	± 0.61	± 0.36	± 0.27	± 0.29
H_2	9.26	15.35	12.67	14.58
	± 0.39	± 0.36	± 0.32	± 0.37
C_1	8.70	11.51	11.39	12.31
	± 0.42	± 0.34	± 0.22	± 0.25
C_2	5.74	10.50	11.17	12.83
	± 0.57	± 0.33	± 0.23	± 0.23
L_1	10.08	9.17	12.31	10.78
	± 0.36	± 0.30	± 0.21	± 0.32
L_2	9.99	12.24	11.02	12.03
	± 0.46	± 0.29	± 0.26	± 0.29
				60
				16.34
				± 0.25
				15.50
				± 0.40
				12.95
				± 0.31
				13.57
				± 0.26
				12.15
				± 0.51
				14.58
				± 0.29

Mean differences necessary for $p < .05$

Between Lines

$$r_2 = 1.99$$

$$r_3 = 2.38$$

$$r_4 = 2.61$$

$$r_5 = 2.78$$

Table 1b

Mean transformed ($\sqrt{\chi+0.5}$) number of Photocell Crossings($\pm$ S.E.M.) as a function of Line, Age and Trial (Experiment 1)

Day	Line	Trial									
		1	2	3	4	5	6	7	8	9	10
15	H ₁	18.98 ±1.17	14.66 ±1.59	14.33 ±1.34	13.54 ±1.15	11.58 ±1.07	11.56 ±1.08	11.11 ±0.69	8.83 ±2.23	8.55 ±2.44	6.13 ±2.24
		9.50 ±1.54	8.64 ±1.56	10.05 ±1.38	10.51 ±1.03	10.73 ±1.11	10.32 ±0.93	9.28 ±1.25	9.63 ±1.77	8.90 ±1.32	9.44 ±1.23
	C ₁	8.44 ±1.75	13.86 ±1.20	10.71 ±1.18	10.49 ±0.93	9.39 ±0.75	8.98 ±0.98	7.94 ±1.15	6.46 ±1.38	7.33 ±1.12	7.68 ±1.04
		10.94 ±2.27	7.06 ±2.13	7.12 ±1.77	5.72 ±1.87	5.38 ±1.94	5.56 ±1.61	4.68 ±1.32	4.26 ±1.70	3.91 ±1.40	5.07 ±1.66
	L ₁	13.55 ±0.36 ^c	11.71 ±0.52	12.11 ±1.12	10.92 ±1.20	10.39 ±1.45	10.97 ±0.86	10.27 ±0.93	9.29 ±0.72	8.11 ±1.40	8.09 ±1.27
		13.66 ±1.57	11.86 ±1.86	9.96 ±1.80	10.28 ±1.58	10.42 ±1.29	8.92 ±1.45	8.24 ±1.57	10.31 ±1.20	10.10 ±1.01	10.70 ±1.00
20	H ₁	18.45 ±1.10	16.89 ±1.01	15.43 ±0.95	14.63 ±1.07	13.36 ±1.07	15.00 ±0.71	14.16 ±1.12	13.36 ±1.11	12.84 ±1.03	12.86 ±0.71
		20.24 ±0.25	18.06 ±0.68	16.47 ±0.78	15.60 ±1.03	15.86 ±0.82	14.82 ±1.06	14.72 ±1.06	15.08 ±1.18	13.95 ±1.19	13.47 ±1.26
	C ₁	14.72 ±0.95	11.82 ±0.92	12.12 ±1.01	10.91 ±0.96	12.59 ±0.83	11.58 ±1.58	11.26 ±0.86	10.65 ±1.40	11.89 ±0.83	12.07 ±0.94

Table 1b (continued)

Day	Line	T r i a l									
		1	2	3	4	5	6	7	8	9	10
25	C ₂	15.72 ±0.69	11.84 ±0.73	11.68 ±0.56	11.27 ±0.57	11.88 ±0.72	11.19 ±0.76	10.59 ±0.39	9.67 ±0.71	8.11 ±0.93	7.70 ±1.28
	L ₁	13.41 ±0.61	10.70 ±0.51	10.40 ±0.63	9.90 ±0.74	9.51 ±0.64	9.22 ±0.51	8.47 ±0.88	8.54 ±1.06	7.87 ±1.24	8.25 ±1.17
	L ₂	15.96 ±0.74	13.36 ±0.83	12.51 ±1.06	12.09 ±0.31	13.17 ±0.93	12.44 ±0.94	12.53 ±0.82	11.69 ±0.80	10.86 ±0.89	12.26 ±0.64
	H ₁	18.04 ±0.51	16.82 ±0.54	17.86 ±0.74	17.23 ±0.61	17.25 ±0.97	16.31 ±0.98	16.59 ±1.02	16.89 ±0.91	15.19 ±0.58	14.54 ±1.00
	H ₂	17.67 ±0.70	14.67 ±0.87	12.72 ±0.51	13.48 ±0.68	12.95 ±0.95	13.58 ±0.90	12.43 ±0.95	12.18 ±0.44	10.94 ±1.16	10.84 ±1.21
	C ₁	14.46 ±0.34	12.19 ±0.52	12.60 ±0.55	11.23 ±0.80	12.23 ±0.40	11.54 ±0.62	10.79 ±0.69	11.37 ±0.59	10.38 ±0.78	11.88 ±0.69
	C ₂	14.45 ±0.67	12.35 ±0.83	12.29 ±0.80	11.75 ±0.53	11.19 ±0.66	11.54 ±0.54	10.91 ±0.52	10.76 ±0.47	10.10 ±0.45	10.98 ±0.44
	L ₁	15.65 ±0.77	12.76 ±0.47	12.55 ±0.59	12.53 ±0.54	12.67 ±0.74	11.88 ±0.59	12.59 ±0.60	12.88 ±0.51	12.10 ±0.61	12.26 ±0.66
	L ₂	14.51 ±0.91	13.27 ±0.76	11.65 ±0.41	12.48 ±0.68	10.30 ±0.64	10.64 ±0.45	11.09 ±0.59	11.13 ±0.89	9.71 ±0.66	10.16 ±0.58
		H ₁	19.51 ±0.70	18.51 ±0.80	17.44 ±0.75	17.39 ±1.04	16.15 ±0.84	16.47 ±0.76	15.35 ±1.03	15.81 ±0.83	15.85 ±0.87
	H ₂	20.71 ±0.63	17.94 ±0.63	15.64 ±0.69	15.43 ±0.87	14.85 ±0.72	13.82 ±0.51	14.13 ±0.86	12.97 ±1.19	12.84 ±0.83	12.24 ±0.91

Table 1b (continued)

Day	Line	T r i a l									
		1	2	3	4	5	6	7	8	9	10
30	C ₁	15.65 ±0.40	13.92 ±0.90	12.19 ±0.95	13.34 ±0.43	12.89 ±0.63	12.28 ±0.80	12.16 ±0.72	11.55 ±0.65	12.57 ±0.68	11.34 ±0.61
	C ₂	16.14 ±0.51	14.25 ±0.47	14.15 ±0.29	13.62 ±0.46	13.86 ±0.68	11.77 ±0.76	11.76 ±0.39	12.69 ±0.50	13.06 ±0.55	11.83 ±0.88
	L ₁	13.13 ±0.47	12.31 ±1.14	11.53 ±1.16	11.13 ±0.86	10.73 ±0.79	11.14 ±0.98	10.25 ±1.18	9.79 ±0.74	11.61 ±0.70	10.92 ±0.72
	L ₂	16.75 ±0.60	14.01 ±0.85	12.83 ±0.81	12.87 ±0.75	11.46 ±0.57	12.13 ±0.65	10.45 ±0.80	11.84 ±0.79	11.23 ±0.81	11.52 ±0.44
60	H ₁	19.82 ±0.59	18.92 ±0.64	17.53 ±0.52	16.77 ±0.33	16.82 ±0.20	16.34 ±0.79	16.54 ±0.46	14.13 ±0.64	14.99 ±0.69	16.42 ±0.80
	H ₂	20.62 ±0.71	18.93 ±1.00	17.65 ±0.69	17.15 ±0.72	15.73 ±0.92	14.37 ±1.09	15.48 ±0.48	13.99 ±0.94	12.71 ±1.27	12.62 ±0.83
	C ₁	16.58 ±0.75	14.50 ±1.01	13.93 ±0.87	13.46 ±0.90	13.16 ±1.02	13.12 ±0.77	13.22 ±0.84	12.33 ±0.99	12.11 ±1.23	11.85 ±0.69
	C ₂	16.32 ±0.88	14.11 ±1.16	14.81 ±0.52	13.36 ±1.12	14.17 ±0.51	13.52 ±0.70	14.50 ±0.61	13.49 ±0.59	13.64 ±0.71	12.57 ±0.63
	L ₁	17.82 ±1.15	15.25 ±1.32	13.57 ±1.78	11.78 ±1.26	12.08 ±1.56	12.71 ±1.34	11.35 ±1.53	11.27 ±1.17	10.45 ±1.26	9.96 ±1.53
	L ₂	18.47 ±0.86	16.62 ±1.03	15.96 ±0.82	14.19 ±0.84	15.07 ±0.77	14.32 ±0.86	14.12 ±0.74	13.82 ±0.79	14.10 ±0.62	13.94 ±0.35

Table 1b (continued)

Mean differences necessary for $p < .05$ of the simple main effects.

<u>Between Lines (pooled error)</u>	<u>Between Trials</u>
$r_2 = 2.76$	$r_2 = 1.99$
$r_3 = 3.30$	$r_3 = 2.38$
$r_4 = 3.62$	$r_4 = 2.61$
$r_5 = 3.85$	$r_5 = 2.78$
$r_6 = 4.01$	$r_6 = 2.90$
	$r_7 = 3.00$
	$r_8 = 3.09$
	$r_9 = 3.16$
	$r_{10} = 3.22$

Table 1c
 Percentage Change in Activity (Trial x/Trial x + Trial 1) ($\pm$ S.E.M.)
 as a Function of Line, Age and Trial (Experiment 1)

Day	Line	T r i a l									
		2	3	4	5	6	7	8	9	10	
15	H ₁	35.80 ±3.05	36.23 ±3.92	32.94 ±2.67	27.61 ±4.01	27.36 ±3.85	25.76 ±3.12	19.16 ±5.96	21.21 ±6.66	13.34 ±5.43	
	H ₂	42.01 ±7.75	50.67 ±8.87	57.86 ±5.87	58.02 ±8.40	56.50 ±10.44	49.41 ±10.81	50.81 ±9.70	47.37 ±11.23	55.01 ±10.59	
	C ₁	73.60 ±8.18	63.87 ±9.58	63.97 ±9.59	60.46 ±9.09	58.34 ±9.14	47.60 ±11.67	39.34 ±10.87	50.83 ±11.39	53.73 ±10.60	
	C ₂	21.00 ±6.00	29.30 ±8.03	15.69 ±6.09	13.40 ±5.67	24.90 ±7.61	24.63 ±12.20	23.78 ±12.10	19.37 ±11.98	23.76 ±13.05	
	L ₁	42.32 ±2.03	43.31 ±4.52	38.81 ±5.20	37.37 ±5.63	38.53 ±3.28	35.42 ±4.24	31.02 ±3.19	26.57 ±6.11	25.83 ±5.71	
	L ₂	43.27 ±6.45	36.49 ±6.87	37.23 ±9.35	36.91 ±8.89	27.40 ±3.85	23.20 ±5.12	38.51 ±7.88	35.47 ±8.72	38.35 ±8.60	
	H ₁	45.59 ±2.36	41.16 ±3.20	38.35 ±4.24	34.66 ±4.70	39.87 ±2.31	36.69 ±3.78	34.33 ±4.82	32.58 ±3.60	32.76 ±3.50	
	H ₂	44.01 ±1.88	39.37 ±2.29	36.75 ±3.03	37.49 ±2.52	34.26 ±3.27	33.87 ±3.17	34.88 ±3.67	31.52 ±3.66	29.86 ±3.35	
	C ₁	38.81 ±3.70	39.52 ±2.60	34.48 ±3.47	42.18 ±3.26	36.56 ±5.96	36.35 ±3.23	33.36 ±5.88	39.59 ±3.92	39.72 ±4.00	

Table 1c (Continued)

Day	Line	Trial									
		2	3	4	5	6	7	8	9	10	
30	C ₁	43.41 ±3.07	37.20 ±3.99	41.75 ±0.90	40.01 ±2.67	37.52 ±3.29	36.91 ±2.42	34.61 ±2.72	38.65 ±2.74	23.74 ±2.45	
	C ₂	43.57 ±1.05	43.38 ±1.53	41.44 ±2.51	42.04 ±2.43	34.35 ±3.83	34.27 ±1.74	37.88 ±2.33	39.28 ±2.67	34.14 ±3.14	
	L ₁	47.77 ±2.98	44.34 ±4.37	43.08 ±2.55	41.65 ±3.70	42.80 ±2.00	37.06 ±2.87	37.44 ±4.11	45.87 ±3.72	42.83 ±4.10	
	L ₂	40.56 ±2.02	36.22 ±1.91	36.43 ±1.72	31.29 ±1.86	33.77 ±1.89	27.21 ±2.97	32.59 ±2.82	30.46 ±3.18	31.70 ±2.05	
60	H ₁	47.60 ±1.85	43.75 ±1.58	41.59 ±0.92	41.80 ±1.10	40.06 ±2.39	40.89 ±1.63	33.18 ±1.71	35.93 ±1.74	40.27 ±2.02	
	H ₂	45.39 ±1.72	42.12 ±2.03	40.57 ±1.43	36.28 ±5.54	32.12 ±3.32	36.01 ±2.81	30.93 ±2.73	27.11 ±4.45	26.80 ±2.94	
	C ₁	42.52 ±2.44	40.81 ±1.73	38.99 ±2.21	37.64 ±2.21	38.04 ±2.04	38.27 ±2.04	34.50 ±2.61	33.19 ±3.36	33.44 ±2.49	
	C ₂	41.90 ±3.03	45.35 ±1.80	39.20 ±2.64	43.17 ±2.75	40.46 ±1.55	44.20 ±2.95	40.51 ±1.81	41.02 ±3.06	36.86 ±1.28	
	L ₁	41.47 ±2.16	34.86 ±3.78	29.30 ±2.29	29.81 ±3.88	32.44 ±2.53	37.39 ±4.38	27.94 ±3.51	23.81 ±5.44	22.47 ±4.08	
	L ₂	44.36 ±2.69	42.49 ±2.06	36.60 ±2.27	39.68 ±2.52	37.19 ±3.06	36.71 ±2.51	35.42 ±1.93	36.81 ±2.92	36.32 ±2.35	

Table 1c (Continued)

Mean differences necessary for $p < .05$ of the simple main effects

<u>Between Lines</u> (pooled error)	<u>Between Trials</u>
$r_2 = 12.22$	$r_2 = 8.84$
$r_3 = 14.60$	$r_3 = 10.56$
$r_4 = 16.01$	$r_4 = 11.58$
$r_5 = 17.02$	$r_5 = 12.31$
	$r_6 = 12.86$
	$r_7 = 13.30$
	$r_8 = 13.69$
	$r_9 = 14.00$

Table 2

Mean Proportion of Alternation as a Function
of Line and Age (Experiment 2)

Line	15	20	25	30	60
H ₁	52.55 ±1.26	48.75 ±4.00	52.24 ±3.41	56.04 ±2.99	59.46 ±2.79
H ₂	45.57 ±3.05	43.75 ±2.71	45.13 ±2.12	50.16 ±1.97	50.19 ±2.71
C ₁	47.59 ±3.26	50.06 ±2.06	63.78 ±3.98	62.66 ±2.29	60.07 ±2.76
C ₂	49.16 ±4.24	59.68 ±3.30	54.61 ±2.74	53.65 ±0.81	56.39 ±2.09
L ₁	43.23 ±5.20	58.52 ±2.42	49.44 ±3.27	49.14 ±2.19	57.07 ±2.77
L ₂	47.75 ±3.04	57.63 ±2.62	55.99 ±3.54	59.01 ±2.82	54.37 ±1.89

Critical differences necessary for $p < .05$ of simple main effects

Between Lines

$r_2 = 8.26$
 $r_3 = 9.83$
 $r_4 = 10.78$
 $r_5 = 11.45$
 $r_6 = 11.97$

Between Ages

$r_2 = 8.26$
 $r_3 = 9.83$
 $r_4 = 10.78$
 $r_5 = 11.45$

Table 3a
Mean Number of Head Dips ($\pm$ S.E.M.)
as a Function of Line and Age (Experiment 3)

Line	Age (Days)				
	15	20	25	30	60
H ₁	59.75 $\pm$ 14.88	309.25 $\pm$ 51.05	541.38 $\pm$ 60.53	397.75 $\pm$ 46.51	573.00 $\pm$ 39.19
H ₂	71.13 $\pm$ 7.45	150.75 $\pm$ 23.02	498.13 $\pm$ 48.70	275.88 $\pm$ 33.93	344.63 $\pm$ 58.05
C ₁	35.38 $\pm$ 7.23	178.25 $\pm$ 22.62	309.25 $\pm$ 12.41	300.13 $\pm$ 28.14	409.25 $\pm$ 16.25
C ₂	20.00 $\pm$ 3.79	130.38 $\pm$ 9.34	150.13 $\pm$ 23.61	168.88 $\pm$ 31.97	196.00 $\pm$ 15.12
L ₁	41.13 $\pm$ 7.11	195.00 $\pm$ 41.23	283.13 $\pm$ 36.82	320.50 $\pm$ 35.41	346.00 $\pm$ 59.09
L ₂	37.00 $\pm$ 8.92	211.25 $\pm$ 39.09	143.50 $\pm$ 32.90	245.50 $\pm$ 40.04	292.63 $\pm$ 56.59

Mean differences necessary for $p < .05$ of simple main effects

Between Lines

$r_2 = 98.25$
 $r_3 = 116.99$
 $r_4 = 128.26$
 $r_5 = 136.22$
 $r_6 = 142.34$

Table 3b
Mean Number of Non-Repetitive Head Dips
as a Function of Line and Age (Experiment 3)

<u>Line</u>	<u>Age (Days)</u>			
	<u>15</u>	<u>20</u>	<u>25</u>	<u>30</u>
H_1	33.63	154.38	285.00	172.50
	± 8.26	± 24.02	± 34.43	± 20.08
H_2	38.25	73.88	261.50	112.38
	± 4.79	± 12.05	± 32.27	± 13.96
C_1	18.88	72.38	115.50	138.50
	± 4.86	± 10.74	± 8.39	± 16.48
C_2	10.63	68.38	68.25	70.88
	± 1.76	± 4.41	± 12.15	± 16.54
L_1	11.00	85.38	91.38	124.75
	± 3.26	± 14.04	± 12.71	± 20.75
L_2	16.50	98.75	55.88	83.75
	± 4.43	± 18.82	± 11.45	± 8.37
				<u>60</u>
				285.50
				± 24.01
				116.38
				± 28.11
				163.50
				± 8.39
				96.38
				± 7.63
				93.75
				± 18.85
				90.75
				± 10.30

Mean differences necessary for $p < .05$ of simple main effects

Between Lines

$r_2 = 45.57$
 $r_3 = 54.26$
 $r_4 = 59.49$
 $r_5 = 63.18$
 $r_6 = 66.02$

Table 3c
Mean Proportion of Head Dips as a
Function of Line and Age (Experiment 3)

<u>Line</u>	<u>Age (Days)</u>			
	<u>15</u>	<u>20</u>	<u>25</u>	<u>30</u>
H ₁	57.69 ±2.37	50.96 ±2.04	53.07 ±2.97	44.04 ±2.46
H ₂	53.28 ±2.38	48.56 ±1.86	51.79 ±1.97	40.70 ±1.37
C ₁	48.77 ±5.84	39.59 ±2.31	37.15 ±1.72	46.14 ±2.74
C ₂	56.41 ±3.99	52.82 ±1.63	44.74 ±3.07	40.25 ±2.71
L ₁	28.24 ±6.33	45.61 ±3.19	32.92 ±2.34	38.24 ±3.02
L ₂	46.52 ±6.89	45.15 ±2.71	40.26 ±2.11	37.06 ±3.57
				60
				49.82 ±1.97
				48.24 ±1.60
				40.19 ±2.28
				49.63 ±3.07
				26.27 ±3.30
				34.51 ±3.67

Mean differences necessary for $p < .05$ of simple main effects

Between Lines

$r_2 = 8.99$
 $r_3 = 10.70$
 $r_4 = 11.73$
 $r_5 = 12.46$
 $r_6 = 13.02$

Table 4a
Mean Number of Photocell Crossings as a Function
of Line, Age, Air Puff and Blocks of Trials (Experiment 4)

<u>Day</u>	<u>Line</u>	<u>Air Puff</u>			<u>Day</u>	<u>Line</u>	<u>No Air Puff</u>		
		<u>1</u>	<u>2</u>	<u>3</u>			<u>1</u>	<u>2</u>	<u>3</u>
15	H ₁	1.55 ±0.62	1.84 ±0.58	2.08 ±0.91	15	H ₁	1.53 ±0.40	1.50 ±0.56	0.62 ±0.30
	H ₂	3.08 ±0.94	1.31 ±0.65	1.32 ±0.53		H ₂	1.30 ±0.68	3.32 ±0.98	3.27 ±0.92
	C ₁	1.47 ±0.38	0.50 ±0.14	0.63 ±0.25		C ₁	2.12 ±0.72	2.83 ±0.80	2.18 ±0.85
	C ₂	1.20 ±0.49	0.88 ±0.39	0.92 ±0.47			0.53 ±0.26	0.90 ±0.76	1.27 ±0.42
	L ₁	1.77 ±0.55	1.48 ±0.49	1.48 ±0.48		L ₁	1.93 ±0.60	1.27 ±0.40	1.37 ±0.40
	L ₂	2.55 ±0.44	0.83 ±0.23	0.65 ±0.26		L ₂	2.27 ±0.73	1.95 ±0.67	2.32 ±0.70
	H ₁	0.93 ±0.42	0.57 ±0.30	0.80 ±0.52		H ₁	6.89 ±1.07	5.22 ±1.27	5.74 ±1.09
	H ₂	0.68 ±0.32	0.58 ±0.35	0.18 ±0.12		H ₂	3.10 ±0.99	4.13 ±0.79	2.77 ±0.94
	C ₁	0.60 ±0.25	0.25 ±0.10	0.82 ±0.52		C ₁	1.95 ±0.59	2.34 ±0.78	3.37 ±0.63

Table 4a (Continued)

<u>Day</u>	<u>Line</u>	<u>B l o c k</u>			<u>Day</u>	<u>Line</u>	<u>B l o c k</u>		
		<u>1</u>	<u>2</u>	<u>3</u>			<u>1</u>	<u>2</u>	<u>3</u>
20	C ₂	1.28	0.63	0.50	20	C ₂	4.37	3.88	2.92
		±0.73	±0.54	±0.30			±0.83	±1.28	±0.99
	L ₁	3.20	0.93	1.75		L ₁	2.34	4.32	4.17
		±0.51	±0.43	±0.78			±0.26	±0.55	±0.79
	L ₂	1.20	0.25	0.58		L ₂	1.35	2.92	2.35
		±0.47	±0.11	±0.39			±0.54	±0.68	±0.59
25	H ₁	1.45	1.85	3.25		H ₁	5.17	5.62	6.55
		±0.46	±0.98	±1.54			±1.09	±1.28	±1.13
	H ₂	0.45	0.29	0.35		H ₂	4.24	3.37	4.43
		±0.19	±0.17	±0.22			±0.73	±0.77	±0.86
	C ₁	0.33	0.05	0.75		C ₁	2.85	4.13	3.98
		±0.12	±0.04	±0.64			±0.63	±0.58	±0.98
25	C ₂	0.25	0.15	0.33	25	C ₂	2.68	2.93	3.38
		±0.15	±0.11	±0.22			±1.27	±1.15	±1.01
	L ₁	1.18	1.35	1.45		L ₁	3.98	3.72	4.42
		±0.38	±0.61	±0.59			±0.87	±0.71	±0.71
	L ₂	0.70	0.17	0.70		L ₂	2.23	2.62	4.60
		±0.23	±0.09	±0.42			±0.53	±0.68	±0.70

Table 4a (Continued)

<u>Day</u>	<u>Line</u>	<u>B l o c k</u>			<u>Day</u>	<u>Line</u>	<u>B l o c k</u>		
		<u>1</u>	<u>2</u>	<u>3</u>			<u>1</u>	<u>2</u>	<u>3</u>
30	H ₁	1.10 ±0.42	0.60 ±0.23	0.62 ±0.35	30	H ₁	9.52 ±0.73	8.57 ±1.41	6.83 ±0.99
	H ₂	1.10 ±0.33	0.33 ±0.12	0.63 ±0.31		H ₂	3.15 ±0.74	3.48 ±1.07	2.85 ±0.83
	C ₁	0.75 ±0.36	0.87 ±0.38	1.25 ±0.46		C ₁	3.48 ±0.71	4.08 ±0.88	4.40 ±0.74
	C ₂	0.77 ±0.28	0.13 ±0.06	0.43 ±0.22		C ₂	2.60 ±0.69	2.53 ±0.74	2.75 ±0.70
	I ₁	2.65 ±0.66	1.27 ±0.55	2.42 ±0.69		I ₁	4.63 ±0.88	3.87 ±0.98	5.08 ±1.17
	I ₂	2.78 ±0.69	1.97 ±0.47	2.75 ±0.56		I ₂	5.00 ±0.81	5.72 ±0.81	5.70 ±1.17
31	H ₁	10.14 ±1.16	7.40 ±0.91	7.97 ±1.13	31	H ₁	9.82 ±0.90	9.43 ±0.90	9.63 ±0.86
	H ₂	5.72 ±1.17	4.47 ±0.89	5.02 ±1.10		H ₂	8.30 ±0.67	7.13 ±1.12	7.48 ±1.19
	C ₁	2.35 ±0.43	1.50 ±0.37	2.40 ±0.66		C ₁	7.35 ±0.69	5.32 ±0.62	6.23 ±1.20

Table 4b

Mean Number of Photocell Crossings (Post-Air Puff) ($\pm$ S.E.M.) as a
Function of Line, Air Puff and Blocks of Trials (Experiment 4)

Day	Line	Air Puff Block					No Air Puff Block					
		1	2	3	4	5	Line	1	2	3	4	5
15	H ₁	21.50 ±5.94	42.80 ±10.93	35.70 ±11.42	31.60 ±10.14	30.10 ±6.54	H ₁	3.00 ±1.34	17.90 ±9.17	12.60 ±5.74	13.60 ±5.21	17.70 ±8.43
	H ₂	19.50 ±6.43	19.50 ±9.03	28.80 ±11.92	35.70 ±5.88	38.40 ±7.68	H ₂	43.20 ±9.64	44.10 ±8.39	39.20 ±10.4	34.80 ±9.06	33.50 ±7.13
	C ₁	17.00 ±10.83	17.80 ±6.49	34.00 ±9.97	38.60 ±10.43	37.80 ±8.74	C ₁	32.30 ±5.52	41.90 ±6.09	26.00 ±8.73	32.30 ±8.13	30.40 ±8.28
	C ₂	10.80 ±5.57	9.90 ±4.89	22.60 ±7.23	22.90 ±5.58	25.40 ±7.44	C ₂	23.10 ±8.29	19.90 ±4.19	27.00 ±8.37	20.00 ±8.43	22.70 ±6.84
	L ₁	19.10 ±8.64	21.30 ±7.33	26.10 ±7.98	24.30 ±7.32	23.00 ±6.18	L ₁	19.50 ±4.62	15.90 ±4.58	33.90 ±6.86	34.00 ±5.67	28.70 ±5.26
	L ₂	7.30 ±2.74	14.90 ±6.87	20.60 ±9.10	33.60 ±6.85	24.50 ±5.84	L ₂	36.50 ±7.49	42.80 ±5.77	29.70 ±4.71	37.30 ±7.93	25.50 ±7.40
	H ₁	26.60 ±13.49	54.40 ±13.81	64.20 ±9.66	64.80 ±15.87	78.00 ±12.31	H ₁	79.60 ±11.15	77.10 ±6.23	58.30 ±15.44	55.20 ±12.60	77.80 ±9.42
	H ₂	0.80 ±0.59	19.90 ±8.21	30.20 ±7.85	52.70 ±8.00	63.80 ±12.83	H ₂	48.50 ±10.22	49.10 ±11.03	24.70 ±8.73	39.60 ±6.54	58.30 ±7.40
	C ₁	15.60 ±7.60	27.20 ±6.07	30.70 ±4.96	45.20 ±9.67	40.20 ±6.41	C ₁	32.20 ±3.39	42.20 ±8.89	34.10 ±9.54	37.10 ±7.96	29.20 ±5.32

Table 4b (Continued)

<u>Air Puff</u>		<u>No Air Puff</u>										
<u>Block</u>		<u>Block</u>										
<u>Day</u>	<u>Line</u>	<u>Day</u>										
		<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>Line</u>	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>
20	C ₂	17.50 ±8.47	28.60 ±6.44	35.50 ±8.62	43.90 ±8.60	49.10 ±6.55	C ₂	32.70 ±9.49	43.60 ±7.41	44.10 ±7.90	39.90 ±10.34	36.00 ±9.49
	L ₁	24.80 ±7.12	43.00 ±10.98	35.50 ±9.70	55.30 ±9.30	56.20 ±7.60	L ₁	41.70 ±8.00	42.60 ±8.24	35.60 ±4.18	44.80 ±9.17	41.80 ±6.09
	L ₂	9.70 ±3.68	17.40 ±6.93	48.20 ±9.09	43.30 ±10.46	35.30 ±10.16	L ₂	34.00 ±7.45	36.40 ±4.71	52.10 ±8.92	43.50 ±12.54	23.60 ±9.09
	H ₁	70.60 ±24.48	86.10 ±24.96	98.80 ±22.37	100.40 ±22.26	92.90 ±20.69		85.80 ±13.29	74.10 ±8.93	80.70 ±13.22	54.70 ±12.58	63.10 ±12.03
25	H ₂	25.80 ±7.90	30.60 ±5.75	33.30 ±8.34	46.00 ±8.39	37.80 ±12.21	H ₂	36.60 ±9.25	42.50 ±11.49	30.60 ±9.52	38.50 ±11.31	47.60 ±8.55
	C ₁	14.90 ±6.99	21.10 ±7.89	19.90 ±8.21	17.40 ±4.94	31.60 ±8.69	C ₁	32.80 ±6.71	42.10 ±8.60	41.50 ±6.29	33.60 ±6.91	39.70 ±9.37
	C ₂	31.70 ±11.87	21.60 ±8.67	41.20 ±10.97	57.80 ±6.08	45.20 ±8.26	C ₂	59.20 ±15.87	48.90 ±15.79	46.70 ±11.63	52.00 ±14.45	43.90 ±15.19
	L ₁	62.10 ±13.02	46.20 ±10.82	47.50 ±7.63	48.00 ±10.57	49.50 ±9.90	L ₁	52.60 ±9.93	48.70 ±11.26	48.10 ±9.66	57.50 ±7.45	57.30 ±8.09
	L ₂	24.40 ±9.37	45.20 ±10.78	45.80 ±15.89	49.80 ±14.30	48.10 ±12.76		48.40 ±8.71	69.40 ±8.32	53.40 ±8.54	45.40 ±9.46	58.80 ±7.48
	H ₁	53.00 ±12.52	66.20 ±12.34	76.00 ±10.27	73.00 ±15.40	63.60 ±12.38	H ₁	99.50 ±14.83	71.50 ±12.70	73.20 ±15.57	106.80 ±9.55	100.80 ±13.97

Table 4b (Continued)

Alr Puff
B l o c k

No Alr Puff
B l o c k

Day	Line	1	2	3	4	5	Day	Line	1	2	3	4	5
30	H ₂	26.20 ±7.64	15.80 ±4.63	14.50 ±9.39	45.40 ±8.55	24.80 ±9.49	30	H ₂	47.10 ±13.47	47.40 ±12.35	23.30 ±8.34	25.10 ±9.06	45.20 ±10.33
	C ₁	61.20 ±11.96	41.10 ±7.14	51.20 ±8.64	63.20 ±9.65	55.50 ±11.24		C ₁	45.50 ±10.29	68.20 ±7.58	67.40 ±8.28	59.20 ±11.98	46.10 ±8.92
	C ₂	22.60 ±7.73	18.50 ±7.23	21.20 ±7.07	23.70 ±8.05	14.60 ±4.66		C ₂	30.50 ±12.31	24.20 ±6.63	44.20 ±6.86	48.20 ±12.10	47.50 ±8.61
	L ₁	50.00 ±12.15	52.30 ±8.48	59.80 ±11.81	45.00 ±9.10	59.10 ±12.53		L ₁	61.90 ±9.78	56.00 ±10.15	39.30 ±7.07	60.20 ±11.77	55.60 ±8.03
	L ₂	80.40 ±9.85	84.80 ±10.46	69.70 ±8.98	69.60 ±12.32	60.80 ±11.22		L ₂	67.50 ±8.41	80.90 ±6.73	76.60 ±13.15	53.70 ±11.67	83.60 ±11.07
60	H ₁	117.40 ±11.21	108.10 ±11.89	98.30 ±10.83	107.60 ±7.78	95.90 ±10.24	60	H ₁	119.40 ±13.36	107.60 ±11.09	108.30 ±6.50	112.10 ±7.34	105.10 ±9.73
	H ₂	105.10 ±10.46	94.40 ±8.06	94.40 ±11.93	97.70 ±10.14	75.30 ±11.18		H ₂	91.80 ±10.19	81.90 ±6.65	74.40 ±16.78	78.60 ±16.90	76.70 ±6.19
	C ₁	63.30 ±10.44	68.20 ±8.86	60.10 ±7.78	64.80 ±6.40	53.50 ±7.74		C ₁	54.20 ±8.95	71.90 ±10.66	71.80 ±9.41	71.50 ±6.23	59.20 ±8.46
	C ₂	76.20 ±9.02	62.30 ±10.08	69.40 ±10.26	68.30 ±9.00	60.80 ±9.73		C ₂	72.20 ±14.72	64.80 ±8.96	54.30 ±14.30	60.70 ±10.96	55.80 ±8.99
	L ₁	55.20 ±7.51	55.00 ±12.03	65.00 ±8.77	52.30 ±6.54	57.90 ±9.51		L ₁	82.60 ±7.90	91.30 ±5.54	85.30 ±8.31	74.60 ±11.82	80.50 ±10.23
	L ₂	84.50 ±7.00	88.10 ±8.31	91.10 ±9.32	93.90 ±7.10	78.20 ±12.01		L ₂	100.70 ±8.04	89.10 ±7.71	104.70 ±8.82	92.20 ±10.10	101.40 ±7.64

Table 4b (Continued)

Mean differences necessary for $p < .05$ of simple main effects, Line x Age x Air Puff.

Between Lines Between Air Puff

$$r_2 = 18.73 \qquad r_2 = 18.73$$

$$r_3 = 22.38$$

$$r_4 = 24.54$$

$$r_5 = 26.09$$

$$r_6 = 27.24$$

Line x Air Puff x Block

Between Lines

Between Air Puff

Between Blocks

$$r_2 = 12.22$$

$$r_3 = 14.60$$

$$r_4 = 16.01$$

$$r_5 = 17.46$$

$$r_6 = 17.77$$

$$r_2 = 9.97$$

$$r_3 = 11.92$$

$$r_4 = 13.07$$

$$r_5 = 13.90$$

Table 4b (Continued)

Age x Air Puff x Blocks

<u>Between Air Puff</u>	<u>Between Blocks</u>
$r_2 = 11.16$	$r_{2,3} = 9.09$
	$r_3 = 10.86$
	$r_4 = 11.91$
	$r_5 = 12.66$

Table 5a
 Mean-Transformed ($\sqrt{x+0.5}$) Number of Photocell Crossings ($\pm$ S.E.M.)
 as a Function of Line, Age and Drug (Experiment 5)

Drug	Line	15 Days									
		Trial									
		1	2	3	4	5	6	7	8	9	10
Saline	H ₁	15.03 ± 2.05	12.81 ± 2.35	11.01 ± 1.86	9.01 ± 1.88	8.71 ± 2.05	7.57 ± 1.85	6.38 ± 1.86	4.88 ± 2.07	5.54 ± 1.83	3.43 ± 1.63
	H ₂	11.57 ± 1.71	6.76 ± 1.68	5.89 ± 1.94	7.29 ± 2.44	6.79 ± 1.74	7.86 ± 2.11	5.63 ± 2.06	7.27 ± 2.05	7.66 ± 2.26	7.70 ± 1.85
	C ₁	8.66 ± 1.80	5.17 ± 2.29	5.16 ± 1.70	5.57 ± 1.40	5.80 ± 1.59	5.20 ± 1.16	4.41 ± 1.22	3.71 ± 1.08	6.55 ± 1.07	6.20 ± 1.22
	C ₂	14.57 ± 1.15	10.80 ± 1.20	8.75 ± 1.73	8.85 ± 1.57	9.04 ± 1.85	9.94 ± 1.47	7.25 ± 1.89	7.81 ± 1.61	3.34 ± 1.45	10.67 ± 0.64
	L ₁	12.81 ± 1.58	12.67 ± 1.67	10.74 ± 1.40	9.22 ± 1.76	8.87 ± 1.97	7.84 ± 1.50	7.16 ± 1.57	7.03 ± 1.99	7.27 ± 1.75	8.61 ± 1.37
	L ₂	10.08 ± 1.83	9.42 ± 1.38	7.27 ± 1.79	6.68 ± 2.05	6.63 ± 1.91	8.89 ± 1.64	9.22 ± 2.04	9.13 ± 2.13	9.07 ± 1.88	9.62 ± 1.78
	H ₁	17.60 ± 1.06	12.76 ± 1.87	9.64 ± 2.07	8.41 ± 2.19	7.71 ± 1.98	7.94 ± 1.91	9.14 ± 2.05	9.09 ± 2.28	10.90 ± 1.87	10.37 ± 2.00
	H ₂	15.45 ± 1.91	12.90 ± 2.61	9.68 ± 3.01	9.45 ± 2.72	9.07 ± 2.63	8.04 ± 2.46	8.24 ± 2.32	8.58 ± 2.34	8.11 ± 2.26	8.19 ± 2.15
	C ₁	5.84 ± 0.70	1.77 ± 0.30	2.02 ± 0.76	3.53 ± 1.81	3.35 ± 1.97	3.51 ± 1.73	4.26 ± 1.95	3.95 ± 1.70	5.45 ± 1.65	5.69 ± 1.59

Table 5a (Continued)

15 Days

Trial

Line

Drug

	1	2	3	4	5	6	7	8	9	10	
D-amphetamine (1.0 mg/kg)	C ₂	11.77 ±1.43	8.50 ±1.55	5.92 ±1.51	4.21 ±1.74	5.03 ±1.70	7.46 ±1.59	10.10 ±0.13	8.58 ±1.55	8.14 ±1.65	7.46 ±1.69
	L ₁	11.65 ±1.74	12.70 ±2.28	10.04 ±2.50	10.81 ±2.28	10.79 ±1.98	10.30 ±1.94	10.33 ±2.12	9.28 ±2.16	8.47 ±1.92	10.12 ±2.35
	L ₂	11.93 ±1.82	10.09 ±1.78	8.85 ±1.84	6.90 ±1.92	7.09 ±2.00	5.63 ±2.14	6.38 ±1.99	6.63 ±1.78	7.30 ±1.64	9.18 ±1.25
	H ₁	12.72 ±1.76	11.89 ±2.61	11.05 ±3.03	10.79 ±3.13	10.38 ±3.43	10.66 ±3.54	10.74 ±3.18	11.04 ±3.22	9.52 ±3.46	9.46 ±3.55
D-amphetamine (3.0 mg/kg)	H ₂	15.12 ±1.22	14.22 ±1.75	11.73 ±2.02	10.59 ±2.57	9.64 ±2.75	9.80 ±2.65	9.87 ±2.64	9.97 ±2.33	9.18 ±2.38	9.39 ±2.43
	C ₁	11.41 ±2.33	9.94 ±3.19	7.91 ±2.62	7.35 ±2.16	6.32 ±1.94	7.77 ±1.72	5.76 ±1.85	5.57 ±1.80	6.35 ±1.95	5.67 ±2.00
	C ₂	16.37 ±1.00	16.98 ±0.75	17.70 ±1.03	16.33 ±1.25	15.41 ±1.39	14.68 ±1.30	14.41 ±1.18	13.78 ±1.44	14.04 ±1.31	12.38 ±2.01
	L ₁	8.55 ±0.87	9.09 ±1.83	9.61 ±2.03	8.85 ±1.85	8.47 ±1.86	8.08 ±1.89	8.59 ±1.66	8.16 ±1.65	8.33 ±1.53	6.48 ±1.30
	L ₂	14.61 ±1.80	13.76 ±2.42	14.08 ±2.30	12.35 ±2.53	11.81 ±2.37	11.23 ±2.16	11.66 ±2.28	11.06 ±2.34	11.34 ±2.08	11.23 ±2.33
	H ₁	14.74 ±1.64	15.80 ±1.63	13.56 ±1.08	12.29 ±1.17	11.73 ±1.56	11.25 ±1.69	10.51 ±2.08	11.12 ±2.32	11.06 ±2.54	10.99 ±2.69

Table 5a (Continued)

Drug	Line	15 Days									
		<u>Trial</u>									
		<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>	<u>9</u>	<u>10</u>
Scopolamine (1.0 mg/kg)	L ₂	6.55 ±1.54	5.01 ±1.86	3.24 ±1.81	4.51 ±2.03	4.16 ±2.05	6.25 ±2.11	7.58 ±1.99	8.09 ±1.93	7.41 ±2.04	7.97 ±2.12
	H ₁	5.57 ±1.19	4.81 ±1.04	4.11 ±1.35	2.61 ±0.56	3.15 ±1.09	2.54 ±0.77	2.85 ±0.95	3.01 ±1.14	3.07 ±1.58	4.08 ±2.04
Scopolamine (2.0 mg/kg)	H ₂	8.49 ±1.89	8.45 ±2.49	8.45 ±2.34	8.99 ±2.20	9.81 ±1.99	11.10 ±1.72	11.94 ±1.76	11.24 ±1.86	11.22 ±1.95	10.30 ±2.28
	C ₁	3.81 ±0.53	2.27 ±0.58	2.91 ±0.95	2.90 ±1.22	3.15 ±1.35	3.36 ±1.07	3.25 ±1.14	3.38 ±1.24	3.45 ±1.31	3.60 ±1.67
Scopolamine (1.0 mg/kg)	C ₂	6.29 ±1.11	2.36 ±0.74	1.85 ±0.83	1.56 ±0.64	0.91 ±0.29	1.75 ±0.53	1.93 ±0.54	3.35 ±1.29	3.86 ±1.16	3.19 ±1.30
	L ₁	4.77 ±1.39	2.01 ±0.67	0.97 ±0.31	1.17 ±0.47	0.50 ±0.10	0.97 ±0.24	2.07 ±0.64	3.22 ±1.05	4.99 ±1.71	5.90 ±2.05
Scopolamine (2.0 mg/kg)	L ₂	3.50 ±0.69	1.16 ±0.44	1.99 ±0.74	1.46 ±0.59	2.11 ±0.98	2.86 ±1.33	2.82 ±1.22	2.67 ±1.00	3.40 ±0.63	2.51 ±0.55
	H ₁	8.84 ±1.63	7.39 ±1.79	5.36 ±1.80	5.96 ±1.81	6.98 ±1.52	6.08 ±1.81	6.22 ±2.27	8.91 ±2.12	8.74 ±2.34	9.25 ±2.60
Scopolamine (2.0 mg/kg)	H ₂	4.90 ±1.13	5.94 ±1.91	5.55 ±1.93	5.77 ±1.85	5.54 ±1.85	6.64 ±1.85	7.48 ±1.83	6.41 ±1.85	6.48 ±2.26	7.99 ±2.49
	C ₁	1.87 ±0.71	4.23 ±1.72	3.43 ±1.75	3.85 ±1.83	2.62 ±1.22	3.84 ±1.79	6.12 ±2.15	5.61 ±1.76	5.75 ±2.12	7.10 ±2.31

Table 5a (Continued)

Drug	Line	15 Days									
		Trial									
		<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>	<u>9</u>	<u>10</u>
C ₂		7.15	4.45	1.65	0.78	0.89	1.21	2.04	1.85	2.46	3.41
		±1.00	±1.29	±1.15	±0.28	±0.26	±0.46	±0.66	±0.86	±1.20	±1.13
		4.57	2.61	1.55	0.68	1.25	0.75	1.63	1.53	3.11	4.18
L ₁		±0.95	±0.71	±0.71	±0.18	±0.53	±0.16	±0.32	±0.59	±1.18	±1.53
		4.96	2.69	1.41	1.64	3.29	3.45	2.84	4.82	4.36	5.35
L ₂		±1.19	±0.74	±0.31	±0.62	±1.01	±1.18	±0.99	±1.13	±1.31	±1.44
20 Days											
H ₁		17.56	17.94	15.82	15.57	15.82	16.30	17.30	17.09	17.16	17.55
		±1.09	±1.20	±1.97	±1.72	±1.34	±1.29	±1.50	±1.29	±1.46	±1.07
H ₂		18.85	16.39	14.10	13.91	14.73	14.60	14.39	11.79	13.41	12.03
		±0.65	±1.16	±1.09	±1.83	±0.78	±0.87	±0.98	±1.63	±0.71	±1.10
C ₁		14.90	14.60	10.74	10.31	11.24	11.45	10.89	10.75	9.73	10.76
		±0.86	±0.91	±0.94	±0.95	±0.70	±0.56	±0.55	±0.91	±0.97	±0.66
C ₂		14.24	9.41	9.46	10.98	9.74	9.71	10.88	9.49	8.62	10.85
		±1.27	±1.40	±0.47	±0.97	±1.40	±0.81	±0.49	±0.72	±1.32	±0.80
L ₁		11.10	6.98	4.77	5.25	6.52	6.06	7.47	6.96	5.83	6.88
		±1.39	±1.75	±1.45	±1.99	±2.00	±1.89	±1.63	±1.88	±1.60	±1.62
L ₂		14.53	11.14	10.54	9.63	11.82	12.17	10.98	10.56	11.35	12.42
		±0.91	±0.90	±0.62	±1.34	±0.60	±0.48	±0.97	±0.83	±0.82	±0.42

Saline

Table 5a (Continued)

Drug	Line	20 Days									
		T r i a l									
		1	2	3	4	5	6	7	8	9	10
D-amphetamine (5.0 mg/kg)	L ₁	17.80 ±1.57	17.93 ±2.01	17.29 ±2.27	16.44 ±2.31	16.45 ±2.22	16.96 ±2.71	14.08 ±2.04	13.30 ±2.58	13.65 ±2.22	12.31 ±2.50
	L ₂	19.86 ±1.12	20.65 ±1.43	19.88 ±1.74	19.89 ±1.70	19.67 ±1.54	19.72 ±1.68	17.58 ±1.94	17.01 ±1.70	16.55 ±2.31	16.62 ±2.25
	H ₁	18.87 ±1.55	19.30 ±1.67	18.95 ±1.57	18.46 ±1.89	18.18 ±2.17	17.68 ±2.16	16.96 ±1.78	16.39 ±2.00	15.99 ±1.51	15.16 ±1.83
	H ₂	20.21 ±1.31	20.11 ±1.17	19.41 ±1.63	19.59 ±1.42	20.05 ±1.53	19.60 ±1.36	19.78 ±1.58	20.23 ±1.61	20.33 ±1.44	20.01 ±1.20
	C ₁	17.38 ±1.16	17.07 ±1.49	16.46 ±1.84	16.24 ±1.87	16.56 ±1.83	16.07 ±1.70	15.47 ±1.87	14.56 ±2.24	14.05 ±1.97	12.69 ±1.97
	C ₂	16.91 ±1.57	16.99 ±2.31	17.97 ±2.36	16.51 ±2.18	16.21 ±2.22	16.04 ±2.40	16.47 ±2.48	16.93 ±2.46	16.57 ±2.28	16.87 ±2.13
	L ₁	17.10 ±0.99	17.14 ±1.61	15.88 ±1.66	14.17 ±2.29	14.22 ±2.44	14.20 ±2.58	13.94 ±2.58	13.78 ±2.78	12.93 ±2.59	14.11 ±2.27
	L ₂	18.24 ±0.85	18.48 ±0.77	17.30 ±1.30	16.23 ±1.57	16.01 ±1.73	15.32 ±1.79	15.59 ±1.35	15.42 ±1.01	14.39 ±1.41	14.11 ±1.34
	H ₁	17.66 ±0.62	15.79 ±0.79	13.38 ±1.65	14.97 ±0.91	13.18 ±1.51	10.57 ±2.58	12.64 ±2.39	14.95 ±0.77	13.80 ±1.02	12.40 ±1.56
	H ₂	15.63 ±1.28	13.60 ±1.78	12.83 ±1.89	11.28 ±2.33	12.20 ±2.10	11.58 ±2.33	11.15 ±2.11	10.52 ±2.05	10.85 ±1.88	10.40 ±1.78
Scopolamine (1.0 mg/kg)	C ₁	13.95 ±0.83	10.53 ±1.84	8.32 ±2.49	8.39 ±2.34	9.83 ±2.12	9.84 ±2.08	9.54 ±1.68	10.22 ±2.06	9.09 ±1.91	10.25 ±1.85

Table 5a (Continued)

20 Days

LineTrial

	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>	<u>9</u>	<u>10</u>
C ₂	14.24 ±1.39	11.74 ±2.12	11.35 ±1.94	11.39 ±2.16	12.16 ±1.29	12.57 ±0.97	11.99 ±1.63	11.54 ±1.49	12.44 ±1.13	11.62 ±1.03
L ₁	15.00 ±2.20	13.67 ±2.15	11.44 ±2.10	12.60 ±1.32	14.03 ±1.04	11.01 ±1.39	11.05 ±1.61	9.98 ±1.65	5.46 ±1.52	6.78 ±1.73
L ₂	13.19 ±1.33	9.28 ±1.52	7.78 ±1.88	10.45 ±1.54	9.33 ±1.74	10.30 ±1.67	10.08 ±2.24	9.35 ±2.08	11.57 ±1.27	12.48 ±1.36
H ₁	11.78 ±2.01	11.42 ±1.75	10.80 ±1.66	10.95 ±1.66	11.75 ±1.61	12.14 ±1.87	13.32 ±1.46	11.54 ±1.82	10.71 ±1.71	12.01 ±1.66
H ₂	14.74 ±1.22	12.55 ±1.51	12.35 ±1.54	12.65 ±1.86	13.98 ±2.23	14.67 ±1.94	15.83 ±1.44	13.75 ±2.12	15.13 ±1.07	15.41 ±1.29
C ₁	15.57 ±1.82	11.38 ±1.52	10.66 ±1.63	11.36 ±1.63	9.24 ±1.64	9.72 ±1.57	8.92 ±1.36	10.96 ±0.87	8.58 ±0.72	8.79 ±1.39
C ₂	10.65 ±1.33	6.83 ±1.02	6.83 ±1.74	8.81 ±1.10	7.66 ±1.95	11.10 ±1.08	13.17 ±0.81	11.26 ±1.94	11.66 ±1.90	9.81 ±2.14
L ₁	14.56 ±1.39	12.89 ±0.67	11.30 ±0.31	10.47 ±0.47	13.29 ±0.10	14.88 ±0.24	14.65 ±0.64	12.94 ±1.05	13.01 ±1.71	12.73 ±2.05
L ₂	13.33 ±1.31	11.10 ±0.96	7.17 ±0.08	9.37 ±1.40	10.78 ±1.44	11.95 ±0.78	12.64 ±0.99	12.78 ±0.81	13.07 ±0.61	12.03 ±1.17

Scopolamine

(1.0 mg/kg)

Table 5a (Continued)

Drug	Line	20 Days									
		T r i a l									
		<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>	<u>9</u>	<u>10</u>
Scopolamine (2.0 mg/kg)	H ₁	11.63 ±1.24	12.07 ±1.49	13.69 ±1.13	14.36 ±1.12	14.20 ±1.19	14.27 ±0.73	14.92 ±0.89	14.07 ±0.79	14.02 ±0.42	12.69 ±0.86
	H ₂	12.75 ±1.95	11.18 ±2.29	9.90 ±2.46	12.43 ±2.45	14.32 ±1.91	14.66 ±1.47	15.35 ±0.96	15.25 ±1.27	14.87 ±1.91	12.37 ±1.94
	C ₁	14.69 ±0.98	12.57 ±1.80	11.07 ±1.92	12.10 ±1.72	13.32 ±1.64	13.00 ±1.93	12.98 ±1.10	12.61 ±0.88	11.85 ±1.23	10.99 ±1.02
	C ₂	11.30 ±1.22	10.96 ±1.09	9.49 ±1.04	10.11 ±1.22	8.92 ±1.46	11.50 ±1.01	13.14 ±1.02	10.94 ±1.96	10.90 ±2.15	9.86 ±2.15
	L ₁	14.59 ±0.91	12.80 ±1.07	12.28 ±1.06	11.66 ±1.00	12.47 ±1.51	13.07 ±1.53	11.39 ±1.75	12.62 ±1.27	10.05 ±1.58	10.40 ±1.49
	L ₂	8.31 ±0.70	5.32 ±1.64	6.08 ±1.70	8.47 ±1.99	10.25 ±1.24	10.46 ±1.26	10.19 ±1.78	12.75 ±1.43	13.37 ±1.14	13.73 ±0.96
						25 Days					
	H ₁	13.34 ±2.12	12.93 ±2.23	12.36 ±2.56	14.34 ±1.96	14.75 ±0.72	14.40 ±1.22	14.83 ±0.74	12.70 ±1.44	12.14 ±1.83	12.30 ±0.72
Saline	H ₂	17.65 ±1.04	14.87 ±1.61	13.91 ±2.04	11.25 ±2.19	14.36 ±1.72	14.48 ±2.16	14.49 ±1.52	10.49 ±2.43	11.64 ±2.30	14.05 ±2.83
	C ₁	13.20 ±0.69	8.12 ±1.53	6.46 ±1.73	7.17 ±1.89	8.34 ±1.65	7.85 ±1.87	8.81 ±1.45	9.23 ±1.01	7.85 ±1.43	9.36 ±1.70
	C ₂	14.97 ±0.87	12.38 ±1.10	10.29 ±1.53	10.09 ±1.18	10.33 ±1.28	9.85 ±1.50	9.26 ±1.24	10.23 ±1.65	8.87 ±0.70	10.07 ±0.91

Table 5a (Continued)

Drug	Line	25 Days T r i a l									
		<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>	<u>9</u>	<u>10</u>
L ₁		15.32 ±0.88	9.59 ±1.13	8.57 ±1.62	8.47 ±1.16	8.26 ±1.38	10.53 ±0.76	10.20 ±0.69	10.64 ±0.42	9.49 ±0.92	8.74 ±1.27
		16.99 ±0.64	14.24 ±0.63	11.33 ±1.31	12.21 ±1.38	12.14 ±0.91	10.70 ±1.35	11.50 ±0.97	12.53 ±0.84	11.76 ±1.15	10.29 ±0.85
H ₁		15.61 ±3.08	14.80 ±2.21	12.90 ±2.80	12.93 ±2.60	13.44 ±2.33	16.73 ±1.59	16.96 ±1.12	16.05 ±1.85	16.37 ±1.15	15.53 ±1.53
		16.10 ±1.38	8.65 ±1.31	5.18 ±0.89	4.40 ±1.46	6.73 ±2.11	9.69 ±2.66	11.84 ±3.14	11.06 ±3.30	13.52 ±3.18	11.28 ±3.33
C ₁		11.04 ±1.09	4.84 ±1.34	3.96 ±1.08	4.67 ±1.55	6.72 ±1.91	6.44 ±1.79	6.40 ±2.30	6.68 ±2.31	5.78 ±1.80	7.89 ±2.65
		13.76 ±1.12	8.86 ±0.90	8.18 ±0.70	7.87 ±1.04	8.21 ±1.24	7.31 ±0.62	6.52 ±0.60	7.89 ±1.19	6.32 ±0.99	6.15 ±1.27
L ₁		12.79 ±2.37	11.09 ±2.44	10.13 ±2.60	9.85 ±2.73	10.30 ±2.73	10.91 ±2.66	9.72 ±2.68	9.70 ±2.64	9.84 ±2.76	10.45 ±2.88
		15.09 ±0.95	11.36 ±1.33	10.68 ±1.27	10.39 ±1.34	10.62 ±1.38	9.89 ±0.87	10.09 ±0.81	9.66 ±1.18	10.89 ±0.69	10.07 ±0.84
H ₁		18.14 ±2.56	16.64 ±2.67	15.11 ±2.67	14.97 ±2.88	14.65 ±2.76	15.18 ±3.02	15.04 ±3.16	14.62 ±2.85	14.19 ±2.79	14.00 ±2.89
		18.21 ±1.77	18.14 ±1.66	17.49 ±1.41	16.82 ±1.73	17.28 ±1.46	16.85 ±1.68	16.55 ±1.78	16.07 ±1.59	15.48 ±1.66	15.26 ±1.54

D-amphetamine
(1.0 mg/kg)

Table 5a (Continued)

Drug	Line	25 Days T r i a l									
		1	2	3	4	5	6	7	8	9	10
D-amphetamine (3.0 mg/kg)	C ₁	12.31 ±1.81	10.09 ±3.57	9.53 ±3.12	8.85 ±3.15	9.96 ±2.87	10.38 ±3.01	11.22 ±2.97	10.94 ±2.38	10.35 ±2.95	10.68 ±2.40
		19.19 ±1.83	19.89 ±2.50	20.13 ±2.51	20.32 ±2.54	20.34 ±2.95	19.67 ±2.52	18.90 ±2.64	18.22 ±2.23	17.94 ±1.81	17.64 ±1.71
	L ₁	17.07 ±2.23	17.77 ±2.83	18.40 ±2.65	17.57 ±2.56	15.48 ±2.92	14.99 ±2.80	13.51 ±3.04	13.46 ±3.07	13.63 ±2.66	13.20 ±2.13
		18.91 ±0.98	19.37 ±1.05	18.98 ±0.82	19.01 ±0.76	18.26 ±1.12	16.18 ±1.20	14.93 ±1.58	15.13 ±1.54	15.06 ±1.50	14.17 ±1.56
	H ₁	17.47 ±1.18	19.01 ±1.53	19.67 ±2.37	19.86 ±2.31	19.11 ±2.60	18.68 ±2.49	19.48 ±2.47	18.14 ±3.20	19.27 ±2.46	18.01 ±2.88
		18.28 ±1.23	20.77 ±1.73	20.55 ±1.70	20.38 ±1.97	20.07 ±1.91	18.64 ±1.74	19.13 ±1.69	19.34 ±1.67	18.72 ±1.77	18.61 ±1.48
	C ₁	17.96 ±0.95	17.19 ±1.81	16.75 ±2.05	16.39 ±2.47	15.74 ±2.16	15.71 ±2.18	16.12 ±2.32	14.63 ±2.47	14.08 ±2.37	13.26 ±2.11
		20.07 ±0.80	19.14 ±1.98	18.22 ±2.56	18.55 ±2.51	19.46 ±2.27	19.25 ±1.80	18.60 ±1.97	18.82 ±1.33	18.40 ±1.76	16.55 ±1.51
D-amphetamine (5.0 mg/kg)	L ₁	18.24 ±1.06	16.19 ±2.28	15.63 ±2.31	14.52 ±2.36	12.69 ±2.75	12.17 ±2.25	11.37 ±2.23	12.37 ±1.88	10.89 ±2.17	11.54 ±2.18
		18.92 ±1.16	19.60 ±1.64	19.21 ±2.18	17.56 ±2.15	18.61 ±1.58	18.31 ±1.93	17.47 ±2.24	17.88 ±2.12	17.46 ±1.96	17.58 ±1.78

Table 5a (Continued)

25 Days

Drug	Line	T r i a l									
		<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>	<u>9</u>	<u>10</u>
Scopolamine (0.5 mg/kg)	H ₁	17.63 ±1.80	16.16 ±1.65	15.24 ±1.66	15.23 ±1.07	15.98 ±0.89	15.42 ±1.35	15.77 ±1.25	15.99 ±1.39	14.86 ±0.88	13.67 ±1.27
	H ₂	19.34 ±1.63	19.68 ±1.88	17.05 ±1.76	14.60 ±2.15	16.15 ±1.76	15.67 ±1.70	17.00 ±1.75	15.92 ±1.89	16.50 ±1.14	15.34 ±0.85
	C ₁	14.78 ±1.07	12.37 ±1.93	11.08 ±1.19	10.65 ±1.34	10.64 ±1.71	12.38 ±1.15	12.62 ±1.34	10.03 ±1.60	11.24 ±1.22	10.84 ±1.56
	C ₂	16.14 ±0.31	13.88 ±0.05	12.96 ±0.94	11.36 ±1.76	12.28 ±1.23	12.63 ±1.07	11.21 ±1.17	11.19 ±1.06	10.28 ±1.17	11.04 ±1.07
	L ₁	17.08 ±1.55	14.65 ±1.83	11.99 ±2.71	13.23 ±2.01	12.57 ±1.64	11.91 ±1.40	13.83 ±1.52	12.42 ±1.53	10.65 ±2.42	8.29 ±2.37
	L ₂	18.11 ±1.13	15.35 ±1.44	12.14 ±2.08	12.34 ±1.86	12.91 ±1.99	15.77 ±0.74	14.68 ±1.23	12.53 ±1.30	13.23 ±1.09	12.52 ±1.29
Scopolamine (1.0 mg/kg)	H ₁	19.42 ±0.94	17.78 ±1.18	15.29 ±1.76	16.04 ±0.94	16.48 ±0.85	13.46 ±1.65	14.05 ±2.13	13.43 ±1.21	13.64 ±1.01	13.88 ±0.87
	H ₂	20.10 ±0.55	20.67 ±0.90	19.34 ±0.91	18.92 ±1.03	18.90 ±0.61	18.20 ±1.17	17.43 ±1.00	17.12 ±1.23	17.40 ±0.58	13.95 ±1.07
	C ₁	14.21 ±0.51	9.98 ±1.71	6.36 ±1.95	7.07 ±2.29	12.36 ±0.76	13.39 ±1.18	14.68 ±0.39	13.66 ±1.14	14.23 ±0.89	12.78 ±1.11
	C ₂	15.39 ±1.35	14.56 ±1.24	14.05 ±1.44	15.17 ±1.01	15.09 ±1.03	14.12 ±1.18	14.04 ±1.34	12.60 ±1.28	12.27 ±1.47	11.79 ±2.01

Table 5a (Continued)
25 Days

Trial

Drug	Line	1	2	3	4	5	6	7	8	9	10
	L ₁	16.67 ±0.78	16.16 ±0.59	15.59 ±0.70	13.75 ±0.64	14.39 ±0.36	14.03 ±0.66	13.49 ±0.94	13.18 ±0.85	13.27 ±0.85	11.13 ±1.20
	L ₂	15.10 ±0.83	15.07 ±1.10	15.04 ±0.69	15.86 ±0.63	15.94 ±0.82	15.14 ±0.74	15.61 ±0.97	14.27 ±1.08	14.48 ±9.05	13.81 ±8.27
	H ₁	19.85 ±0.68	16.93 ±1.66	15.07 ±1.70	14.28 ±2.60	15.97 ±1.08	15.62 ±1.98	16.57 ±0.69	15.18 ±0.66	15.19 ±1.40	11.70 ±0.82
	H ₂	19.74 ±1.06	19.12 ±1.77	17.27 ±1.95	16.83 ±2.56	14.20 ±2.57	16.25 ±1.85	15.57 ±2.20	13.50 ±2.92	11.95 ±2.64	13.00 ±2.60
	C ₁	16.97 ±0.95	14.25 ±1.52	14.51 ±0.74	13.18 ±1.39	13.88 ±1.47	15.58 ±0.97	14.95 ±0.38	14.29 ±0.69	14.24 ±0.71	14.22 ±0.78
	C ₂	13.94 ±1.93	13.55 ±1.72	13.16 ±1.62	14.30 ±1.10	15.10 ±0.81	14.58 ±0.63	15.18 ±0.97	15.19 ±1.05	14.56 ±1.07	14.35 ±1.38
	L ₁	14.53 ±1.16	13.27 ±1.94	12.46 ±2.01	12.29 ±2.20	11.78 ±2.02	13.46 ±1.14	13.91 ±1.19	14.07 ±1.05	13.70 ±0.90	13.90 ±1.34
	L ₂	15.33 ±1.29	14.28 ±1.36	12.67 ±1.48	13.88 ±1.14	14.74 ±0.70	14.91 ±0.71	15.34 ±0.77	15.87 ±0.81	15.26 ±0.55	15.30 ±1.04
		30 Days									
	H ₁	17.87 ±1.13	15.40 ±1.91	14.39 ±1.38	12.95 ±1.51	14.08 ±0.68	13.35 ±1.33	12.80 ±1.33	12.63 ±1.22	14.26 ±0.31	14.23 ±0.64
	H ₂	17.19 ±1.17	14.19 ±1.24	13.27 ±1.39	14.21 ±0.93	13.65 ±0.98	12.35 ±1.75	13.73 ±1.28	10.50 ±0.63	11.24 ±1.00	9.53 ±1.79

Scopolamine

(2.0 mg/kg)

4

4

OF/DE

Table 5a (Continued)

30 Days

Drug Line

Trial

	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>	<u>9</u>	<u>10</u>
Saline										
C ₁	13.02 ±0.58	11.58 ±0.57	12.45 ±0.74	12.06 ±1.06	11.61 ±0.68	11.22 ±0.96	11.25 ±0.56	12.04 ±0.64	11.86 ±0.82	11.04 ±0.69
C ₂	16.50 ±0.74	14.08 ±1.13	13.39 ±0.88	12.54 ±0.66	11.83 ±1.01	11.83 ±0.52	12.68 ±0.75	10.61 ±1.14	11.52 ±0.73	10.83 ±1.23
L ₁	11.00 ±1.56	8.43 ±1.32	7.97 ±1.36	7.58 ±1.54	9.33 ±1.14	11.13 ±0.53	10.57 ±1.04	9.49 ±0.92	10.12 ±0.82	8.86 ±1.22
L ₂	14.74 ±0.80	11.51 ±1.17	10.13 ±1.44	8.58 ±1.52	10.80 ±1.27	9.39 ±1.27	9.63 ±1.10	9.36 ±1.13	9.60 ±1.18	9.65 ±1.32
H ₁	15.33 ±1.67	12.25 ±2.24	11.11 ±2.14	12.37 ±2.11	10.79 ±2.33	10.27 ±2.72	11.08 ±2.40	10.61 ±2.60	10.00 ±2.37	9.62 ±2.37
H ₂	18.56 ±1.45	14.52 ±1.39	11.50 ±1.87	12.30 ±1.46	12.54 ±1.59	12.49 ±1.87	12.16 ±2.08	12.02 ±1.89	11.83 ±1.68	10.39 ±2.13
D-amphetamine (1.0 mg/kg)										
C ₁	12.43 ±1.29	6.27 ±1.24	4.98 ±1.68	5.48 ±1.74	4.30 ±1.51	6.57 ±1.72	6.31 ±1.45	5.54 ±1.79	4.68 ±1.64	6.46 ±1.70
C ₂	16.47 ±0.87	14.13 ±1.51	11.81 ±0.89	10.67 ±1.09	9.46 ±1.69	7.67 ±1.72	8.56 ±1.92	8.91 ±1.28	10.04 ±1.60	9.32 ±2.02
L ₁	10.54 ±1.76	7.07 ±1.55	4.70 ±1.49	5.93 ±1.50	8.82 ±1.47	9.51 ±1.07	8.11 ±1.60	8.65 ±1.87	8.45 ±1.87	7.65 ±1.71
L ₂	15.85 ±1.11	12.73 ±1.78	13.43 ±1.25	13.61 ±1.49	12.97 ±1.56	13.46 ±1.43	11.96 ±1.52	13.26 ±0.95	13.94 ±0.74	12.65 ±0.58

Table 5a (Continued)

30 Days

Trial

LifeDrug

	1	2	3	4	5	6	7	8	9	10
L ₁	13.81 ±2.59	12.62 ±3.03	13.35 ±3.23	12.57 ±3.07	12.37 ±2.95	12.12 ±3.00	13.29 ±3.13	12.98 ±2.48	13.71 ±2.58	14.03 ±2.35
L ₂	17.34 ±1.82	20.11 ±2.20	20.33 ±2.04	20.06 ±2.33	19.43 ±2.11	19.06 ±2.11	18.70 ±2.42	18.17 ±2.56	18.02 ±2.29	17.25 ±2.36
H ₁	18.49 ±3.92	16.65 ±0.98	15.50 ±0.97	14.99 ±2.12	15.20 ±2.18	14.97 ±1.15	15.42 ±1.22	15.01 ±2.16	11.58 ±1.92	9.98 ±2.41
H ₂	21.36 ±0.70	22.12 ±0.72	20.01 ±0.50	17.57 ±1.36	16.28 ±1.60	16.58 ±1.26	16.24 ±1.48	15.87 ±0.92	13.47 ±1.31	13.73 ±1.52
C ₁	17.13 ±0.60	13.55 ±1.01	11.47 ±2.02	11.09 ±2.38	12.81 ±1.07	13.97 ±0.45	13.98 ±0.43	12.39 ±0.63	12.75 ±0.68	11.98 ±0.80
C ₂	18.49 ±0.99	18.92 ±1.36	16.05 ±1.00	14.29 ±1.33	14.47 ±1.54	14.69 ±0.86	13.19 ±1.78	12.75 ±1.70	12.24 ±2.05	13.87 ±0.86
L ₁	14.78 ±1.16	12.55 ±1.54	11.34 ±2.08	12.39 ±1.35	13.25 ±1.72	12.64 ±1.39	11.65 ±1.12	11.72 ±1.74	10.12 ±1.65	10.62 ±1.68
L ₂	18.33 ±1.23	15.15 ±1.25	13.44 ±2.24	11.32 ±2.22	11.67 ±2.04	11.87 ±1.68	12.32 ±1.68	10.99 ±2.12	11.75 ±1.44	10.98 ±1.62
H ₁	19.92 ±0.90	18.49 ±1.18	16.98 ±0.96	17.38 ±0.79	16.41 ±1.09	16.40 ±1.45	16.35 ±0.96	15.70 ±1.05	15.34 ±0.77	16.48 ±0.85
H ₂	18.88 ±1.30	18.48 ±1.06	16.14 ±1.68	13.82 ±2.38	15.02 ±1.43	15.34 ±1.63	13.84 ±2.01	12.29 ±1.88	8.10 ±1.57	11.80 ±0.99

Scopolamine
(0.5 mg/kg)

Table 5a (Continued)

30 Days

Trial

Line

Drug

	1	2	3	4	5	6	7	8	9	10
Scopolamine (1.0 mg/kg)	C ₁	18.85 ±0.83	16.80 ±1.44	15.72 ±1.29	16.34 ±1.18	16.02 ±0.84	15.38 ±1.07	15.48 ±0.91	14.96 ±0.85	13.34 ±0.86
	C ₂	17.20 ±1.35	16.33 ±1.25	15.73 ±1.33	14.17 ±2.13	13.03 ±1.99	12.98 ±2.07	13.78 ±1.50	14.11 ±1.35	14.37 ±1.12
	L ₁	17.25 ±1.24	16.25 ±0.72	16.00 ±0.67	14.61 ±0.63	14.75 ±0.59	15.15 ±0.63	15.23 ±0.82	14.98 ±0.87	13.25 ±0.88
	L ₂	18.45 ±0.86	17.69 ±1.22	16.31 ±1.17	15.49 ±1.38	15.43 ±0.93	15.39 ±0.86	15.56 ±0.74	14.79 ±0.71	13.88 ±1.12
	H ₁	17.95 ±1.44	15.63 ±1.53	15.38 ±1.59	15.58 ±1.07	16.35 ±1.11	17.11 ±1.30	16.45 ±1.18	16.77 ±1.18	15.98 ±1.57
Scopolamine (2.0 mg/kg)	H ₂	19.74 ±1.59	19.12 ±1.35	17.27 ±1.10	16.83 ±0.98	14.21 ±0.90	16.25 ±1.10	15.57 ±0.98	13.50 ±1.06	13.00 ±0.36
	C ₁	18.32 ±1.61	15.33 ±1.41	13.74 ±1.34	14.73 ±1.18	14.05 ±0.91	14.77 ±0.83	14.85 ±0.68	13.92 ±0.45	14.06 ±0.64
	C ₂	20.19 ±0.74	19.13 ±0.68	16.63 ±1.20	17.26 ±1.01	16.74 ±1.04	17.41 ±0.99	17.31 ±0.74	17.04 ±0.77	15.03 ±0.83
	L ₁	17.93 ±1.23	17.50 ±1.38	17.38 ±1.27	16.49 ±1.38	15.92 ±1.05	16.64 ±1.13	15.27 ±1.13	15.10 ±1.03	14.53 ±1.25
	L ₂	16.42 ±1.72	13.02 ±1.20	9.47 ±2.16	9.12 ±2.37	10.71 ±2.54	14.73 ±1.76	14.38 ±2.09	16.17 ±1.16	14.94 ±1.49

Table 5a (Continued)

60 Days

Drug	Line	T r i a l									
		<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>	<u>9</u>	<u>10</u>
D-amphetamine (3.0 mg/kg)	L ₁	21.49 ±1.58	19.04 ±1.85	18.07 ±1.98	17.36 ±2.11	15.07 ±1.88	13.55 ±2.36	14.84 ±1.67	15.48 ±1.69	15.28 ±1.70	14.09 ±1.36
	L ₂	17.85 ±1.23	13.92 ±1.95	12.75 ±1.68	10.41 ±2.31	10.92 ±2.19	11.25 ±2.07	10.61 ±1.92	11.17 ±2.58	11.30 ±2.30	12.40 ±1.94
	H ₁	20.05 ±1.45	21.62 ±0.98	21.50 ±1.17	21.22 ±1.22	21.15 ±1.08	20.94 ±0.88	21.26 ±0.88	21.95 ±1.04	21.21 ±1.24	20.17 ±1.38
	H ₂	19.83 ±1.04	22.00 ±1.38	20.76 ±1.72	19.74 ±2.12	16.07 ±3.09	17.74 ±3.33	15.59 ±2.74	17.22 ±1.89	16.46 ±1.81	14.70 ±2.60
	C ₁	18.71 ±0.85	19.08 ±2.16	19.37 ±2.57	18.36 ±2.60	17.52 ±2.44	16.84 ±2.33	15.36 ±2.23	15.40 ±2.29	15.48 ±2.30	13.18 ±2.37
	C ₂	21.24 ±1.26	21.57 ±1.40	21.05 ±1.65	20.24 ±2.13	19.65 ±2.35	19.57 ±2.51	18.93 ±2.89	19.71 ±2.31	18.89 ±2.42	18.00 ±2.94
	L ₁	19.77 ±1.33	19.55 ±2.69	20.11 ±2.83	19.86 ±3.10	20.09 ±3.14	17.32 ±4.20	19.65 ±3.02	18.16 ±3.61	17.60 ±3.32	16.62 ±2.72
	L ₂	19.49 ±0.81	19.69 ±1.20	20.09 ±1.75	20.25 ±2.18	18.87 ±2.31	19.34 ±2.20	17.74 ±2.53	18.49 ±1.96	16.82 ±1.91	14.86 ±1.45
	H ₁	18.55 ±1.70	20.24 ±2.08	21.06 ±2.10	21.55 ±1.79	21.72 ±1.62	21.60 ±1.64	22.12 ±1.20	22.39 ±1.30	24.06 ±1.19	23.57 ±1.57
	H ₂	20.35 ±2.06	21.21 ±1.94	20.97 ±1.49	20.92 ±1.39	20.02 ±1.45	20.40 ±1.48	19.41 ±1.17	19.91 ±1.23	18.85 ±1.34	19.35 ±1.22

Table 5a (Continued)

60 Days
TrialDrugLine

	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>	<u>9</u>	<u>10</u>	
D-amphetamine (5.0 mg/kg)	C ₁	19.91 ±1.56	22.19 ±1.92	24.42 ±1.83	23.15 ±1.76	23.32 ±1.81	23.15 ±1.68	22.63 ±1.45	22.18 ±0.86	21.38 ±0.98	20.83 ±0.74
	C ₂	19.85 ±1.64	22.00 ±2.09	21.11 ±2.13	21.30 ±2.53	21.25 ±2.50	22.21 ±2.07	22.81 ±1.95	21.90 ±2.43	22.45 ±1.77	22.84 ±1.52
	L ₁	19.08 ±1.68	19.18 ±2.34	19.86 ±2.80	19.70 ±2.27	19.89 ±2.51	19.39 ±2.05	18.54 ±1.87	19.02 ±2.01	18.61 ±2.26	18.34 ±2.38
	L ₂	20.20 ±2.85	20.83 ±3.15	20.71 ±3.13	20.59 ±3.01	20.36 ±3.11	19.66 ±2.81	20.25 ±2.92	20.09 ±2.68	20.45 ±2.68	19.42 ±2.54
	H ₁	19.06 ±1.13	21.46 ±1.65	21.15 ±1.62	19.99 ±1.64	20.17 ±1.75	19.76 ±1.61	19.75 ±1.62	18.56 ±1.72	18.57 ±1.85	18.94 ±1.90
	H ₂	19.48 ±1.22	19.97 ±1.69	18.64 ±1.49	18.19 ±1.27	17.42 ±1.15	17.38 ±0.41	18.05 ±0.71	16.53 ±0.68	17.03 ±0.51	16.36 ±0.65
Scopolamine (0.5 mg/kg)	C ₁	18.03 ±1.15	16.19 ±1.66	14.32 ±2.15	14.26 ±1.95	14.55 ±1.78	15.30 ±1.68	15.11 ±1.30	14.62 ±1.30	14.45 ±1.65	13.53 ±1.30
	C ₂	18.57 ±0.76	19.73 ±0.63	19.01 ±0.65	19.13 ±0.88	18.22 ±0.68	18.68 ±0.89	18.24 ±1.13	17.32 ±1.27	16.98 ±1.29	16.46 ±1.27
	L ₁	18.55 ±0.61	17.78 ±0.62	17.77 ±1.14	17.78 ±0.93	17.06 ±1.04	16.62 ±1.28	16.85 ±1.23	16.03 ±1.08	15.07 ±1.31	14.79 ±0.99
	L ₂	20.85 ±1.49	19.49 ±1.57	18.99 ±1.18	18.37 ±1.20	18.67 ±1.81	18.39 ±1.27	18.10 ±1.20	17.86 ±1.19	17.04 ±1.33	16.09 ±1.53

Table 5a (Continued)

Drug	Line	60 Days									
		T r i a l									
		1	2	3	4	5	6	7	8	9	10
Scopolamine (1.0 mg/kg)	H ₁	20.53 ±1.64	20.85 ±1.38	20.15 ±1.13	19.57 ±0.46	20.61 ±0.58	20.80 ±1.01	20.24 ±1.22	20.22 ±1.59	18.87 ±1.27	18.00 ±1.19
	H ₂	21.46 ±1.58	22.88 ±1.43	22.30 ±1.04	21.74 ±0.93	19.50 ±1.61	20.66 ±0.94	17.32 ±1.22	18.57 ±0.89	18.02 ±0.92	18.17 ±1.04
	C ₁	18.92 ±1.10	16.26 ±2.04	15.79 ±1.87	15.88 ±1.50	16.46 ±1.67	16.16 ±1.58	15.68 ±1.63	14.82 ±1.87	13.95 ±1.83	13.98 ±1.68
	C ₂	18.78 ±0.77	19.16 ±1.06	18.69 ±0.99	16.83 ±1.06	17.57 ±1.30	18.55 ±0.98	17.98 ±0.75	16.96 ±0.89	16.51 ±0.83	16.11 ±0.94
	L ₁	18.15 ±1.26	17.84 ±1.40	17.57 ±1.44	17.95 ±1.23	17.75 ±1.07	18.10 ±1.03	17.07 ±1.12	17.90 ±0.90	17.64 ±0.74	17.37 ±0.94
	L ₂	19.96 ±1.61	19.69 ±1.40	18.96 ±1.14	18.74 ±0.95	20.21 ±0.98	19.89 ±1.44	20.21 ±1.02	19.72 ±1.01	19.54 ±0.83	19.04 ±0.68
Scopolamine (2.0 mg/kg)	H ₁	15.76 ±1.49	17.59 ±1.55	16.56 ±1.20	17.35 ±1.19	17.96 ±1.63	18.07 ±1.36	17.86 ±1.00	17.88 ±1.19	17.97 ±1.07	16.82 ±0.80
	H ₂	21.46 ±1.50	22.35 ±1.36	20.60 ±1.40	20.75 ±1.52	20.22 ±1.80	22.13 ±0.68	20.45 ±1.39	20.45 ±1.21	19.70 ±0.82	20.47 ±0.82
	C ₁	18.96 ±1.20	17.99 ±1.31	17.66 ±1.27	17.20 ±1.45	16.86 ±1.11	17.85 ±0.94	17.60 ±0.89	17.37 ±0.94	16.91 ±0.97	16.75 ±1.06
	C ₂	17.77 ±1.11	17.45 ±1.02	17.09 ±1.30	17.25 ±1.07	17.76 ±1.42	17.86 ±0.76	18.37 ±1.01	17.43 ±1.02	16.84 ±0.81	17.10 ±0.93

Table 5a (Continued)

Drug	Line	60 Days									
		T r i a l									
		1	2	3	4	5	6	7	8	9	10
L ₁		20.04	21.66	20.99	20.17	20.72	20.46	19.58	18.71	18.53	16.76
		±0.48	±1.21	±0.69	±1.23	±1.32	±1.25	±1.19	±1.62	±2.28	±2.68
L ₂		16.80	17.08	17.40	17.76	17.49	17.49	16.91	17.14	17.05	16.81
		±2.17	±2.19	±1.99	±1.89	±2.03	±2.45	±2.44	±2.35	±2.41	±2.16

Mean differences necessary for $p < .05$ of the simple main effects

Between Trials		Between Lines (Pooled error)		Between Drug (Pooled error)	
$r_2 = 2.69$		$r_2 = 4.74$		$r_2 = 4.74$	
$r_3 = 3.21$		$r_3 = 5.66$		$r_3 = 5.66$	
$r_4 = 3.52$		$r_4 = 6.21$		$r_4 = 6.21$	
$r_5 = 3.74$		$r_5 = 6.60$		$r_5 = 6.60$	
$r_6 = 3.91$		$r_6 = 6.89$		$r_6 = 6.89$	
$r_7 = 4.05$				$r_7 = 7.13$	
$r_8 = 4.16$					
$r_9 = 4.26$					
$r_{10} = 4.36$					

Table 5b

Mean Percentage Change (Trial x/Trial x + Trial 1) in Number of
Photoceall Crossings ($\pm$ S.E.M.) as a Function of Line, Age and Drug (Experiment 5)

Line	15 Days									
	Trial									
	2	3	4	5	6	7	8	9	10	
H ₁	39.65	36.62	24.50	25.68	18.95	14.13	14.25	14.88	7.34	
	± 6.24	± 7.14	± 5.80	± 8.02	± 4.86	± 4.88	± 8.46	± 6.55	± 4.54	
H ₂	25.76	21.56	26.37	25.10	36.60	20.75	34.15	33.31	36.19	
	± 7.07	± 9.26	± 10.71	± 9.17	± 11.28	± 10.35	± 9.40	± 13.72	± 13.11	
C ₁	17.80	29.76	37.32	40.21	37.88	34.49	29.22	44.23	44.08	
	± 9.13	± 11.16	± 12.14	± 11.92	± 12.27	± 15.01	± 12.35	± 12.90	± 9.74	
C ₂	34.00	25.79	25.78	27.56	30.90	20.44	22.08	24.53	35.73	
	± 2.38	± 5.71	± 5.01	± 6.29	± 4.90	± 6.11	± 5.55	± 4.62	± 5.09	
L ₁	48.89	40.49	37.53	35.62	30.82	27.75	28.82	28.00	31.17	
	± 3.40	± 3.85	± 7.08	± 9.75	± 7.04	± 8.09	± 10.26	± 8.66	± 7.70	
L ₂	50.80	32.42	29.43	29.22	41.60	40.80	40.18	45.13	49.77	
	± 4.98	± 5.75	± 10.43	± 9.87	± 8.24	± 9.56	± 10.20	± 8.71	± 9.53	
H ₁	32.55	22.22	19.17	16.45	17.77	21.88	22.16	27.46	27.24	
	± 5.17	± 5.53	± 5.85	± 4.66	± 4.55	± 6.63	± 7.21	± 5.98	± 6.33	
H ₂	37.42	26.36	23.84	25.77	18.67	23.29	24.37	23.55	23.85	
	± 6.40	± 8.07	± 7.67	± 7.18	± 5.97	± 5.87	± 9.93	± 8.76	± 8.44	
C ₁	17.08	12.59	26.84	24.20	28.41	37.82	35.86	43.78	51.32	
	± 7.19	± 5.75	± 12.71	± 12.12	± 12.39	± 14.46	± 14.04	± 13.00	± 12.28	

D-amphetamine
(1.0 mg/kg)

Table 5b (Continued)

15 Days

Line	Trial									
	2	3	4	5	6	7	8	9	10	
C ₂	33.04 ±6.27	19.18 ±5.97	12.70 ±5.91	16.21 ±6.70	29.97 ±6.91	43.71 ±10.17	36.59 ±10.00	35.50 ±9.81	33.53 ±8.26	
	49.13 ±7.56	39.66 ±8.50	42.33 ±9.93	45.41 ±10.94	43.82 ±11.59	43.11 ±11.58	38.82 ±12.81	36.36 ±12.38	40.91 ±12.00	
L ₂	42.73 ±9.65	39.75 ±9.51	30.10 ±7.61	29.37 ±7.95	18.08 ±7.78	20.54 ±6.83	27.46 ±8.24	27.06 ±7.47	39.79 ±9.32	
H ₁	40.55 ±5.78	34.44 ±8.12	33.73 ±8.48	30.25 ±9.42	32.06 ±10.69	33.10 ±9.95	34.92 ±9.88	29.47 ±10.64	29.51 ±11.24	
	45.18 ±4.73	35.79 ±7.14	32.12 ±9.04	28.88 ±8.99	28.98 ±8.56	30.73 ±8.47	30.00 ±7.76	25.87 ±7.80	28.11 ±6.86	
C ₁	35.60 ±7.09	24.85 ±7.01	24.72 ±6.86	18.73 ±5.56	27.89 ±5.27	17.35 ±5.22	15.64 ±4.89	22.76 ±8.29	17.47 ±6.41	
C ₂	52.20 ±2.35	53.98 ±2.79	49.52 ±3.00	46.26 ±3.85	43.86 ±3.24	43.03 ±2.71	39.88 ±3.55	41.29 ±2.19	34.53 ±5.58	
L ₁	46.75 ±8.44	47.60 ±9.80	44.37 ±10.90	42.83 ±10.69	44.69 ±9.35	45.81 ±9.11	42.95 ±8.45	43.74 ±8.99	33.49 ±7.96	
L ₂	43.15 ±6.76	44.17 ±7.22	37.06 ±7.38	35.38 ±6.36	36.27 ±7.84	38.08 ±8.55	36.20 ±7.64	37.47 ±7.27	36.50 ±6.29	

D-amphetamine
(3.0 mg/kg)

D-amphetamine
(3.0 mg/kg)

Table 5b (Continued)

15 Days

LineTrial

	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>	<u>9</u>	<u>10</u>	
D-amphetamine (5.0 mg/kg)	H ₁	52.84 ±4.76	46.81 ±4.38	41.74 ±4.13	38.76 ±3.92	35.99 ±5.84	32.96 ±6.88	31.94 ±4.57	31.47 ±8.33	31.28 ±8.73
	H ₂	43.90 ±6.71	40.53 ±6.64	38.74 ±7.21	38.21 ±6.51	29.04 ±6.16	33.97 ±7.45	39.21 ±6.03	40.27 ±6.93	36.70 ±8.15
	C ₁	42.51 ±4.19	36.57 ±5.35	37.43 ±5.51	38.71 ±7.84	38.57 ±8.85	35.66 ±10.31	32.42 ±9.25	31.86 ±9.64	31.37 ±10.67
	C ₂	47.05 ±3.01	38.82 ±5.30	33.16 ±5.77	33.12 ±4.94	29.74 ±4.57	29.93 ±3.85	28.51 ±3.87	28.98 ±5.16	30.26 ±4.46
	L ₁	38.96 ±4.94	29.66 ±6.89	23.89 ±9.07	23.76 ±8.41	18.78 ±7.05	19.63 ±7.21	27.35 ±8.98	22.50 ±7.36	25.10 ±8.70
	L ₂	44.27 ±6.58	41.66 ±5.57	36.58 ±7.46	31.42 ±7.41	25.23 ±7.30	24.72 ±7.34	21.71 ±8.13	26.80 ±9.03	32.86 ±8.95
Scopolamine (0.5 mg/kg)	H ₁	42.03 ±6.66	37.08 ±11.04	33.94 ±12.96	47.50 ±11.24	47.38 ±10.50	56.51 ±11.50	54.99 ±12.42	48.31 ±13.96	57.34 ±13.10
	H ₂	49.38 ±12.29	40.07 ±12.61	57.20 ±11.73	76.60 ±4.06	69.15 ±10.51	56.64 ±12.93	64.49 ±10.23	67.28 ±10.69	67.27 ±11.00
	C ₁	12.47 ±8.60	20.94 ±10.50	17.22 ±11.62	33.60 ±13.77	34.16 ±14.13	39.06 ±15.25	56.42 ±14.34	49.39 ±15.39	53.35 ±14.85
	C ₂	11.58 ±9.16	1.21 ±0.64	6.25 ±6.20	8.90 ±6.07	21.71 ±9.21	32.60 ±10.70	27.08 ±10.62	31.40 ±10.37	27.81 ±11.86

Table 5b (Continued)

15 Days

Line

T r i a l

	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>	<u>9</u>	<u>10</u>
L ₁	5.83 ±3.91	5.94 ±3.90	25.03 ±8.77	19.86 ±11.09	9.37 ±5.52	22.91 ±10.49	15.91 ±8.06	5.32 ±5.32	15.52 ±6.79
L ₂	23.77 ±8.74	11.64 ±7.36	20.07 ±9.68	26.41 ±12.45	39.07 ±11.08	49.06 ±10.92	53.61 ±10.20	49.54 ±12.16	43.44 ±11.05
H ₁	38.75 ±11.61	26.81 ±9.34	21.65 ±8.73	22.65 ±8.17	18.76 ±7.27	22.85 ±9.61	24.96 ±14.37	22.13 ±13.08	22.77 ±13.56
H ₂	41.93 ±11.73	38.18 ±12.29	42.77 ±10.50	52.41 ±9.72	59.15 ±11.00	59.61 ±11.99	57.31 ±12.67	55.27 ±11.01	49.85 ±12.28
C ₁	23.46 ±7.69	34.08 ±12.71	27.65 ±13.61	28.88 ±14.19	31.62 ±12.28	31.61 ±12.92	29.95 ±13.75	33.55 ±13.22	29.11 ±13.91
C ₂	14.74 ±6.15	7.75 ±3.81	7.95 ±5.17	3.43 ±2.54	13.43 ±7.66	13.05 ±7.20	26.40 ±9.70	29.80 ±9.28	17.55 ±7.39
L ₁	15.99 ±8.06	9.74 ±9.33	6.47 ±5.31	0.10 ±0.01	12.50 ±6.75	27.86 ±13.33	30.27 ±11.71	40.29 ±12.02	45.82 ±13.25
L ₂	11.84 ±7.90	20.75 ±11.67	11.33 ±6.93	19.75 ±12.20	22.52 ±12.80	26.64 ±14.41	31.85 ±13.69	45.88 ±11.05	41.32 ±13.02
H ₁	36.98 ±8.91	25.01 ±10.49	27.61 ±10.09	35.99 ±9.62	28.33 ±9.36	23.25 ±9.12	40.47 ±11.28	37.99 ±11.66	40.63 ±12.99
H ₂	50.34 ±11.22	47.02 ±12.72	47.34 ±14.79	51.16 ±14.42	49.79 ±14.43	56.37 ±14.21	48.56 ±13.81	49.12 ±14.67	51.93 ±13.92

Scopolamine

(1.0 mg/kg)

Table 5b (Continued)

15 Days

Trial

Line

	1	2	3	4	5	6	7	8	9	10
Scopolamine (2.0 mg/kg)	C ₁	47.09 ±13.36	31.37 ±15.39	45.57 ±13.99	28.12 ±13.74	53.31 ±16.06	48.56 ±14.89	51.53 ±15.82	46.04 ±17.52	45.78 ±17.37
	C ₂	22.76 ±6.71	5.45 ±5.40	3.13 ±3.12	4.75 ±3.59	4.18 ±3.03	6.82 ±3.27	6.87 ±5.18	10.33 ±7.27	17.91 ±6.56
	L ₁	26.80 ±10.20	19.20 ±12.87	0.34 ±0.30	4.22 ±2.78	3.20 ±2.50	17.14 ±8.08	17.94 ±8.54	27.31 ±11.69	34.02 ±14.38
	L ₂	23.23 ±8.06	13.59 ±7.02	10.54 ±8.60	27.75 ±10.30	26.83 ±11.12	28.56 ±12.26	49.88 ±12.59	41.17 ±12.95	48.32 ±11.77
20 Days										
Saline	H ₁	51.13 ±5.17	44.07 ±5.53	42.16 ±5.85	44.37 ±4.66	45.83 ±4.55	48.58 ±6.63	48.36 ±7.21	48.06 ±5.98	50.10 ±6.33
	H ₂	42.35 ±3.20	35.03 ±3.09	35.50 ±5.30	37.42 ±2.01	37.21 ±3.45	36.22 ±2.97	27.85 ±5.05	33.01 ±1.91	28.26 ±3.60
	C ₁	37.08 ±2.56	33.32 ±3.41	31.77 ±4.66	36.14 ±2.97	37.04 ±2.11	34.83 ±3.38	33.76 ±4.01	30.00 ±4.52	33.86 ±1.88
	C ₂	28.06 ±4.39	32.32 ±4.91	38.56 ±6.70	33.20 ±8.82	34.42 ±6.73	34.45 ±5.03	33.24 ±6.89	29.97 ±7.70	37.73 ±5.79
	L ₁	26.22 ±6.54	16.58 ±6.13	18.62 ±7.89	32.74 ±11.82	29.33 ±9.64	35.82 ±10.11	31.93 ±11.90	26.89 ±9.89	32.65 ±10.54
	L ₂	36.52 ±3.43	34.27 ±2.63	30.94 ±6.69	39.98 ±3.43	41.43 ±2.43	35.65 ±3.73	33.65 ±1.76	33.65 ±3.59	37.55 ±3.58

Table 5b (Continued)

Line	20 Days									
	T r i a l									
	2	3	4	5	6	7	8	9	10	
D-amphetamine (1.0 mg/kg)	H ₁	45.78 ±5.91	52.34 ±5.83	50.54 ±5.49	52.38 ±6.10	57.19 ±5.12	55.28 ±5.05	51.45 ±6.26	51.76 ±5.95	52.31 ±5.81
	H ₂	34.86 ±6.40	36.14 ±8.07	39.51 ±7.67	41.57 ±7.18	53.68 ±5.97	52.98 ±5.87	53.85 ±9.93	49.57 ±9.76	51.46 ±8.44
	C ₁	21.20 ±6.39	21.15 ±7.14	23.59 ±4.59	24.51 ±6.03	20.75 ±5.06	21.30 ±6.75	21.91 ±6.72	17.10 ±6.53	21.35 ±8.00
	C ₂	27.84 ±3.31	25.62 ±5.79	24.30 ±5.58	20.97 ±4.87	24.31 ±5.70	24.79 ±5.36	27.42 ±4.38	25.55 ±5.70	21.44 ±5.65
	L ₁	22.57 ±5.75	13.80 ±3.81	9.53 ±3.74	9.97 ±4.15	17.78 ±7.92	19.39 ±7.38	19.52 ±8.09	16.75 ±9.25	29.46 ±9.12
	L ₂	26.48 ±4.73	21.67 ±4.14	18.30 ±5.04	18.27 ±4.96	19.70 ±5.31	26.46 ±5.17	14.45 ±5.08	20.13 ±5.22	18.06 ±4.76
D-amphetamine (3.0 mg/kg)	H ₁	35.19 ±4.85	40.41 ±4.67	40.48 ±6.04	42.92 ±6.60	47.05 ±5.58	42.62 ±8.51	43.96 ±8.17	46.99 ±8.47	56.08 ±6.22
	H ₂	50.97 ±1.70	49.56 ±3.27	48.62 ±3.29	46.50 ±3.46	41.99 ±5.81	41.34 ±5.17	37.25 ±6.32	34.80 ±8.61	33.97 ±7.86
	C ₁	38.23 ±5.02	32.24 ±7.32	23.92 ±7.89	25.79 ±8.45	23.01 ±8.23	33.76 ±9.23	34.48 ±9.91	44.96 ±8.22	31.75 ±9.84
	C ₂	41.95 ±3.48	42.55 ±2.39	40.42 ±2.25	37.27 ±3.92	38.67 ±4.34	35.80 ±2.45	28.28 ±3.41	31.51 ±3.80	30.72 ±4.65

Table 5b (Continued)

Line	20 Days									
	Trial									
	2	3	4	5	6	7	8	9	10	
L ₁	49.52 ±2.91	46.91 ±4.34	44.52 ±4.99	45.10 ±4.82	42.03 ±6.19	36.84 ±4.19	35.72 ±6.29	35.26 ±6.34	32.71 ±7.05	
	51.63 ±1.59	49.18 ±2.24	49.37 ±1.94	49.02 ±1.95	48.84 ±2.33	42.38 ±2.32	40.98 ±2.64	38.63 ±4.06	38.90 ±4.04	
H ₁	50.79 ±3.00	49.98 ±3.57	47.67 ±5.25	46.16 ±6.64	44.68 ±6.88	43.41 ±6.02	41.38 ±6.95	41.27 ±4.98	37.90 ±5.45	
	49.71 ±2.73	47.44 ±4.19	48.11 ±3.38	49.19 ±3.68	48.24 ±3.11	48.39 ±3.64	49.49 ±3.30	49.87 ±3.44	49.30 ±2.61	
C ₁	48.53 ±2.41	46.23 ±4.38	45.77 ±5.91	46.82 ±5.88	45.63 ±6.08	43.38 ±6.16	39.92 ±7.50	38.88 ±6.57	35.01 ±7.06	
	47.46 ±9.72	50.99 ±3.03	46.42 ±3.60	44.86 ±4.92	43.74 ±5.51	44.79 ±5.83	46.39 ±5.75	46.20 ±4.41	43.84 ±4.88	
L ₁	48.86 ±2.95	44.82 ±4.18	38.29 ±6.72	37.76 ±7.44	38.80 ±7.98	38.01 ±7.65	37.57 ±8.13	35.63 ±7.19	38.50 ±6.37	
	50.76 ±2.21	46.83 ±4.82	43.57 ±5.75	42.75 ±6.23	40.49 ±6.34	41.69 ±5.11	41.41 ±4.09	37.68 ±5.67	36.82 ±5.51	
H ₁	44.04 ±2.16	35.00 ±5.19	41.18 ±2.41	34.92 ±5.23	28.29 ±7.72	34.29 ±7.33	41.34 ±3.21	37.09 ±2.78	32.32 ±4.89	
	40.55 ±4.40	37.33 ±5.34	32.01 ±6.93	35.61 ±6.94	33.72 ±7.56	31.97 ±6.68	31.51 ±6.62	31.91 ±5.54	30.27 ±5.61	

D-amphetamine
(5.0 mg/kg)

Table 5b (Continued)

Line	20 Days									
	Trial									
	2	3	4	5	6	7	8	9	10	
Scopolamine (2.0 mg/kg)	H ₁	51.31 ±2.14	58.55 ±4.85	61.23 ±5.15	59.62 ±5.86	60.70 ±5.13	62.50 ±5.08	59.69 ±5.83	60.66 ±4.70	54.57 ±6.95
	H ₂	40.32 ±8.06	34.24 ±9.62	42.69 ±9.45	53.98 ±6.72	58.05 ±5.60	61.42 ±6.19	60.12 ±7.01	57.66 ±10.14	49.97 ±10.46
	C ₁	39.53 ±5.66	33.90 ±6.31	37.78 ±6.29	43.18 ±6.54	42.23 ±6.56	42.99 ±3.51	41.99 ±1.99	38.11 ±4.47	35.38 ±3.44
	C ₂	48.89 ±3.60	41.58 ±6.75	44.52 ±6.62	36.39 ±7.53	51.38 ±3.66	58.58 ±2.19	46.03 ±8.26	44.14 ±8.96	40.37 ±9.45
	L ₁	42.95 ±3.68	40.97 ±5.27	38.67 ±4.68	41.90 ±6.94	43.84 ±6.28	38.12 ±6.76	42.30 ±6.78	32.54 ±7.52	34.13 ±7.92
	L ₂	25.87 ±9.63	34.49 ±10.28	45.89 ±10.96	59.27 ±7.85	59.74 ±7.93	57.62 ±9.61	66.59 ±8.41	70.63 ±5.88	73.32 ±3.61
Saline	25 Days									
	H ₁	46.82 ±12.04	43.80 ±13.24	52.19 ±10.92	56.07 ±8.94	54.19 ±9.54	56.39 ±8.31	47.94 ±11.08	48.40 ±11.20	49.44 ±9.27
	H ₂	40.23 ±3.83	36.83 ±5.35	26.51 ±5.40	38.30 ±3.91	37.94 ±5.06	39.05 ±2.83	23.97 ±6.23	29.05 ±6.22	37.50 ±2.61
	C ₁	26.01 ±6.57	20.71 ±7.46	24.37 ±7.93	27.94 ±6.29	25.48 ±7.10	31.28 ±5.41	32.03 ±4.49	26.82 ±5.83	33.59 ±6.80
	C ₂	39.56 ±3.51	31.49 ±4.85	30.08 ±4.29	30.92 ±4.55	29.81 ±5.03	26.59 ±4.47	31.21 ±5.73	25.57 ±3.64	31.05 ±4.54

Table 5b (Continued)

25 Days

Line

T r i a l

	2	3	4	5	6	7	8	9	10
L ₁	26.67 ±3.40	22.94 ±4.86	21.86 ±3.60	21.50 ±4.65	31.23 ±2.31	30.03 ±2.30	32.33 ±1.86	26.96 ±3.98	24.42 ±3.93
L ₂	41.01 ±2.60	30.56 ±4.86	34.24 ±4.98	33.27 ±3.84	27.11 ±3.63	30.67 ±3.61	35.09 ±3.77	31.15 ±3.37	26.01 ±3.41
H ₁	46.01 ±8.19	40.81 ±6.81	39.93 ±4.68	48.63 ±8.20	55.27 ±9.20	57.84 ±8.42	55.12 ±9.40	55.35 ±9.44	50.72 ±10.82
H ₂	21.30 ±4.65	9.11 ±2.53	7.12 ±2.83	13.51 ±5.01	25.41 ±8.41	31.64 ±9.33	28.96 ±9.55	37.95 ±9.19	31.84 ±10.95
C ₁	16.67 ±6.13	12.63 ±5.31	16.27 ±6.79	27.28 ±8.15	25.83 ±8.47	26.64 ±10.30	27.27 ±10.72	22.86 ±9.44	30.16 ±12.19
C ₂	29.58 ±4.10	26.79 ±4.34	24.23 ±4.76	24.88 ±5.12	22.49 ±3.43	19.13 ±4.19	25.28 ±5.36	20.42 ±6.28	18.80 ±6.77
L ₁	40.06 ±10.05	35.94 ±10.71	33.53 ±9.15	33.05 ±7.59	41.35 ±7.14	30.20 ±7.58	27.83 ±8.30	27.88 ±9.03	30.93 ±8.75
L ₂	34.43 ±2.61	32.63 ±4.87	31.38 ±5.12	32.34 ±5.01	29.76 ±4.44	31.53 ±5.34	30.02 ±5.22	34.13 ±4.18	35.10 ±4.95
H ₁	44.52 ±2.69	40.03 ±2.78	38.91 ±5.34	32.07 ±4.53	37.82 ±5.32	36.03 ±6.71	35.29 ±5.29	34.21 ±5.38	32.69 ±6.09
H ₂	50.14 ±1.82	49.12 ±3.60	47.00 ±5.61	48.48 ±4.51	47.15 ±5.84	46.37 ±6.47	44.57 ±4.85	42.45 ±5.75	41.88 ±5.56

D-amphetamine

(1.0 mg/kg)

Table 5b (Continued)

Line	25 Days									
	T r a f a l									
	2	3	4	5	6	7	8	9	10	
D-amphetamine										
(3.0 mg/kg)										
C ₁	34.17 ±7.57	29.87 ±8.96	26.27 ±9.49	31.31 ±8.96	34.57 ±10.30	37.64 ±9.97	38.43 ±7.97	34.08 ±10.09	37.11 ±7.99	
C ₂	49.13 ±4.88	49.52 ±5.51	50.01 ±5.41	49.50 ±7.42	48.13 ±6.59	46.01 ±7.32	44.86 ±6.29	45.61 ±5.18	45.51 ±4.93	
L ₁	47.23 ±5.48	53.15 ±3.81	50.65 ±5.33	38.90 ±7.94	39.51 ±7.01	34.66 ±8.20	33.23 ±8.57	35.00 ±6.80	38.27 ±6.62	
L ₂	51.15 ±1.85	50.31 ±2.44	50.43 ±2.48	48.02 ±3.29	41.88 ±3.94	37.21 ±5.18	37.75 ±4.42	37.57 ±4.19	34.66 ±4.58	
H ₁	53.60 ±4.96	53.49 ±7.14	53.97 ±7.27	51.18 ±8.38	50.33 ±8.42	52.72 ±8.29	48.38 ±10.25	51.99 ±7.96	47.95 ±9.64	
H ₂	55.95 ±2.24	55.40 ±2.18	54.45 ±2.73	53.71 ±2.80	49.94 ±3.23	51.40 ±3.06	51.94 ±3.24	50.12 ±3.26	50.47 ±2.64	
C ₁	46.17 ±3.29	44.20 ±4.69	41.97 ±6.12	40.93 ±4.87	40.87 ±5.42	41.87 ±6.01	36.66 ±6.61	35.52 ±6.29	32.75 ±5.62	
C ₂	46.27 ±5.21	43.21 ±6.71	43.98 ±6.37	46.78 ±6.25	46.86 ±5.25	44.90 ±5.99	46.18 ±3.77	44.40 ±4.19	39.52 ±3.94	
L ₁	41.35 ±4.99	39.49 ±5.70	36.05 ±6.30	30.85 ±7.41	28.93 ±6.46	28.10 ±5.54	30.85 ±6.31	26.22 ±6.64	26.83 ±5.88	
L ₂	51.12 ±3.07	49.06 ±4.85	44.81 ±5.41	48.53 ±2.13	47.16 ±2.58	44.22 ±4.73	45.58 ±3.94	44.62 ±3.18	45.29 ±2.42	

Table 5b (Continued)

Line	25 Days									
	T r i a l									
	2	3	4	5	6	7	8	9	10	
Scopolamine (0.5 mg/kg)	H ₁	46.03 ±4.30	43.31 ±5.32	44.19 ±6.10	46.58 ±5.45	44.78 ±5.83	45.41 ±6.56	46.10 ±6.30	43.47 ±5.72	39.57 ±7.22
	H ₂	50.46 ±3.12	43.12 ±4.00	34.34 ±6.50	41.31 ±5.75	39.50 ±5.39	43.75 ±5.25	39.72 ±4.37	42.78 ±3.45	39.80 ±3.89
	C ₁	39.94 ±6.11	35.02 ±3.69	33.64 ±4.36	33.32 ±5.49	40.37 ±1.88	41.17 ±3.18	33.51 ±4.38	35.47 ±2.34	33.43 ±5.05
	C ₂	41.80 ±2.76	38.50 ±3.69	33.77 ±5.87	36.23 ±4.72	37.15 ±4.23	31.89 ±4.49	32.24 ±4.28	28.33 ±4.46	31.45 ±4.22
	L ₁	40.73 ±3.09	30.95 ±6.76	35.79 ±4.98	33.37 ±3.70	31.30 ±3.11	39.11 ±3.53	33.99 ±4.22	28.75 ±6.80	19.07 ±6.54
	L ₂	41.06 ±3.56	30.24 ±6.16	32.77 ±7.03	35.07 ±5.63	43.43 ±1.88	38.91 ±2.95	30.95 ±3.24	34.46 ±3.19	32.39 ±4.47
Scopolamine (1.0 mg/kg)	H ₁	45.11 ±2.37	37.71 ±5.18	40.43 ±2.90	41.66 ±1.57	32.51 ±5.08	35.51 ±5.53	31.27 ±2.38	32.46 ±2.95	33.81 ±3.62
	H ₂	51.23 ±1.27	47.82 ±1.76	46.52 ±2.12	46.80 ±1.47	44.50 ±3.23	42.38 ±2.60	41.25 ±3.21	42.67 ±1.79	31.84 ±3.26
	C ₁	30.94 ±6.75	18.07 ±7.12	21.26 ±7.92	42.47 ±2.31	45.64 ±3.75	51.82 ±1.58	46.77 ±3.42	49.65 ±2.75	43.33 ±3.42
	C ₂	47.15 ±2.40	45.14 ±5.97	50.14 ±4.91	49.69 ±3.83	46.20 ±5.21	45.69 ±5.11	40.21 ±4.84	39.98 ±6.93	37.88 ±6.99

Table 5b (Continued)

Line	25 Days									
	Trial									
	2	3	4	5	6	7	8	9	10	
L ₁	48.57 ±1.30	46.60 ±1.75	40.53 ±2.89	42.91 ±2.76	41.33 ±3.04	39.16 ±3.81	38.12 ±4.07	38.54 ±3.90	30.63 ±4.58	
L ₂	49.44 ±2.62	49.98 ±3.31	52.70 ±4.00	52.76 ±4.02	50.31 ±3.85	51.59 ±4.63	47.03 ±5.60	47.88 ±4.58	45.47 ±4.35	
H ₁	41.10 ±4.76	35.37 ±5.45	33.55 ±7.62	37.09 ±4.04	37.49 ±6.02	41.01 ±3.40	36.64 ±2.94	36.19 ±4.79	25.64 ±3.59	
H ₂	47.05 ±4.51	41.65 ±5.52	40.78 ±6.83	32.45 ±6.31	39.02 ±4.98	37.75 ±5.81	31.15 ±7.22	26.52 ±6.25	29.26 ±6.50	
C ₁	40.21 ±4.73	42.15 ±2.24	37.07 ±5.21	39.19 ±4.76	45.40 ±2.81	43.98 ±1.68	41.39 ±1.96	41.20 ±1.42	41.11 ±2.57	
C ₂	48.37 ±2.39	48.38 ±5.69	53.36 ±7.18	56.85 ±5.69	55.20 ±5.83	56.56 ±6.56	57.05 ±5.35	54.87 ±5.68	53.93 ±5.74	
L ₁	43.71 ±5.91	40.85 ±6.98	41.60 ±7.22	39.34 ±7.21	46.35 ±4.83	47.68 ±2.72	48.26 ±4.56	47.44 ±4.13	47.26 ±4.43	
L ₂	45.99 ±1.46	38.95 ±2.75	45.01 ±0.92	48.93 ±2.79	49.58 ±4.80	50.98 ±3.53	52.61 ±4.31	50.88 ±4.96	50.55 ±5.58	
30 Days										
H ₁	40.62 ±5.01	38.21 ±2.89	33.29 ±4.47	38.41 ±2.07	35.00 ±4.77	34.27 ±5.17	34.12 ±5.73	39.48 ±2.88	39.25 ±3.18	
H ₂	40.06 ±3.87	36.98 ±4.80	40.81 ±3.44	38.62 ±3.86	34.27 ±6.92	38.14 ±3.71	27.06 ±2.34	30.03 ±4.23	26.40 ±6.86	

Scoopamine

(2.0 mg/kg)

Table 5b (Continued)

Line	30 Days									
	Trial									
	2	3	4	5	6	7	8	9	10	
D-amphetamine (3.0 mg/kg)	H ₁	52.39 ±2.54	51.42 ±2.75	48.49 ±3.16	44.82 ±3.13	37.62 ±5.74	37.49 ±5.51	40.73 ±5.54	37.23 ±4.30	
	H ₂	44.20 ±2.94	42.22 ±4.54	41.72 ±5.31	40.36 ±7.44	40.39 ±6.61	43.75 ±6.66	40.77 ±7.14	39.27 ±7.99	
	C ₁	46.54 ±5.72	46.97 ±7.80	45.65 ±8.83	43.39 ±9.25	45.68 ±9.26	43.76 ±9.13	37.80 ±8.97	38.30 ±6.31	
	C ₂	48.41 ±3.37	47.85 ±4.09	48.10 ±3.79	50.01 ±3.46	46.92 ±3.57	43.66 ±3.65	42.97 ±3.50	40.05 ±3.27	
	L ₁	52.78 ±4.47	54.32 ±4.74	55.62 ±4.94	52.27 ±5.50	53.07 ±4.92	50.24 ±6.31	46.71 ±7.22	47.61 ±5.95	
	L ₂	50.26 ±4.60	51.16 ±6.47	50.39 ±7.45	48.26 ±7.46	45.98 ±9.12	45.70 ±8.24	47.04 ±4.82	39.71 ±4.44	
D-amphetamine (5.0 mg/kg)	H ₁	51.50 ±2.88	49.12 ±3.56	48.40 ±3.68	48.33 ±4.25	48.31 ±4.53	45.41 ±4.93	36.31 ±4.40	34.88 ±4.97	
	H ₂	56.44 ±3.78	51.97 ±7.31	48.69 ±7.99	51.85 ±7.09	52.15 ±6.86	55.89 ±4.87	57.00 ±3.97	55.05 ±4.10	
	C ₁	47.72 ±3.69	45.50 ±4.92	41.94 ±5.91	39.99 ±7.04	35.03 ±8.46	37.07 ±8.51	39.85 ±6.64	34.21 ±8.70	
	C ₂	51.51 ±2.76	49.96 ±3.95	47.65 ±3.95	46.45 ±5.00	45.58 ±5.55	44.53 ±6.23	42.36 ±5.38	40.91 ±4.70	
	L ₁	40.24 ±7.36	43.74 ±6.33	42.14 ±7.42	42.21 ±9.73	40.39 ±9.17	45.01 ±10.15	44.77 ±10.15	47.30 ±8.72	
	L ₂	56.62 ±3.02	57.64 ±2.94	55.94 ±3.64	54.66 ±4.80	53.53 ±5.22	51.51 ±5.79	50.07 ±6.41	47.59 ±7.05	

Table 5b (Continued)

Line	30 Days									
	T r i a l									
	2	3	4	5	6	7	8	9	10	
Scoopalamine (0.5 mg/kg)	H ₁	45.09 ±3.60	40.87 ±3.21	39.36 ±6.50	39.13 ±6.68	38.98 ±3.49	40.42 ±4.33	38.41 ±6.67	28.09 ±6.53	24.99 ±6.22
	H ₂	51.79 ±1.11	46.78 ±1.85	39.63 ±3.36	36.00 ±4.01	36.80 ±2.64	35.62 ±3.41	35.02 ±1.85	27.96 ±3.99	28.49 ±3.96
	C ₁	37.56 ±2.69	29.94 ±5.82	29.75 ±6.71	35.11 ±3.86	39.74 ±1.80	39.81 ±1.99	33.85 ±2.43	35.35 ±3.03	32.04 ±2.31
	C ₂	44.77 ±2.35	42.62 ±1.76	36.27 ±3.08	36.58 ±3.95	38.30 ±1.78	32.07 ±5.21	31.99 ±5.01	30.03 ±5.63	35.48 ±1.69
	L ₁	40.22 ±5.95	35.82 ±7.99	40.29 ±5.37	42.91 ±6.91	41.17 ±5.56	38.01 ±4.95	37.11 ±6.70	32.01 ±7.09	33.71 ±7.32
	L ₂	38.47 ±5.36	32.51 ±6.09	25.89 ±6.05	26.77 ±5.38	28.94 ±4.82	30.40 ±4.68	25.78 ±5.29	27.76 ±4.06	26.60 ±4.64
Scoopalamine (1.0 mg/kg)	H ₁	45.92 ±3.19	41.76 ±1.95	43.09 ±1.94	40.00 ±3.42	39.63 ±4.11	39.96 ±2.94	37.99 ±3.58	37.05 ±2.65	40.48 ±3.11
	H ₂	49.17 ±2.31	41.75 ±5.05	36.68 ±6.50	39.17 ±6.46	39.83 ±5.85	36.72 ±6.23	32.15 ±6.99	18.99 ±5.48	29.64 ±5.77
	C ₁	43.14 2.87	40.45 ±3.81	42.28 ±2.81	41.63 ±1.82	39.23 ±2.33	39.99 ±2.70	38.19 ±2.24	38.38 ±2.17	32.87 ±2.42
	C ₂	47.81 ±3.71	46.38 ±6.84	42.77 ±8.65	39.66 ±7.78	38.14 ±5.71	38.88 ±4.64	40.18 ±3.57	43.47 ±2.69	41.11 ±2.78
	L ₁	47.59 ±3.99	46.72 ±4.61	42.18 ±5.09	42.82 ±4.95	44.17 ±5.15	44.08 ±5.89	43.10 ±6.00	37.26 ±6.08	37.55 ±6.32

Table 5b (Continued)

Deep	30 Days									
	T r i a l									
	2	3	4	5	6	7	8	9	10	
Scopolamine (2.0 mg/kg)	L ₂	47.32 ±2.13	43.22 ±2.23	40.32 ±3.41	40.71 ±1.93	40.72 ±2.26	38.12 ±2.31	38.88 ±1.99	38.45 ±3.05	35.64 ±4.04
	H ₁	42.33 ±2.86	41.04 ±3.94	43.22 ±2.79	45.91 ±4.48	47.72 ±3.97	45.74 ±3.20	46.97 ±2.61	45.59 ±2.91	43.57 ±3.35
	H ₂	47.27 ±3.23	45.31 ±3.47	45.61 ±3.89	46.50 ±4.39	46.98 ±4.66	41.89 ±5.43	43.74 ±5.76	43.57 ±5.12	38.30 ±4.80
	C ₁	40.89 ±4.74	34.86 ±3.90	38.47 ±3.59	36.58 ±3.18	38.86 ±2.28	39.22 ±1.45	36.21 ±0.78	38.28 ±2.37	36.72 ±2.43
	C ₂	47.26 ±1.64	39.65 ±3.15	41.95 ±3.20	40.51 ±3.53	42.39 ±3.27	42.30 ±3.11	41.57 ±3.42	37.02 ±4.66	35.64 ±3.64
Saline	L ₁	48.23 ±1.85	48.23 ±2.17	45.10 ±2.28	44.08 ±2.16	46.39 ±2.63	41.78 ±2.52	44.44 ±2.41	42.08 ±2.71	39.68 ±4.27
	L ₂	39.75 ±1.15	26.00 ±7.80	25.57 ±6.96	28.37 ±7.86	44.31 ±4.77	44.47 ±6.99	50.19 ±4.13	45.70 ±4.80	45.45 ±5.12
	H ₁	41.18 ±1.30	38.13 ±2.66	39.29 ±3.19	38.04 ±2.75	41.48 ±3.20	38.15 ±3.53	36.82 ±2.56	32.27 ±3.56	34.98 ±4.15
	H ₂	40.37 ±3.26	36.38 ±4.05	38.31 ±3.10	35.63 ±2.92	35.10 ±3.59	33.01 ±3.06	35.05 ±2.28	33.66 ±2.28	27.93 ±3.71
	C ₁	37.12 ±2.27	35.79 ±4.28	37.35 ±2.56	37.92 ±4.12	39.03 ±3.97	40.70 ±3.52	39.14 ±3.28	32.98 ±3.98	31.09 ±3.29
	C ₂	40.21 1.73	37.38 ±4.40	33.71 ±4.94	34.27 ±3.99	36.05 ±2.15	36.25 ±3.56	30.40 ±3.58	36.67 ±2.50	33.78 ±4.21

Table 5b (Continued)

Line	60 Days									
	Trial									
	2	3	4	5	6	7	8	9	10	
L ₁	37.28 ±3.65	35.58 ±3.42	33.76 ±3.49	35.84 ±4.64	28.26 ±5.26	29.16 ±4.55	32.46 ±3.69	33.07 ±3.26	27.93 ±3.44	
L ₂	38.00 ±2.94	36.00 ±1.03	36.60 ±3.87	35.16 ±2.61	34.91 ±3.21	35.93 ±1.76	32.95 ±2.40	33.28 ±2.40	30.25 ±3.17	
H ₁	42.07 ±2.69	39.99 ±2.93	33.42 ±3.58	33.56 ±4.90	33.50 ±4.98	28.82 ±3.39	33.34 ±5.18	30.35 ±4.63	34.99 ±3.78	
H ₂	51.66 ±3.25	52.29 ±3.24	50.66 ±4.18	45.66 ±4.91	48.00 ±5.40	46.55 ±4.47	46.15 ±4.59	43.94 ±4.44	42.86 ±3.93	
C ₁	26.33 ±3.40	25.96 ±7.18	15.82 ±5.58	25.61 ±10.66	27.13 ±7.11	24.79 ±7.11	25.06 ±6.75	27.01 ±7.23	28.11 ±7.37	
C ₂	41.19 ±3.40	33.13 ±5.19	29.26 ±3.65	24.53 ±5.59	17.52 ±5.39	22.30 ±6.04	23.61 ±5.79	28.78 ±6.75	25.44 ±6.46	
L ₁	42.96 ±2.92	39.92 ±3.09	37.85 ±4.53	31.39 ±3.80	28.82 ±5.17	31.45 ±4.51	33.18 ±4.18	32.78 ±4.19	29.20 ±2.28	
L ₂	35.54 ±4.35	31.65 ±3.39	24.13 ±5.80	24.92 ±9.68	26.78 ±5.85	24.33 ±4.60	27.97 ±6.54	28.30 ±6.77	31.01 ±5.93	

D-amphetamline
(1.0 mg/kg)

Table 5b (Continued)

60 Days

Trial

Line

	2	3	4	5	6	7	8	9	10	
D-amphetamine (3.0 mg/kg)	H ₁	54.45 ±3.48	53.86 ±4.90	53.06 ±5.22	52.94 ±5.00	52.57 ±5.11	53.47 ±4.48	54.76 ±4.89	53.22 ±4.75	50.40 ±6.21
	H ₂	55.12 ±1.74	51.72 ±2.67	48.45 ±3.36	37.20 ±7.91	42.54 ±5.71	36.43 ±7.64	41.64 ±5.24	39.66 ±5.21	34.28 ±5.93
	C ₁	48.72 ±4.91	48.58 ±6.05	45.89 ±6.89	44.03 ±7.00	42.38 ±6.94	38.23 ±6.89	38.37 ±7.07	38.53 ±7.21	32.22 ±7.70
	C ₂	50.64 ±2.02	48.99 ±2.53	46.28 ±4.48	44.86 ±5.68	43.60 ±5.62	41.02 ±6.89	44.26 ±4.82	42.02 ±5.81	38.93 ±7.22
	L ₁	47.48 ±6.18	47.86 ±3.09	47.30 ±7.00	46.99 ±7.08	38.20 ±9.96	46.02 ±6.65	43.26 ±7.71	41.78 ±7.44	38.47 ±6.48
	L ₂	50.18 ±2.11	50.43 ±3.85	49.99 ±5.24	46.92 ±6.22	47.71 ±6.08	43.54 ±7.26	45.86 ±5.75	41.42 ±5.78	36.10 ±4.72
D-amphetamine (5.0 mg/kg)	H ₁	53.18 ±4.18	55.47 ±3.72	57.60 ±2.91	58.39 ±3.03	58.13 ±3.34	59.77 ±3.68	60.21 ±3.88	63.53 ±4.19	62.37 ±4.10
	H ₂	52.39 ±1.75	52.45 ±2.30	52.49 ±2.49	50.13 ±2.57	51.09 ±3.34	48.93 ±3.55	50.15 ±3.05	47.25 ±3.47	48.74 ±3.20
	C ₁	55.36 ±0.89	60.29 ±1.38	57.64 ±1.41	57.77 ±1.82	57.60 ±1.88	56.68 ±2.03	56.14 ±2.93	54.33 ±4.14	53.13 ±3.89
	C ₂	54.69 ±2.38	52.22 ±3.07	51.26 ±5.84	51.17 ±6.13	54.75 ±4.20	56.66 ±4.23	53.03 ±5.49	56.20 ±4.18	57.35 ±4.37
	L ₁	48.70 ±2.95	49.09 ±4.33	50.66 ±2.55	50.89 ±3.27	50.40 ±3.66	48.31 ±3.69	49.15 ±3.20	47.60 ±4.24	45.97 ±4.71

Table 5b (Continued)

60 Days

Trial

Line

	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>	<u>9</u>	<u>10</u>
L ₂	50.40 ±2.27	50.62 ±2.66	51.10 ±4.49	50.38 ±5.58	48.98 ±4.27	50.70 ±5.07	50.81 ±4.32	51.86 ±4.25	49.52 ±4.45
H ₁	55.55 ±3.30	54.78 ±3.35	51.84 ±3.44	52.28 ±3.78	51.36 ±4.26	51.50 ±3.97	48.11 ±4.17	48.18 ±5.04	48.75 ±3.50
H ₂	50.58 ±2.19	47.25 ±1.69	46.33 ±1.63	44.36 ±2.37	44.89 ±2.33	46.60 ±2.49	42.25 ±3.71	43.91 ±3.30	41.79 ±3.35
C ₁	43.57 ±3.66	36.84 ±5.60	36.52 ±4.95	37.61 ±3.41	40.62 ±4.20	40.76 ±3.11	38.99 ±2.98	38.05 ±4.02	35.25 ±3.09
C ₂	53.25 ±0.95	51.28 ±2.39	51.46 ±2.04	49.10 ±1.94	50.21 ±1.87	48.71 ±2.64	45.92 ±3.47	44.87 ±3.50	43.24 ±3.11
L ₁	47.84 ±1.68	47.34 ±2.66	47.58 ±2.27	45.38 ±2.82	43.88 ±3.67	44.50 ±3.07	42.13 ±2.88	38.99 ±4.21	39.20 ±2.78
L ₂	46.60 ±3.22	45.70 ±2.83	44.01 ±3.10	44.10 ±4.42	44.19 ±4.30	43.41 ±4.17	42.83 ±4.95	40.63 ±5.15	38.17 ±5.22
H ₁	51.20 ±3.76	49.71 ±4.68	48.69 ±4.05	51.21 ±3.88	51.47 ±3.76	49.95 ±3.69	49.62 ±4.07	46.55 ±4.71	44.11 ±3.37
H ₂	53.22 ±3.39	52.33 ±3.12	51.06 ±3.52	46.42 ±6.07	48.43 ±3.74	40.82 ±3.73	43.30 ±3.75	41.75 ±2.71	42.13 ±3.66
C ₁	40.93 ±4.95	39.61 ±4.17	40.28 ±3.22	41.61 ±3.02	40.90 ±3.43	39.41 ±4.03	36.32 ±4.53	34.03 ±5.00	33.75 ±4.67
C ₂	50.74 ±1.77	49.56 ±2.02	44.08 ±2.60	45.86 ±3.29	49.15 ±3.22	47.80 ±1.89	44.65 ±2.63	43.46 ±2.74	42.05 ±3.02

Scoopamine

(0.5 mg/kg)

Scoopamine

(1.0 mg/kg)

Table 5b (Continued)

Line	60 Days									
	T r i a l									
	2	3	4	5	6	7	8	9	10	
L ₁	48.81 ±1.47	47.90 ±1.33	49.36 ±2.01	49.01 ±2.25	49.98 ±3.74	47.19 ±5.19	49.67 ±3.89	49.11 ±4.06	45.33 ±5.21	
L ₂	49.62 ±2.45	47.83 ±3.87	47.30 ±4.35	51.04 ±4.25	49.59 ±4.76	50.89 ±4.54	49.60 ±4.98	49.55 ±4.99	48.31 ±4.73	
H ₁	55.13 ±4.65	52.88 ±3.66	55.31 ±4.17	56.20 ±4.71	56.84 ±4.98	56.93 ±4.56	56.76 ±4.52	57.18 ±4.68	54.26 ±5.20	
H ₂	47.27 ±1.42	45.31 ±1.54	45.61 ±1.59	46.50 ±5.40	46.98 ±3.40	41.89 ±5.83	43.74 ±4.61	43.56 ±4.23	38.30 ±3.85	
C ₁	47.00 ±1.93	46.12 ±2.18	44.39 ±2.39	43.98 ±2.36	47.14 ±2.67	46.46 ±2.59	45.76 ±2.68	44.38 ±2.70	43.82 ±2.86	
C ₂	49.24 ±2.47	47.85 ±4.47	48.55 ±3.96	49.51 ±4.62	50.67 ±3.83	51.74 ±4.56	49.04 ±4.57	47.59 ±4.84	48.21 ±4.27	
L ₁	53.47 ±2.72	52.26 ±1.66	49.80 ±3.17	51.09 ±3.18	50.51 ±3.00	48.31 ±2.64	45.56 ±4.63	44.92 ±6.43	41.08 ±6.83	
L ₂	50.95 ±4.83	52.43 ±4.85	53.34 ±5.91	51.91 ±6.73	50.73 ±8.08	48.51 ±8.88	49.95 ±8.25	49.86 ±9.01	50.00 ±9.10	

Scopolamine
(2.0 mg/kg)

Table 5b (Continued)

Mean differences necessary for $p < .05$ of the simple main effects

<u>Between Trials</u>	<u>Between Lines (Pooled error)</u>	<u>Between Drug (Pooled error)</u>
$r_2 = 11.86$	$r_2 = 17.87$	$r_2 = 17.87$
$r_3 = 14.17$	$r_3 = 21.35$	$r_3 = 21.35$
$r_4 = 15.54$	$r_4 = 23.41$	$r_4 = 23.41$
$r_5 = 16.52$	$r_5 = 24.90$	$r_5 = 24.90$
$r_6 = 17.24$	$r_6 = 25.99$	$r_6 = 25.99$
$r_7 = 17.85$		$r_7 = 26.90$
$r_8 = 18.36$		
$r_9 = 18.79$		
$r_{10} = 19.13$		

Table 6

Mean Proportion of Alternation ($\pm$ S.E.M.) as a
Function of Line, Age and Drug (Experiment 6)

<u>Line</u>	<u>Saline</u>				<u>D-amp. (3.0 mg/kg)</u>				
	<u>Age</u>				<u>Age</u>				
	<u>15</u>	<u>20</u>	<u>25</u>	<u>30</u>	<u>15</u>	<u>20</u>	<u>25</u>	<u>30</u>	<u>60</u>
H_1	52.78 ±3.40	52.07 ±4.10	50.00 ±2.69	50.57 ±5.52	30.19 ±5.29	38.13 ±3.35	43.71 ±2.26	25.17 ±6.25	47.53 ±6.22
H_2	46.53 ±3.43	48.80 ±4.65	48.46 ±2.52	49.26 ±3.54	34.24 ±7.66	30.77 ±4.44	29.98 ±5.62	37.08 ±6.81	46.09 ±5.71
C_1	52.99 ±5.29	55.14 ±3.73	57.38 ±2.97	58.97 ±3.45	31.20 ±6.74	38.11 ±7.93	50.39 ±8.73	41.00 ±4.20	30.40 ±6.86
C_2	62.92 ±3.15	54.62 ±1.97	54.65 ±1.92	55.44 ±3.47	37.76 ±6.63	40.27 ±6.74	39.17 ±9.03	36.44 ±9.51	39.34 ±6.16
L_1	49.43 ±10.79	51.85 ±2.39	53.50 ±3.94	55.30 ±5.78	38.60 ±5.56	28.33 ±7.51	41.11 ±6.01	33.37 ±5.60	36.12 ±9.07
L_2	48.07 ±6.05	55.33 ±4.20	51.36 ±3.78	53.50 ±6.43	37.14 ±7.41	37.70 ±7.24	23.90 ±6.77	38.60 ±6.53	26.29 ±6.93
<u>Scoop. (0.5 mg/kg)</u>									
H_1	25.85 ±7.74	33.52 ±5.63	46.40 ±5.01	45.15 ±8.12	37.97 ±4.09	38.97 ±8.20	52.61 ±3.68	57.97 ±4.51	48.28 ±4.32
H_2	29.42 ±9.18	32.85 ±2.73	33.76 ±7.62	29.99 ±8.66	29.69 ±6.85	28.38 ±6.74	38.69 ±6.42	39.70 ±5.26	44.49 ±2.79
C_1	24.44 ±3.99	35.46 ±5.92	32.37 ±5.39	36.06 ±8.11	40.43 ±5.59	50.13 ±2.57	59.96 ±4.30	56.43 ±4.62	54.07 ±3.13

Table 6 (Continued)

D-amp (5.0 mg/kg)						Scoop. (0.5 mg/kg)					
Line	Age					Line	Age				
	15	20	25	30	60		15	20	25	30	60
C ₂	18.70	30.11	33.43	38.77	26.40	C ₂	56.02	47.60	41.37	46.21	42.47
	±5.25	±5.73	±9.17	±4.41	±7.28		±5.60	±7.48	±2.12	±6.40	±6.28
L ₁	39.17	22.63	46.22	23.54	39.33	L ₁	45.68	42.86	44.44	40.67	37.69
	±4.88	±6.96	±3.67	±8.35	±9.07		±5.10	±3.82	±6.98	±4.79	±7.84
L ₂	43.43	31.55	36.95	38.74	25.71	L ₂	45.68	49.10	47.31	55.61	44.28
	±6.55	±3.89	±6.98	±7.66	±5.68		±5.10	±5.02	±6.26	±3.64	±4.06
Scoop. (2.0 mg/kg)											
H ₁	53.18	38.50	44.27	50.30	50.82	H ₁	50.30				
	±6.05	±8.14	±3.13	±2.91	±3.83						
H ₂	40.38	40.71	46.27	46.01	51.03	H ₂	51.03				
	±6.80	±2.61	±2.24	±2.75	±3.64						
C ₁	43.57	51.19	45.36	53.44	49.58	C ₁	49.58				
	±3.72	±4.45	±7.15	±2.01	±5.65						
C ₂	48.20	51.10	38.00	49.27	55.00	C ₂	55.00				
	±4.19	±8.14	±6.80	±4.79	±5.65						
L ₁	48.97	52.12	39.86	45.75	44.83	L ₁	44.83				
	±9.03	±7.22	±6.16	±2.58	±4.84						
L ₂	48.97	50.36	56.26	45.50	39.32	L ₂	39.32				
	±9.03	±9.40	±4.08	±3.42	±7.76						

Table 6 (Continued)

Mean differences necessary for $p < .05$ of main effects

Between Drug

$$r_2 = 2.94$$

$$r_3 = 3.51$$

$$r_4 = 3.85$$

$$r_5 = 4.09$$

Mean differences necessary for $p < .05$ of simple main effects

Between Lines

$$r_2 = 7.23$$

$$r_3 = 8.64$$

$$r_4 = 9.47$$

$$r_5 = 10.08$$

$$r_6 = 10.52$$

Between Ages

$$r_2 = 7.23$$

$$r_3 = 8.64$$

$$r_4 = 9.47$$

$$r_5 = 10.08$$

APPENDIX C

Table 1

χ^2 Analysis of Total Number of Group Alternation and
Non-Alternation Responses (Experiment 2)

<u>H₁</u>			
<u>Age</u>	<u>A</u>	<u>N</u>	<u>χ^2</u>
15	94	84	0.46
20	190	206	0.74
25	268	250	0.56
30	279	202	12.00*
60	305	217	14.50*

<u>H₂</u>			
<u>Age</u>	<u>A</u>	<u>N</u>	<u>χ^2</u>
15	173	214	3.74
20	308	413	15.58*
25	281	354	8.62*
30	338	337	0
60	459	444	0.22

<u>L₁</u>			
<u>Age</u>	<u>A</u>	<u>N</u>	<u>χ^2</u>
15	102	116	1.04
20	146	106	6.04*
25	150	148	0
30	170	188	1.00
60	270	210	7.26*

<u>L₂</u>			
<u>Age</u>	<u>A</u>	<u>N</u>	<u>χ^2</u>
15	96	104	0.40
20	132	91	7.18*
25	191	160	2.60
30	195	136	10.16*
60	296	252	3.38

Table 1 (Continued)

C₁

<u>Age</u>	<u>A</u>	<u>N</u>	<u>χ²</u>
15	155	194	4.58*
20	216	218	0.02
25	207	127	18.68*
30	221	129	23.66*
60	362	242	23.44*

C₂

<u>Age</u>	<u>A</u>	<u>N</u>	<u>χ²</u>
15	157	156	0
20	181	124	10.28*
25	215	182	2.58
30	330	290	2.46
60	394	303	11.62*

* P < .05

Table 2
 χ^2 Analysis of Total Number of Group Alternation
 and Non Alternation Responses (Experiment 6)

Day	Line	Drug Treatment						Scoop (0.5 mg/kg)						Scoop. (2 mg/kg)					
		Saline			D-amp (3 mg/kg)			D-amp (5 mg/kg)			A			A			A		
		A	N	χ^2	A	N	χ^2	A	N	χ^2	A	N	χ^2	A	N	χ^2	A	N	χ^2
15	H ₁	135	127	0.18	105	212	36.80*	143	272	40.72*	139	249	31.76*	111	116	0.16	111	116	0.16
	H ₂	147	160	0.64	60	141	33.46*	61	224	94.38*	150	245	23.34*	73	88	1.56	73	88	1.56
	C ₁	163	166	0.04	76	158	29.44*	105	280	80.46*	176	206	2.52	190	240	6.04*	190	240	6.04*
	C ₂	156	106	9.16*	147	222	15.66*	59	233	104.88*	130	134	0.10	78	77	0	78	77	0
	L ₁	70	62	0.38	79	139	17.06*	89	162	21.80*	122	129	0.26	199	198	0	199	198	0
	L ₂	82	85	0.10	43	90	17.32*	67	90	3.66	96	114	1.72	150	139	0.34	150	139	0.34
20	H ₁	174	156	0.88	210	317	22.14*	216	395	53.02*	185	296	26.08*	151	300	49.90*	151	300	49.90*
	H ₂	187	230	4.64*	74	402	227.38*	219	418	62.80*	153	295	45.64*	185	251	10.30*	185	251	10.30*
	C ₁	178	147	2.78	160	208	6.52*	154	310	53.12*	350	350	0	367	354	0.18	367	354	0.18
	C ₂	114	101	0.70	117	158	6.42*	127	260	46.40*	255	294	2.92	147	182	3.94*	147	182	3.94*
	L ₁	134	115	1.30	95	222	51.68*	62	172	52.66*	109	136	3.20	139	103	5.06*	139	103	5.06*
	L ₂	113	85	3.68	126	268	51.90*	94	209	44.42*	153	130	1.72	73	70	0.02	73	70	0.02
25	H ₁	286	293	0.10	258	334	10.02*	394	424	1.18	381	344	1.78	281	402	21.80*	281	402	21.80*
	H ₂	244	246	0.02	158	381	93.10*	119	225	33.28*	422	611	34.94*	347	406	4.78*	347	406	4.78*
	C ₁	160	129	3.12	97	143	9.20*	129	262	45.92	178	131	6.84*	181	191	0.32	181	191	0.32
	C ₂	178	150	2.22	169	263	20.90*	110	227	41.32*	256	367	20.14*	235	282	4.46*	235	282	4.46*
	L ₁	174	147	2.10	200	288	16.32*	83	93	0.68	239	282	3.72	183	205	1.36	183	205	1.36
	L ₂	230	220	0.18	57	343	205.92*	121	137	1.12	222	201	0.94	219	160	8.88*	219	160	8.88*

Table 2 (Continued)

Day	Line	Drug Treatment											
		Saline				D-amp (3 mg/kg)				D-amp (5 mg/kg)			
		A	N	$\bar{X}$	$\bar{X}^2$	A	N	$\bar{X}$	$\bar{X}^2$	A	N	$\bar{X}$	$\bar{X}^2$
30	H ₁	234	230	0.02	0.02	135	319	75.38*	7.26*	226	286	7.26*	0.08
	H ₂	155	153	0	0	248	340	14.72*	16.70*	116	186	16.70*	30.26*
	C ₁	169	126	5.98*	5.98*	165	228	10.42*	93.30*	169	398	93.30*	2.22
	C ₂	271	216	5.98*	5.98*	120	264	54.76*	27.80*	219	343	27.80*	0.84
	L ₁	136	122	0.66	0.66	268	282	20.34*	128.20*	63	268	128.20*	11.88*
	L ₂	176	125	8.30*	8.30*	128	176	7.90*	77.94*	122	303	77.94*	6.66*
		A	N	$\bar{X}$	$\bar{X}^2$	A	N	$\bar{X}$	$\bar{X}^2$	A	N	$\bar{X}$	$\bar{X}^2$
		315	317	0.02	0.02	323	414	11.48*	0.18	258	247	0.18	0.02
		158	159	0.02	0.02	250	284	2.30	0.18	225	233	0.18	0.16
60	H ₁	385	255	26.00*	0.94	270	247	0.94	18.04*	208	303	18.04*	1.32
	H ₂	416	376	1.92	7.80*	315	388	7.80*	31.56*	218	351	31.56*	20.14*
	C ₁	335	180	46.06*	32.46*	156	273	32.46*	67.20*	143	318	67.20*	6.18*
	C ₂	265	160	25.46*	5.92*	142	185	5.92*	199.60*	106	433	199.60*	11.98*
	L ₁	220	214	0.06	10.02*	230	302	10.02*	8.50*	235	303	8.50*	16.94*
	L ₂	316	278	2.30	69.92*	109	271	69.92*	85.66*	134	333	85.66*	5.22*
		A	N	$\bar{X}$	$\bar{X}^2$	A	N	$\bar{X}$	$\bar{X}^2$	A	N	$\bar{X}$	$\bar{X}^2$
		314	303	0.16	0.60	429	451	0.60	0.06	346	351	0.06	2.92
		181	149	2.92	1.04	340	366	1.04	7.70*	219	280	7.70*	5.22*

END

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FIN