following statement from that paper probably provides the most appropriate conclusion to this introduction: 'Concentration on genetic variability is not a matter of ideology but of practicality: a genetic difference is, by definition, resistant to masking influences due to plasticity or environmental factors and, thereby, more convenient to work with'.

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Cerebral lateralization as a source of interindividual differences in behavior

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Summary. Cerebral laterality can no longer be considered an exclusively human trait, as over the last 15 years there has been an emergence of data to suggest that animal brains are also lateralized. Morphologic, chemical and behavioral indices of brain asymmetry in the rodent have been reported, and it is suggested that variations in the magnitude and direction of these indices are determined by a complex interaction of genetic, hormonal and experiential factors. Interindividual differences in cerebral laterality have been shown to covary with, or predict, individual differences in spatial behavior and stress reactivity, as well as susceptibility to stress pathology and drug sensitivity. Such findings suggest that it is possible to study individual differences in lateralized brain function through the use of animal models.
Key words. Brain asymmetry; rotational behavior; genetic models; testosterone; brain development; stress; strain differences; sexual dimorphism; hemispheric differences.

Introduction

Findings accumulated over the last 100 years have repeatedly demonstrated that the human brain is functionally and anatomically lateralized. It has been shown that the left hemisphere is dominant in the control of language and handedness[33,43] and the right hemisphere dominant for emotion[40,41] and affect[23]. Implicit in these accounts of human brain laterality has been the assumption that, to some degree, individual differences in behavioral function could be accounted for by variation in the degree of such laterality. The tenability of such an assumption has been reviewed by others[23,42,93]. Until relatively recently, it had been assumed that cerebral lateralization of function is a distinctly human trait, e.g. Levy[74]. Over the past 15 years, however, findings have accumulated to suggest that cerebral lateralization of function is an evolutionary principle and not simply one indigenous to humans. Such brain asymmetries have been reported in species that range from songbirds[3,79] to non-human primates[71,72]. These findings have presented the opportunity to determine experimentally, using animal models, the degree to which individual differences in brain laterality may covary with, or determine, individual differences in behavioral functions.

Research conducted in this laboratory, and in others, has established that normal rats have functional and neurochemical asymmetries in several brain regions, and that wide individual differences exist on these measures. Much of this work has focused on the dopamine-containing nigrostriatal pathways: striatal asymmetries in dopamine levels, dopamine metabolites, dopamine release and dopamine uptake have been functionally related to rats' circling or rotational behavior, occurring either spontaneously at night or in response to drugs (e.g., d-amphetamine) during the day. Other work has focused

upon the cortex and has sought to determine how lateralized cortical function may modulate these striatal functions. A rotational preference appears to result from a persistent side or orienting bias; such a bias may serve as a proprioceptive reference, enabling discrimination between left and right as well as mediating lateralized and stereotypic motor reactions in times of exigency[48, 57].

In recent years, data have begun to accumulate which indicate that individual rats display varying degrees of lateral bias which are related to patterns of brain organization that subserve various behavioral functions. Systematic study of these differences suggests that they are brought about by combinations of genetic, hormonal and experiential factors. The present review summarizes recent findings concerning the origins of individual differences in lateralized processes in the rodent brain, and considers their implications for the understanding of individual differences in behavioral processes.

Chemical and morphologic asymmetries

Asymmetry in the rat brain was first indicated by the observations that d-amphetamine would enhance side preferences[46, 54] and induce rotation (or circling) in normal, intact rats[64, 65]. As it was known[14, 101–103] at the time that rats with unilateral lesions of the nigrostriatal system would turn in circles at high rates (5–10 rotations/min), it was postulated that the less intense circling (0.5–4 rotations/min) seen in non-lesioned rats was due to an endogenous physiological asymmetry in the same dopaminergic system[54, 64]. Subsequently, normal asymmetries in striatal dopamine content[112], striatal dopamine metabolism and dopamine-stimulated adenylate cyclase activity[66] were demonstrated directly, and shown to be related to spontaneous side preferences[112] and to nocturnal[66] and d-amphetamine-induced[55, 65] circling behavior. Numerous studies of asymmetry in the rat brain followed in this and many other laboratories. Thus the striatal dopamine asymmetry was confirmed[84, 87] and many other biochemical asymmetries were reported. The latter include side-to-side differences in: norepinephrine content in thalamus[80] and striatum[88]; GABA (gamma-aminobutyric acid) levels in substantia nigra, nucleus accumbens, thalamus and striatum[88]; serotonin levels in striatum[68, 88], nucleus accumbens[88] and hippocampus[68]; dopamine release[86], dopamine uptake[95] and dopamine (D2) receptors[35, 92] in striatum; dopamine levels in nucleus accumbens[88] and frontal cortex[98]; and LHRH (luteinizing hormone releasing hormone) content in hypothalamus[44]. Other studies have described morphological asymmetries, for example in cortex[30, 37, 96] and hippocampus[32], or functional asymmetries, as evidenced by differential effects of lesions on either side of the brain, for example in striatum[50, 51, 78, 91], cortex[22, 26, 81] and hippocampus[99]. Many of these asymmetries are more complex than immediately apparent, there being both sex differences[4, 7, 87] and strain differences[49, 58, 59] in the magnitudes and directions of asymmetries.

Determinants of brain asymmetry in the individual and in the population

A fundamental issue in the consideration of individual differences in brain asymmetry is the question of its origin. Here, as with most unique characteristics, an essential consideration is the degree to which brain asymmetry differences are brought about by genetic factors. Another important consideration involves the mutability or plasticity of brain asymmetry as it may change over the lifetime of the organism. Studies have suggested that these processes interact with one another. Related to these issues are the criteria that are used to determine if a lateralized property exists. While some approaches have sought to establish the existence of cerebral laterality at the level of the population, by demonstrating a left or right directional bias[25], others have suggested that distributions of lateralized properties that favor a particular direction will not necessarily be seen at the population level[20] and are even less desirable, from a scientific point of view. It is variation in the magnitude and direction of cerebral laterality that offers the possibility of studying it as a science of individual differences. It has been suggested[19] that populations that have an even distribution of strongly to weakly lateralized features in both directions provide a 'maximum variance' preparation and are optimally suited for studies that seek to account for individual differences in behavioral function in terms of variance in cerebral laterality. The current approaches that are used in this laboratory rely upon the use of experimental subjects (laboratory rats) who, at the population level, exhibit substantial heterogeneity on the cerebral laterality measures we use. However, within certain subpopulations of these subjects, distributions are skewed (toward directional biases of varying strengths); and this allows for the assessment of differences in various behavioral characteristics as they covary with lateralized characteristics in these subpopulations. Examples of this approach will be given below.

Genetic factors

As a trait that is a pervasive indicator of cerebral asymmetry, i.e. handedess, occurs in humans, and variations in asymmetry have been associated with behavioral variation, it is perhaps not too surprising that numerous genetic models of human brain asymmetry have been presented[2, 13, 18, 21, 73]. More recent genetic models of human asymmetry have assumed that a classic Mendelian gene pair is not solely involved, and a general conceptual approach for evaluating both non-Mendelian and genetic factors has been presented[19]. The study of possible heritable determinants of cerebral laterality in animals has been spurred by studies of families of left-

handed humans reporting a greater frequency of immune diseases[45] and learning disabilities[2]. These findings suggested that genetic factors controlling handedness in humans might account for at least part of individual differences occurring in these individuals and might be associated with variation in genes controlling the major histocompatibility complex (MHC) in man. This hypothesis derives, in part, from data showing that genetic loci of the MHC control testosterone levels[63], that testosterone slows the growth of the left hemisphere, and that variations in this influence, as they interact with genetic determinants, might account for individual differences in cerebral laterality. Studies in animals are generally supportive of this hypothesis. The offspring of rats having opposite or same-sided turning biases were tested for turning biases as adults and the degree of similarity to the parents' biases assessed. There were significant and equivalent tendencies for the male offspring to have the same bias as the male parent and the opposite bias as the female parent. Also reported was a significant tendency for female offspring to have biases that were different from those of the female parent in litters having more males than females[47]. Based upon reports indicating that there is a relationship between the sex ratio of a litter and female levels of testosterone[77,105], it was suggested that exposure to testosterone reverses the coding of a heritable female influence and induces a tendency for offspring to have biases opposite to those of the female parent. Attempts have also been made in this laboratory to breed strains of strongly and weakly rotating rats[49]. A strain difference in rotational parameters was limited to females and developed gradually over eight generations before asymptoting. A left-sided rotational bias developed in both male and female rats bred for weak rotation. These findings were again consistent with the suggestion that testosterone modulates the expression of heritable influences by slowing the growth of the left hemisphere. In animals bred for weak rotation, this effect of testosterone on brain maturation may have been exerted independently of heritable influences inducing a leftward rotational bias.

A major genetic model of cerebral lateralization has also been undertaken using inbred strains of mice over the past twenty years[20]. Mice exhibit a paw preference that is not task-specific and is consistent upon repeated measurement[15]. Its strength may be assessed in a simple food reaching task with animals reaching into a narrow tube. Studies in C57BL/6J mice indicated that though highly inbred, nearly maximum genetic variation in paw preference still occurred[16]. When testing occurred in an 'unbiased world' (tube located equidistant from chamber walls), a U-shaped distribution of paw preferences resulted and there was a sexual dimorphism in the strength of this preference, with females exhibiting a stronger bias than males. However, when the location of the tube was 'biased' (i.e. located adjacent to the left or right wall), the distribution was J-shaped, with 90% of mice exhibiting a bias consistent with the tube bias, and males showing a stronger preference than females[17]. From these studies it was concluded that highly inbred mice (possessing minimum genetic heterogeneity) exhibit an enduring, non-task-specific paw preference that is sexually dimorphic (stronger in females) and modifiable by environmental influences. Clearly there was an indication that genetic factors might determine the strength, but not the direction, of lateralization. Attempts have been undertaken to derive, by selective breeding, two populations of mice which differ markedly in the degree of paw preference[20]. Large potential genetic variability was insured by using an 8-way cross in parental strains. After eleven generations of selective breeding, mice from the two selected lines differed markedly in their degree of paw preference, as well as from a random-bred control line[20]. Morphologic studies have indicated that the brains of the two strains also differ. In 4 of 5 horizontal sections from mid-dorsoventral planes, strongly lateralized mice had greater asymmetries and the two lines could be best discriminated by asymmetries in the hippocampus and orbitofrontal cortex[75]. The brains of strongly lateralized mice were heavier and those of weakly lateralized mice lighter than those of control mice of the same body weight, and in both selected lines the corpus callosum was found to be smaller than that in the random-bred control line[107]. From these accumulated findings it has been suggested[20] that genetic elements control the degree or strength of brain asymmetry but that the direction of asymmetry is strongly influenced by environmental (non-genetic) processes which modulate the strength of directional bias. Other findings have shown that variations in paw or hand preferences also occur in other species such as cats[38,109] and monkeys[36,108], though there have been conflicting results concerning the relationship between paw preference and cerebral dominance in these species. Nonetheless, the appearance of lateralized behaviors such as handedness across species attests to the evolutionary pervasiveness of lateralized function. It further supports the notion that interspecies comparisons of individual differences in this genetically influenced lateralized function are a conceptually valid pursuit.

Environmental influences on cerebral laterality

Developmental influences. A fairly extensive body of evidence has indicated that numerous non-genetic factors can modulate the expression of individual differences in cerebral laterality. Of particular interest are events that take place while the brain is developing. As noted above, testosterone has been suggested to play a major role in asymmetric brain development. Other influences, such as prenatal stress[37,39], exposure to enriched environments[50] and handling during infancy[113] have also been shown to influence asymmetrical brain development. Sexually dimorphic cortical asymmetries are apparent in the neonatal rat[104]. Morphologic studies indicate that

the male right neocortex is thicker during development [31] and at adulthood [30, 34] while, in female animals, a trend toward left > right differences is seen [30]. Energy metabolism (as indicated by 2-deoxyglucose uptake) is greater on the left at these times in the female rat [56]. During development, cerebral asymmetries change in a complex way [90], and are susceptible to alteration from external events. Other findings suggest that these changes may begin to occur during prenatal development. For example, it has been shown that prenatal stress feminizes the behavior of male rats [106] and inhibits normal masculine development of the sexually dimorphic nucleus of the medial preoptic area of the hypothalamus [1]. Anatomical studies of neocortical thickness suggest that similar, sex-related changes in cortical asymmetry take place following prenatal stress (heat/light/restraint during the third trimester) in the Long-Evans rat: normal male (right > left) asymmetries are eliminated and female-like (i.e. left > right) differences are seen [37]. Also reported are data which suggest that random noise stress throughout gestation resulted in a shift of normal asymmetric differences in dopamine activity in the prefrontal cortex, nucleus accumbens and striatum [39]. Finally, an extensive series of studies has also demonstrated that the rat brain exerts an asymmetric control over numerous behavioral functions. Furthermore, the extent to which this happens may be critically dependent upon the organism's early experience. Denenberg and his group [28] have shown that the effects of early experience are asymmetrically distributed between the two hemispheres [26]. For their first twenty days of life, rats were either handled or not handled for 3 min daily; at weaning, half of the animals were placed in enriched environments and at the age of fifty days, all animals were placed in standard laboratory cages. As adults, males from each group were selected randomly for either a left neocortical ablation, right neocortical ablation or sham surgery. After recovery the animals were tested in an open field and their activity monitored. It was found that the handling and the enriched environment parameters interacted with the right brain intact versus control comparison, as well as with the right versus left comparison. It was concluded that, in the handled enriched group, there normally is right hemisphere dominance. These findings have been extended [97] to show that nonhandled rats with a left hemisphere lesion were significantly more biased in going to the ipsilateral side than were their siblings with a right hemisphere lesion. Intact handled rats were found to have a significant left bias, suggesting to Denenberg et al. that, in nonhandled animals, behavioral symmetry in making spatial choices is due to balanced brain asymmetry in which the right hemisphere biases the animal to move to the left while the left hemisphere acts to inhibit this response. In contrast, for handled rats, the conclusion was made that the right hemisphere controls spatial preference. Based on these findings and others [27], Denenberg has suggested a model for brain function in the rat which involves three major hypothetical brain processes: hemispheric activation, interhemispheric inhibition, and interhemispheric coupling [24, 25]. The generality of this theory has been discussed [83]. The accumulated findings suggest that individual differences in cerebral laterality are strongly modulated by the developing organism's early experience and that the effects of this influence may be seen in anatomical, neurochemical and behavioral measures. Individual differences in cerebral laterality are thus determined by a relatively complex interaction of genetic, hormonal and experimental influences.

Influences in adulthood. A recent series of studies conducted in this laboratory has shown that stressors experienced in adulthood can alter certain manifestations of cerebral asymmetry. Exposure to footshock causes a selective change in cerebral laterality as indicated by alterations in the intensity and direction of d-amphetamine induced rotational behavior. Male and female Sprague-Dawley (Zivic Miller) rats, selected on the basis of their rotational behavior in response to d-amphetamine, were exposed to either escapable footshock (ESC), identical yoke inescapable footshock (YOK) or to no stress or (CTL) in a triadic design (see Maier and Seligman [76]), and were then given a shuttlebox escape task on the subsequent day. Following testing, the magnitude and direction of the animals' rotational responses to d-amphetamine were determined again. Inescapable footshock induced a selective change in the direction and intensity of rotational behavior that was dependent upon the subjects' sex and pre-existing rotational bias. Right-rotating males and left-rotating females shifted their directional bias toward the opposite side, while left-rotating males and right-rotating females displayed increased rotation in their pre-stress or direction [10]. The results were dependent upon the uncontrollable nature of the stressor since ESC and YOK animals received identical footshock. Nonetheless, these animals displayed different patterns of rotational change.

In experiments using neurochemical techniques it was found that food deprivation is a stressor that will selectively activate mesocortical dopamine neurons [12] in a manner that is similar to footshock [100]. As these cortical regions are lateralized (see above) and can modulate activity in the striatum, thus influencing rotational behavior [89], we sought to determine whether the effects of food deprivation would resemble those of footshock. In these studies male and female Long-Evans rats (Blue Spruce) rats were used. The findings indicated that food deprivation also exerted an asymmetrical effect on d-A induced rotational behavior which changed in direction as it was prolonged [11]. While 24 h food deprivation caused a shift toward right rotation, 48 h of the same caused a significant change in the number of left runs. Surprisingly, in the Long-Evans rat these changes were in the same direction in both males and females. The rotational shift in favor of right turns seen at 24 h was similar to that

previously seen in Long-Evans rats exposed to ESC footshock [9]. What was perhaps more intriguing was the 48 h reversal in rotational direction; a leftward directional shift was also seen with YOK footshock in Long-Evans rats of both sexes. What was suggested by these findings is that systems whose activity is enhanced at 24 h may be depleted as food deprivation is prolonged. Data from a parallel neurochemical experiment implicated prefrontal cortical DA activity as that system. Control (non-deprived) animals displayed left > right cortical asymmetries in dopamine and this was consistent with previously reported findings (see above). Food-deprived animals exhibited a symmetrical increase in both DOPAC and DOPAC/DA at 24 h, and a significant bilateral decrease in both of these measures at 48 h. The data suggested that the activation of prefrontal cortical DA by food deprivation exhibits a time course where it changes from increased activation to decreased activation between 24 and 48 h. The opposing changes in DA activation paralleled the rotational changes seen in the behavioral experiment, and were compatible with hypotheses suggesting that the degree of activation of the prefrontal cortex may govern the intensity and direction of d-A induced rotational behavior through an influence on striatal function. The changes also paralleled those seen for ESC and YOK footshock. The results suggested that individual differences in cerebral laterality can be induced, at least temporarily, by stress experienced in adulthood. They further indicated that the degree (duration) or nature (controllable or uncontrollable) of the stressor was important in that systematic manipulations of these caused lateralized shifts in opposing directions. Furthermore, it was indicated that the nature of these effects were strain-dependent, since they were directionally sexually dimorphic in the Sprague-Dawley but not the Long-Evans rat. Thus, stress-induced differences in cerebral laterality occurring among rats are themselves determined by genetic (strain) differences.

Differences in cerebral laterality among rats obtained from different suppliers

The foregoing studies indicate that differences in the direction and degree of cerebral laterality in animals are complexly determined by an interaction of genetic, hormonal, developmental and experiental factors. A reasonable conclusion from these data is that, at the population level, there should be sizable variation among rats. However, among samples of rats where genetic and environmental influences are more homogeneous, the magnitude of this variation should be diminished and differences among these samples in measures of laterality should be seen. Indications that this is true were obtained as a consequence of this laboratory moving from the Mount Sinai School of Medicine to Albany Medical College in July of 1984. For the ten years preceding the move, Sprague-Dawley derived rats had been obtained from Perfection Breeders, Douglassville, PA. Because shipping the same rats to Albany would have increased their costs considerably, it was decided to switch breeders and purchase naive rats from a closer breeder; there were two nearby, Taconic Farms and Blue Spruce. More than two dozen rats of each sex from both breeders were eventually tested for nocturnal rotation. Quite surprisingly, both male and female rats, from both sources, rotated much less than had the rats from Perfection Breeders in New York. Rats from Perfection Breeders were then purchased and tested in Albany – and the data very closely resembled data obtained a couple of months earlier in New York (i.e., there was no evidence of there being anything peculiar about the new environment in Albany). Rats from two other breeders – Harlan and Charles River – were then purchased; rates of nocturnal rotation exhibited by rats from each of these latter sources were intermediate between Taconic/Blue Spruce and Perfection. It was then decided that, despite the added cost, to return to Perfection rats. This decision, made more than two months after the initial Albany shipment of Perfection rats was tested above, resulted in the unaccountable and frustrating finding that Perfection rats now also rotated at relatively low rates. Several dozen Perfection rats were tested with increasing bewilderment. An inquiry to the breeder resolved this exasperating puzzle: unlike the other breeders, and unbeknown to us, Perfection's colony of rats was not 'closed' – new breeding rats from an outside source were periodically introduced and new lines established every few years. The Perfection rats initially tested in Albany were from the same 'old' line used in New York whereas the subsequent shipments only contained rats from a 'new' line, the 'old' line having been discontinued. This disconcerting news prompted a decision to order rats from a 'closed' colony breeder. Because it was also desirable to use rats that had a behavioral baseline similar to the rats used for several years in New York, Zivic-Miller rats were purchased and tested – these rats had been used in New York from 1971 to 1974 and were indistinguishable, in 1974, from Perfection rats; the switch to Perfection in 1974 was made because of a much lower cost per rat at the time. The newly arrived Zivic-Miller rats indeed rotated at rates comparable to those of the 'old' line Perfection and formerly used Zivic-Miller rats. As all rats tested were Sprague-Dawley derived, the foregoing search had essentially characterized a continuum of rats' rotational behavior and located sources for providing rats at quantitative steps along this continuum. Listed in the table are the net rotation data for the various rats. Data derived from laboratory-bred rats are added for comparison.

There are several interesting aspects to these data. First, it should be noted that, of the commercially bred rats, a sex difference was only apparent in the 'old' Perfection rats and in the Zivic-Miller rats ($p < 0.05$, t-test for each of the three cases above). Similarly, there was no sex difference in weakly rotating (WL) rats bred in this labo-

Differences in the strength of rotational behavior among Sprague-Dawley rats obtained from different suppliers. Data are expressed as 'Net rotations' (turns in the dominant direction minus turns in the nondominant direction) +/− SEM. See text for explanation regarding the Perfection rat groups.

Source	Sex (N)	Net rotations
Perfection ('old' – N.Y.)	Female (64)	41.8 ± 4.1
Douglasville, PA	Male (64)	31.2 ± 3.0
Perfection ('old' – Albany)	Female (24)	42.8 ± 5.1
Douglasville, PA	Male (24)	30.4 ± 3.1
Perfection ('new')	Female (64)	20.7 ± 2.8
Douglasville, PA	Male (48)	19.7 ± 2.1
Taconic	Female (48)	6.2 ± 1.4
Germantown, NY	Male (36)	5.0 ± 1.1
Blue Spruce	Female (24)	6.7 ± 1.9
Altamont, NY	Male (24)	6.1 ± 1.7
Harlan	Female (24)	18.1 ± 3.6
Walkersville, MD	Male (24)	16.4 ± 3.6
Charles River	Female (24)	24.5 ± 5.1
Wilmington, MA	Male (24)	20.1 ± 4.4
Zivic-Miller	Female (48)	42.1 ± 4.8
Allison Park, PA	Male (48)	28.8 ± 3.3
Laboratory-bred: WL	Female (106)	33.0 ± 4.3
(see Glick[49])	Male (103)	31.4 ± 4.5
Laboratory-bred: SL	Female (137)	71.9 ± 8.2
(see Glick[49])	Male (135)	34.0 ± 4.7

ratory, whereas an exaggerated sex difference occurred in laboratory-bred, strongly rotating (SL) rats (see above). Most intriguing was the finding that Taconic and Blue Spruce rats clearly ($p < 0.01$) rotated less than our own WL rats. It is therefore possible for weak rotation to be bred in males as well as in females – perhaps continued inbreeding in the laboratory would have yet produced this effect (cf.[47]). Because a left population bias was observed in both male and female WL rats[49], it was of interest to know whether such a bias was always a consequence of breeding for weak rotation. So far, this indeed seems to be the case, as there were left biases in both sexes among rats from each of the five low-rotating sources above (the % left-sided rats ranged from 54.2% in female Charles River rats to 61.1% in male Taconic rats). Although the individual Ns were small, such that this bias was not significant in either sex from any source by itself, it was significant (Chi square tests, $p < 0.05$) for each sex when rats from all of the five sources were combined; % left-sided females and males were 58.2% and 58.9%, respectively – comparable to the 58.4% and 60.0% figures in WL rats[49]. In contrast, there were non-significant biases in the combined stronger rotating 'old' Perfection and Zivic-Miller rats above; % left-sided females and males were 44.9% and 48.5%, respectively – figures comparable to those reported earlier for similar rats[49, 58].

Functional significance of differences in cerebral laterality

Spatial behavior

The results of an experiment conducted a few years ago indicated that the very existence of a lateral bias may be a major determinant of whether left can be discriminated from right[113]. Rats identified as rotators or non-rotators were trained to perform a spatially-elicited escape response. Rats were placed individually in the long arm of a Plexiglas (black) T-maze (stem = 30 cm; arms = 15 cm), with scrambled foot shock (0.6 mA a.c.) administered through a grid floor. Only one of the two arms (left or right) was deemed 'safe' or 'correct'; the side ipsilateral to the direction of rotation was correct for 11 rotators and incorrect for 11 rotators, whereas for 9 non-rotators, the correct side was assigned randomly. When a rat entered the correct side, shock was terminated; if a rat chose the incorrect side, the shock was not terminated and a correction was allowed. In both cases the animal was then removed from the arm of the maze and placed in the stem for the next trial. Testing continued in this manner until the subject had made the last five out of six choices to the correct side. The number of trials required to reach this criterion was taken as the learning score. One day later, all rats were re-trained with the identical procedure. The difference between the number of trials to criterion during re-learning and learning was an indication of retention. Both groups of rotators had significant retention whereas the non-rotators did not. Although the learning scores for the two groups of rotators were similar, the ipsilateral group re-learned in significantly fewer trials than the contralateral group. The non-rotator group took significantly more trials to reach criterion than either of the other groups on both test days. The results suggested that some degree of behavioral laterality is necessary for 'normal' left-right discrimination. Rats without demonstrable evidence of such bias had great difficulty acquiring the discrimination and failed to show any retention. To some extent, the direction of the inherent asymmetry was important; that is, the discrimination was better retained if training reinforced, rather than opposed, the direction of rotation.

Left- vs right-sidedness: population bias, cortical asymmetry and individual differences in response to stressors

For several years results in this laboratory seemed to indicate that left-right biases in rotation and side preference occurred randomly in a rat population. A typical experiment generally found that approximately 50% of rats rotated to the right and 50% to the left. In contrast were several findings of left-right asymmetry in rat cortex: differences in cortical thickness[29], differences in behavioral effects of left and right cortical lesions[26, 82] and, based on measurements of labeled deoxyglucose uptake, a difference in frontal cortical energy metabolism[56]. The latter deoxyglucose results suggested that the left-right asymmetry in frontal cortex modulated the nigrostriatal asymmetry: rats' side preferences were stronger if deoxyglucose uptake was greater in the contralateral than in the ipsilateral frontal cortex. Because left frontal cortex was usually more active, in terms of deoxyglucose uptake, it was postulated that, in a large population,

more rats should have right side preferences than left side preferences, and right preferences should be stronger than left preferences. Data of 602 rats (all female Sprague-Dawley derived), tested for nocturnal or amphetamine-induced rotation were reviewed and indeed, there was a small (54.8%) but significant ($p < 0.025$) right population bias. Right-sided rats were also more active and had, as predicted, stronger side preferences than left-sided rats[58]. If frontal cortex is lateralized and modulates spatial bias in the proposed manner, it might be expected that bilateral lesions of frontal cortex, by removing this modulation, would decrease side preferences and activity in right-sided rats and have opposite effects in left-sided rats. This is exactly what occurred experimentally[89].

More pronounced differences between left- and right-sided rats' rotational behavior were subsequently observed in response to cocaine[53]. Right-rotating female (Sprague-Dawley derived) rats rotated much more than left rotators, while left-rotating male rats rotated much more than right rotators. These findings were in sharp contrast to those obtained with amphetamine, where no significant rotational differences between left- and right-biased rats of either sex were found. While cocaine and amphetamine are known to be similar in many of their neurochemical and behavioral effects, some difference(s) must obviously exist. For example, although both drugs activate dopaminergic pathways in the brain, amphetamine preferentially affects nigrostriatal neurons[6] and cocaine preferentially affects mesocortical neurons[60]. Mesocortical dopamine neurons are also known to be activated selectively by inescapable footshocks[5,62,70,100]. It was therefore postulated that cocaine-like effects on rotational behavior might be produced by a combination of inescapable shocks and amphetamine. This expectation was verified in studies where it was indicated that, indeed, uncontrollable stressors exerted an effect on d-amphetamine induced rotational behavior to cause it to resemble that induced by cocaine: right rotation was selectively increased in females and left rotation was selectively increased in males (see above). One of the consequences of exposure to uncontrollable shock is to provoke profound disturbances of several behaviors including shock escape (learned helplessness effects[76]). In order to assess the relationship of this phenomenon to rotational behavior, we included exposure to a shuttlebox shock-escape task following rotational testing. Significant correlations were noted between the intensity of pre-stressor rotational behavior and the magnitude of performance deficits measured on the task[10]. *Positive* correlations were seen between the strength of rotational bias and the magnitude of the behavioral deficit for right rotating males, while *negative* correlations were seen between the two measures for left rotators. These findings led us to perform a systematic inquiry as to the relative susceptibilities to the effects of uncontrollable shock in left and right biased

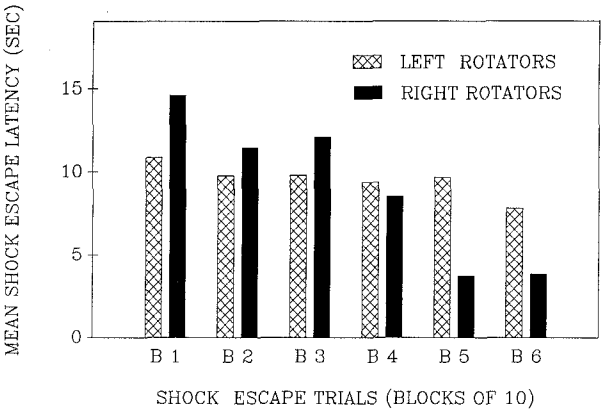

Figure 1. Mean phase 1 shock escape latencies over trial blocks for lateralized male Long-Evans rats exposed to sixty 0.6 mA RMS AC footshocks that were escapable by the performance of a fixed ratio 2 bar press response. Right rotators learned to escape shock in that they improved their performance over trial blocks, as indicated by significant ($p < 0.05$) simple main effect of TRIAL BLOCKS on a repeated measures analysis of variance (ANOVA). Left rotators were initially more reactive to shock, as indicated by a significantly shorter escape latency at B1, but did not learn to escape shock as indicated by a nonsignificant ($p < 1.0$) ANOVA. Yoked to each of these animals was a partner that was matched on rotational behavior and received an identical pattern of shock that was inescapable.

rats. Male Zivic-Miller Sprague-Dawley rats of moderate to strong rotational bias (net turns > 20) were subjected in matched pairs to ESC escapable or YOK inescapable shock with identical shock insured through a yoking procedure (Phase 1). 24 h later the animals were tested in the shuttlebox test (Phase 2). Left and right biased rats differed in their performance in the Phase 1 bar press shock escape task. As shown in figure 1, right biased rats were, at first, much less reactive to shock but learned to escape shock (i.e., their performance improved over trial blocks). Left biased rats were very reactive to shock but exhibited no learning curve on this measure.

Analyses of phase 2 shuttlebox test data (fig. 2) also indicated large differences between right and left biased rats. Whereas right biased ESC rats were better at learning to escape shock in phase 1, their YOK counterparts were better at learning to be helpless. Right biased YOK rats became helpless while right biased ESC rats learned the task readily. Left biased YOK rats did not become helpless; they rapidly escaped on early trials and slightly improved their performance over trials. At B1 and B4 their performance was actually better than that of their ESC counterparts.

These findings indicated that animals of differing rotational bias are differentially reactive to footshock stress (left turners are more reactive than right turners), differ in sensitivity to the performance deficits engendered by uncontrollable shocks (right turners are more sensitive than left turners), and that the magnitude of this sensitivity may be predicted by the strength of this bias. The finding of greater stress reactivity in left turners appears to be consistent with a recent report suggesting a greater plasma adrenocorticotropin and norepinephrine re-

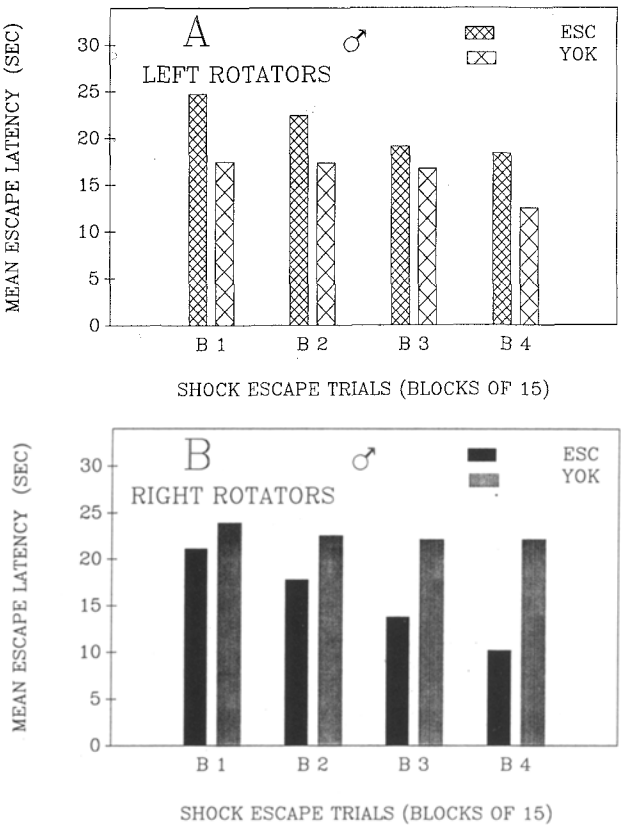

Figure 2. Mean phase 2 shuttlebox escape latencies over 60 trials for left (A) and right (B) rotating rats, exposed to either escapable footshock (ESC) or identical inescapable footshock (YOK) in phase 1. Inescapable footshock induced a shock escape deficit (i.e. learned helplessness effect) in right rotators: ESC animals showed a significant ($p < 0.05$) simple main effect of TRIAL BLOCKS (ANOVA) whereas YOK animals did not. Among left rotators, a learned helplessness affect did not occur; while ESC animals improved their performance over trial blocks ($p < 0.05$), YOK animal actually performed better in the last trial block (B4).

sponse following novelty stress in left turning, amphetamine-sensitized male Sprague-Dawley rats[69]. These findings are also important in that they demonstrated individual differences in susceptibility to effects within the learned helplessness model which has received considerable attention as an animal analog of human depression[111]. One serious shortcoming of the learned helpless model is that it makes exclusive use of animals with intact and 'normally' functioning neural substrates[67] and makes no provision for individual differences in sensitivity to its effects. A survey of the reported data on the phenomenon does, however, suggest that not all animals exposed to uncontrollable shock-stressors actually acquire the behavioral state. In the original studies with dogs[94], 63% of the animals exposed to uncontrollable shock subsequently failed to learn to escape shock. Other studies using outbred Sprague-Dawley rats have only yielded from 5–20% susceptible animals[61]. Finally, a recent, comprehensive study using rats from 8 different stocks has shown that 4 of these are insensitive to uncontrollable stress effects (for example Fisher 344) while the others (Harlan Sprague-Dawley, Buffalo, Wistar Kyoto, Charles River Holtzman) vary from 28 to 55% in susceptibility[110]. When these findings are viewed in light of data on the rotational behavior of rats from different stocks, some interesting predictions emerge. We have already shown, for example, that male Sprague-Dawley rats from Zivic-Miller, that are strongly lateralized, show large differences in both stress reactivity and in sensitivity to uncontrollable shocks depending upon whether sthey are left- (insensitive) or right-biased (sensitive). These rats show maximal interindividual differences in sensitivity. As at the population level there is a tendency for these rats to be left-biased, they are only moderately (i.e. < 50%) sensitive to uncontrollable stressor effects. We would hypothesize that a very sensitive line of rats (for example Charles River Holtzman) would contain many strongly lateralized right rotators. Conversely, in Fisher 344 rats, that are as a group insensitive to uncontrollable shocks, strongly lateralized left rotators but weakly lateralized right rotators would be expected; and we have seen just this in preliminary observations[52].

Drug sensitivity

As was reviewed above, it was seen that Sprague-Dawley derived rats from seven different sources varied severalfold in their nocturnal rotational behavior[59]. Further analyses were undertaken with some of these animals to assess potential differences in sensitivity to d-amphetamine, and sensitization to d-amphetamine upon repeated testing. Rats from three sources were tested twice (a week between tests) for rotation induced by d-amphetamine. Rats from two of these sources showed evidence of sensitization, there being significantly greater rotation in response to the second dose than in response to the first dose; the d-amphetamine-induced rotational behavior of rats from the third source did not significantly change from one week to the next. However, the latter rats had a greater initial response to the first dose of d-amphetamine than did rats from the other two breeders. Further analysis revealed that, among rats from all three breeders, rats rotating weakly in response to d-amphetamine of the first test tended to rotate more on the second test, whereas rats rotating strongly in response to d-amphetamine on the first test tended to rotate less on the second test. This relationship was found to apply to previously collected data as well. A mechanism involving asymmetry in sensitization to d-amphetamine-induced release of striatal dopamine was proposed in our report of these data[59].

Subsequent to our characterization of these differences among Sprague-Dawley derived rats, we tested Long-Evans rats from a local source (Blue Spruce). These rats exhibited a good degree of variation: strongly lateralized and non-lateralized rats each comprised about one-third of the total population. Except for very weakly lateralized rats, there was no evidence of sensitization to d-amphetamine upon repeated testing. Further testing revealed that these Long-Evans derived (LEd) rats differed

in another important respect from most (Perfection and Zivic-Miller) of the Sprague-Dawley derived (SDd) rats we had used: population biases were sex-dependent for SDd rats but not for LEd rats. That is, the majority (55%) of female SDd rats had right-sided rotational (nocturnal and d-amphetamine-induced) preferences [58], whereas males as a group tended (52%) to have left-sided biases [85]. In contrast, both female and male LEd rats had a preponderance of left-sided biases (62% and 56%, respectively, based on approximately 120 rats of each sex). Previous work had shown that cocaine elicited sex-dependent differences in rotation between left- and right-biased SDd rats and that uncontrollable stress elicited similar differences, as reviewed above. In view of the left-right population differences between SDd and LEd rats, we repeated the cocaine experiment in LEd rats: cocaine (20 mg/kg, i.p.) elicited more intense rotation in left- than in right-sided rats of both sexes [8]. Similarly, exposure to stressors, such as uncontrollable footshock [9] or 48 h of food deprivation [11], selectively enhanced left rotation in both sexes of LEd rats. Overall, in both LEd and SDd rats, females rotated more than males in response to d-amphetamine and cocaine, as well as nocturnally. The differential interactions between sex and side variables in LEd and SDd rats should be very useful in assessing the relative contributions of these variables in determining individual differences in drug sensitivity, and in the response to stressors, in future experiments.

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The AA and ANA rat lines, selected for differences in voluntary alcohol consumption

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Summary. The offspring of rats that voluntarily select larger quantities of alcohol are heavier consumers of alcohol than the offspring of rats that tend to avoid it. Such selective breeding, repeated over many generations, was used to develop the AA (Alko, Alcohol) line of rats which prefer 10% alcohol to water, and the ANA (Alko, Non-Alcohol) line of rats which choose water to the virtual exclusion of alcohol. In addition to demonstrating the likely role of genetic factors in alcohol consumption, these lines have been used to find behavioral, metabolic, and neurochemical correlates of differential alcohol intake. Some of the line differences that have been found involve the reinforcing effects of ethanol, the changes in consumption produced by alcohol deprivation and nutritional factors, the behavioral and adrenal monoamine reactions to mild stress, the development of tolerance, the accumulation of acetaldehyde during ethanol metabolism, and the brain levels of serotonin. It is hoped that these studies will lead to a better understanding of the genetically-determined mechanisms that influence the selection of alcohol.
Key words. AA and ANA rats; alcohol consumption; genetic selection; neurochemistry; stress; alcohol withdrawal; behavior; ethanol metabolism.

Introduction

A rapidly developing area in alcohol research is the study of genetic factors underlying alcoholism. It is now generally accepted that genetic factors are responsible for a predisposition in some people for becoming alcoholics. Genetics alone does not, of course, cause alcoholism. Environmental factors are necessary for the manifestation of the disease: at the very least, the individual must first have experience with alcohol drinking, probably for many years, before any symptoms of alcoholism are shown. Genetic factors are important, however, in help-