

Akaysha C. Tang

Department of Psychology
Department of Neurosciences
Department of Computer Science
University of New Mexico
Albuquerque, NM 87131
E-mail: akaysha@unm.edu

Bethany C. Reeb

Department of Psychology
University of New Mexico
Albuquerque, NM 87131

Neonatal Novelty Exposure, Dynamics of Brain Asymmetry, and Social Recognition Memory

ABSTRACT: Brief and transient early-life stimulation via neonatal handling and neonatal novelty exposure can lead to differential changes within the right and left brains. In rats, these lateralized changes have been demonstrated behaviorally, neuroanatomically, and neurophysiologically. Recently, we found that neonatal novelty exposure can prolong the duration of social recognition memory from less than 2 hr to at least 24 hr among male rats reared in social isolation and that this enhancement is associated with an initial right-turn preference in a novel testing cage. In contrast to stable forms of asymmetry, such as handedness, we show that this turning asymmetry is dynamic—decreasing as the animal adjusts to the novel testing environment over a 2-day period. This change in turning asymmetry was found only among animals that experienced neonatal novelty exposure during the first 3 weeks of their lives. Furthermore, individual differences in short-term social recognition memory for a conspecific can be predicted by this change in functional asymmetry. © 2003 Wiley Periodicals, Inc. *Dev Psychobiol* 44: 84–93, 2004.

Keywords: asymmetry; social recognition memory; right-turn preference; neonatal novelty exposure

Brain asymmetry has been observed not only in humans but in other animals as well (Denenberg, 1981; Hiscock & Kinsbourne, 1995; Rogers & Andrew, 2002; Tang, 2003). More than two decades ago, Denenberg and colleagues (Denenberg, 1981; Denenberg, Garbanati, Sherman, Yutzey, & Kaplan, 1978) first demonstrated in the rat that the development of cerebral asymmetry was sensitive to neonatal stimulation. Cerebral asymmetry was inferred by a differential left versus right lesion effect on open-field activity. Specifically, they found that it was only among the handled rats that a right-hemisphere lesion produced a greater disinhibition of activity than the left-hemisphere lesion. This conclusion was further supported by a parietal lesion study (Maier, Vandenhoff, & Crowne, 1988). When multiple measures of asymmetry were used (rotational preference in a rotometer, turning in the open field and T-maze, and neurochemical asymmetry), the precise

directions of changes in asymmetry differed among the different tasks. Yet, the general conclusion that neonatal handling modified cerebral asymmetry remained the same (Camp, Robinson, & Becker, 1984).

Rats that experienced neonatal novelty exposure (Tang, 2001), a method that is derived but differs from the handling method (Denenberg, 1964; Levine, 1957), displayed a left shift in paw preference during adulthood (7 months of age) (Tang & Verstynen, 2002). Consistent with this peripheral and behavioral left shift, the same neonatal treatment resulted in a central right shift in the hippocampal volumetric asymmetry at 8 months of age (Verstynen, Tierney, Urbanski, & Tang, 2001) and a selective right-sided enhancement in hippocampal synaptic plasticity (Tang, 2003; Zou, Reeb, & Tang, 2002). These results, obtained at different levels of analysis and with different methodologies, offered converging evidence supporting the claim that neonatal stimulation induces brain lateralization, specifically a right-brain dominance (Denenberg, 1981).

Neonatal novelty exposure treatment differs from the well-known handling procedure (Denenberg, 1964; Levine, 1957) in that it isolates the novelty exposure component from two confounding factors, maternal

Received 5 December 2003; Accepted 30 July 2003

Correspondence to: A. C. Tang

Published online in Wiley InterScience

(www.interscience.wiley.com). DOI 10.1002/dev.10158

© 2003 Wiley Periodicals, Inc.

separation and experimenter handling, by replacing a between-litter design with a split-litter design. As a result of this procedural modification, we were able to conclude that neonatal novelty exposure was sufficient for modifying or enhancing various forms of asymmetry (Tang, 2003; Tang, Reeb, Romeo, & McEwen, 2003; Tang & Verstynen, 2002; Verstynen et al., 2001; Zou et al., 2002) whereas maternal separation and the experimenter handling were not necessary for inducing such asymmetry.

Parallel to these findings of induced behavioral, anatomical, and physiological asymmetries, we also found enhanced learning and memory performance in a variety of tasks, including spatial and nonspatial, positive and negative reinforcement, social and nonsocial tasks, and tasks inducing different stress levels (Caplan, Reeb, & Tang, 2002; Caplan, Verstynen, & Tang, 2001; Reeb, Brown, & Tang, 2001; Tang, 2001; Tang et al., 2003). These parallel changes in asymmetry and learning along with results from the computational modeling literature (Kosslyn, Sokolov, & Chen, 1989; Levitan & Reggia, 2000; Reggia, Goodall, & Shkuro, 1998) provided further support for the hypothesis that the development of cerebral asymmetry may have a functional consequence for cognitive development (Güntürkün et al., 2000; Rogers, 2000). In a recent study, we found that neonatal novelty exposure led to prolongation of social recognition memory from less than 2 hr to at least 24 hr during adulthood and that individual differences in this form of adult recognition memory can be predicted by the turning asymmetry measured immediately prior to the social recognition test (Reeb et al., 2001; Tang et al., 2003).

In the present article, using data from the same set of experiments, we focused on the *dynamic* aspect of brain asymmetry and its relation to adult social recognition memory. We investigated whether brain asymmetry measured by turning can change systematically in the absence of changes in the sensory input, whether neonatal novelty exposure affects the dynamics of this turn bias, and what the implications of individual differences in this measure are with regard to social recognition memory.

METHODS

Experimental Animals

Nine pregnant Long-Evans hooded dams (Harlan Sprague-Dawley) were housed in the Psychology Department vivarium for 11 days prior to giving birth. The litters were culled to maintain a litter size of approximately 8 pups to achieve a total of 73 pups (21 females). Twenty-four male pups born of these dams were included in this study. Pups were housed with the dams until weaning at postnatal Day 21. Postweaning, the dams and pups

were housed individually in translucent plastic cages (51 × 25 × 22 cm) with a 7 a.m. to 7 p.m. light:dark cycle and food and water ad lib. All procedures were carried out in accordance with the guidelines established by the National Institutes of Health's (1986) *Guide for the Care and Use of Laboratory Animals*.

Neonatal Novelty Exposure

This procedure was derived but differed from the well-known handling method (Denenberg, 1964; Levine, 1957; Meaney, Aiken, Bhatnager, Vanberkel, & Sapolsky, 1988). We exposed rat pups to a novel nonhome cage for 3-min daily throughout the first 3 weeks of life (Tang, 2001) (Figure 1a). On postnatal Day 1, approximately one half of each litter was randomly assigned to the Novel and the other half to the Home conditions (split-litter design), with weights approximately matched between the Novel and Home animals. The number of male pups kept was maximized. As neonates do not have ears on postnatal Day 1, the standard ear-punching method for identification could not be applied. Group membership was therefore marked via a toe-clipping procedure, which was similar to the standard ear-punching procedure in that it was performed without anesthesia very rapidly, lasting only a fraction of a second. The amount of tissue removed was very small (~0.25 mm³), and the procedure was no more stressful than the standard identification method. To avoid interference with a lateralized effect (Denenberg et al., 1978), we marked both the left and right hindpaws of the Novel (N) and Home (H) pups using two different digit combinations: (a) left first and right fifth, and (b) right first and left fifth. The precise patterns of marking were counterbalanced between the Novel and Home groups. During neonatal novelty exposure, the dam was first removed from the home cage. The Novel and Home pups were then picked up and identified by an experimenter. The identified Novel rats were placed in a new cage lined with fresh sawdust for their 3-min exposure and subsequently returned to their home cage, in which the Home rats remained. During this transfer, each Novel pup was yoked to a Home pup, which received a matching amount of experimenter contact at approximately the same time as the yoked Novel pup. The dam was returned to the litter after both the Novel and Home pups were reunited in the home cage. The amount of touching by the experimenter and the duration of maternal separation during this novelty exposure procedure were matched between the Novel and Home rats, insuring that any difference in social recognition and turning behavior between groups was due to neither the separation from the dam nor the handling, per se, by the experimenter. This procedure was carried out at ambient temperature (21°C), with a humidity of 25%.

Turning Asymmetry During Habituation to a Novel Testing Cage

At approximately 7 months of age, immediately prior to the social-exposure sessions, animals were first exposed to the testing cage without access to their partner for 5 min to habituate to the testing cage and to allow assessment of turning asymmetry. A fitted cardboard partition was securely fastened to the middle of the testing cage (51 × 25 × 22 cm) to separate the pair of animals

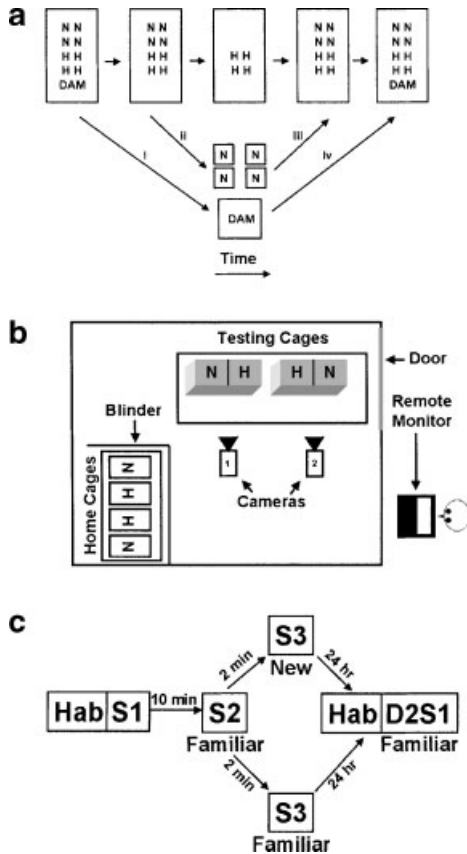


FIGURE 1 Methods: The neonatal novelty-exposure procedure employs a within-litter design and consists of (i) transfer of the dam to a separate cage, (ii) transfer of the Novel (N) rats to their separate new cages, (iii) return of the Novel rats to the home cage, and (iv) return of the dam to the home cage. Home (H) rats remained in the home cage, but were picked up and placed back to the same location within the home cage to match the time and amount of experimenter handling received by the yoked Novel (N) rats. The Novel and Home animals were handled equally by the experimenter and were separated from the dam for equal amount of time (a). Room arrangement during testing (b). The habituation paradigm for social-recognition memory. All animals were first habituated to a neutral testing cage (Hab: 5 min) prior to multiple social-exposure sessions (S) of 5 min duration. Nonsibling Novel and Home rats were weight matched and paired in neutral testing cages (Day 1: S1–S3; Day 2: D2S1) to assess both short term (10 min, S1–S2) and long-term (24 hr, S1–D2S1) recognition memory. During the last session on Day 1 (S3), some animals were exposed to a new conspecific while others experienced the same rat encountered during the first two sessions (c).

(Figure 1b). It is understood that the partition during cage habituation (Hab) did not prevent the rats from perceiving olfactory cues from each other. Because these animals were housed in the same room throughout their life, they were familiar with olfactory cues from each other. Therefore, having access to olfactory cues during the Hab session does not confound social recognition memory measures.

In this setup, the space available for free movement was sufficiently small such that only rearing and left and right turns in the horizontal plane were possible. By limiting forward movement, this small space created ample opportunity for continuous turns without the contamination of forward movement, thus offering a relatively clean measure for turning bias. To better understand the morphology of turns within the horizontal plane, we additionally sampled from videotapes of turns made by neonates before their hindlimbs became functional. Using isolated initial forelimb movement in these neonates, the relationship between forelimb dominance and turn direction can be more clearly established than among adults. We measured the frequency of left and right turns by counting each 90-degree left or right turn made. To evaluate the dynamics of potential functional asymmetry, cage habituation was conducted over 2 consecutive days.

To insure that potential left- and right-turn frequency differences between the Novel and Home groups were not due to environmental asymmetry, two pairs of animals were tested at the same time (Figure 1b). The relative positions of the Novel and Home rats within the testing room were counterbalanced. For example, for the first pair, if the Novel rat was closer than the Home rat to the door of the testing room, a potential source of noise, then for the second pair, the relative distance of Novel and Home rats was interchanged. When the experimenter moved the animals from their housing cage to the testing cage, one pair of Novel and Home rats was moved together using both hands. To insure that the experimenter's handedness did not interact with the animals subsequent turning behavior, if the Novel rat in the first pair was handled by the left hand, then the Novel rat in the second pair was handled by the contralateral hand. To avoid potential experimenter expectancy effects during the experiment and data coding, animals' identifications were recoded and relabeled by another person not involved in this experiment. To distinguish the two animals within a pair, animals were color labeled on the dorsal, lateral surfaces of their trunk with either green or red odorless food coloring. Colors were applied with a Q-tip in the testing room while the animal was in its home cage. To avoid any potential guess of group membership by the experimenter or coder, half of the Novel and Home animals received the color green while the other half received the color red.

Social Recognition Memory Test

After weaning, all animals were housed individually until 7 months of age, when adult social recognition memory was assessed. The adult–juvenile pairing used in a typical social recognition memory test entails a component of social dominance of the testing animal (adult) over the stimulus animal (juvenile). To study social recognition in the absence of dominance-related issues, we tested Novel–Home pairs of identical age in a fresh, neutral testing cage with the weights of the pair matched. The probability of aggression, motivated by territorial instinct in the home cage, was minimized by testing the pair in a neutral cage and by reducing the within-pair weight difference. Few incidences of aggressive behaviors, such as biting and pinning, were observed in this experiment.

Social recognition memory was assessed by examining the habituation of social investigatory behaviors over repeated

exposures to a conspecific during multiple 5-min testing sessions in a neutral testing cage (Figure 1c). Novel and Home rats were exposed to each other in a neutral testing cage in pairs on 2 consecutive days in a total of four paired-exposure sessions following the cage habituation session on each day (Day 1: Hab, S1–S3; Day 2: Hab, D2S1). A fresh testing cage lined with clean sawdust was used for each pair on each day. New cages were used for the Day-2 sessions. We used short intertrial intervals (ITIs) of 10 and 2 min between S1–S3 on Day 1. These short ITIs were selected to maximize the amount of habituation to allow improved discrimination among individual animals. During Day 1 S1 and S2 and Day 2 S1, all animals were paired with the same partner (familiar) that they experienced on Day 1 S1. During Day 1 S3, some (two thirds) of the animals were exposed to a new partner. This was achieved by testing two pairs of animals at a time and swapping one animal from each of the two cages on S3. During the ITIs, animals were returned to their home cages, which were placed on a table in the corner of the testing room.

To reduce the number of animals needed in the study,¹ we used Novel and Home animals as their own social stimuli as opposed to using a separate group of animals. To further avoid the potential influence of weight differences on social investigation, 2 days prior to the social memory test, animals were first weighed and then Novel–Home pairs were formed pseudorandomly with the following constraints: No siblings were used in a pair and on average, and the weights of Novel rats did not differ significantly from the weights of Home rats (within 5 g). The latter constraint insured that any differences in social behavior could not be explained by weight differences and associated social dominance.

All sessions were videotaped for offline analysis. The experimenter and the data coder were both blind to the identity of the animals. Social investigatory behaviors were defined as being proximally oriented to a conspecific (the tip of the nose within approximately 1 cm) or in direct contact while sniffing, following, nosing, grooming, and generally inspecting any body surface (Thor & Holloway, 1982). The frequencies of these behaviors were measured in 5-s increments offline from video recordings made during all social-exposure sessions. If the behavior was present during the 5-s duration, an occurrence of one was counted. As a result of pairing animals of similar age and weight, a large percentage of social investigation time was spent on mutual investigation (~45%). This mutual investigation only adds a constant value to both the Novel and Home measures. To increase the sensitivity of the measures to the novelty manipulation, we performed analysis on only the unidirectional investigation.

Data Analysis

Turning asymmetry was measured by computing a lateralization score (L score) defined as $(R-L)/(L+R)*100\%$, where R and L are frequencies of right and left turns, respectively. The division by $(L+R)$ is to remove individual differences in the total turns.

¹Due to the nature of this developmental study, animals had to be maintained for an extended period of time. This high demand for resources required us to minimize the number of animals used in the experiments.

The multiplication by 100 is to express the bias in terms of percentage. This L score has been used in many previous lateralization studies, particularly in indexing rodent turn and paw preference (Glick, Meibach, Cox, & Maayani, 1980; Glick & Ross, 1981; Rothman & Glick, 1976; Tang & Verstynen, 2002; Verstynen et al., 2001; Whishaw, Pellis, & Gorny, 1992). An alternative index of $(R-L)$ divided by the square root of $(L+R)$ has been favored by other handedness researchers as a preferred index (Michel, 1998; Michel, Sheu, & Brumley, 2002). To make our results comparable to previous rodent lateralization reports, we present our results mainly in the conventional L score. We also present distributions of the alternative index to facilitate comparison. Note that one cannot determine from this distribution the laterality of a given individual given the present experimental design.²

Because more than one animal from a litter was used, we tested for a litter effect using analysis of variance. Since litter effects on left- and right-turn frequencies and the lateralization scores for either of the 2 days did not reach statistical significance, we performed the rest of the analysis using animals as units. Due to heterogeneity of variance in the raw data, Spearman's rank order correlations r_s were used. Findings concerning neonatal novelty induced enhancement in short- and long-term social recognition memory, in blood basal concentration of corticosterone, and the relationship between turning asymmetry and the long-term social recognition memory have been reported elsewhere (Tang et al., 2003). In this article, we provide more detailed description of the turning movement. Specifically, we focus on measures of dynamics of turning asymmetry over 2 days of repeated testing, the dependency of this dynamic asymmetry on neonatal novelty exposure, and the implications for short-term social recognition memory, defined as $(S1 - S2)/S1*100\%$.³

RESULTS

Three types of movements were observed during the 5-min cage habituation sessions: rearing, left, and right turns. An image captured from the videotape (Figure 2a) shows an example of a right turn, which involved an apparent dominant push by the forelimb contralateral to the direction of turn. Because the adult form of turning is almost inevitably contaminated by other motor components (e.g., rearing) sometimes executed at the same time, we examined images of turns made by neonates on a single day before their hindlimbs became functional to help reveal the relationship between turn directions and dominant sides of motor output. Figure 2b shows captured

²To determine individual laterality, one must obtain multiple independent samples from a given individual repeatedly. A forced-choice experimental design with discrete trials is needed and should be combined with an estimation of p value from a binomial distribution (Agestri & Finlay, 1997). Because ongoing turning behavior, as opposed to discrete trials, were used in this study, we were unable to determine the statistical significance of an individual's lateralization score.

³Long-term habituation (24 hr) and interference effect from exposure to a new conspecific on S3 were reported in a previous study (Tang et al., 2003).

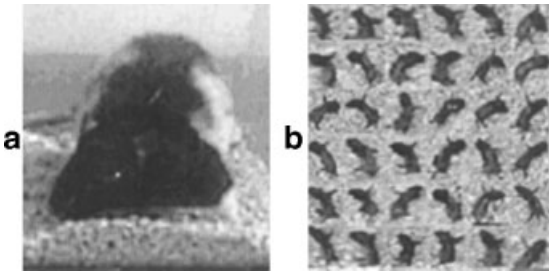


FIGURE 2 Turns are initiated by a dominant force exerted by the forelimb contralateral to the direction of movement. An adult rat initiating a right turn in the testing cage (a). Neonates initiating left and right turns on postnatal Day 3 during the 3-min neonatal novelty exposure (b).

images from 36 neonates (postnatal Day 3) initiating left or right turns. These images clearly demonstrate that the direction of a turn is contralateral to a dominant force exerted by the forelimbs.

Left- and Right-Turn Frequencies

Figure 3a,c displays the left- and right-turn frequencies for Novel and Home rats during the initial cage-habituation session (Day 1) and the second cage-habituation session (Day 2). When examined for each individual day, Novel rats made significantly greater right turns than home rats only on Day 1. The changes in left and right turns over the 2 testing days were computed as the reduction in turn frequencies from Day 1 to Day 2 (Figure 3b,d). Novel rats significantly reduced their right-turn frequency, $t = 4.725$, $df = 11$, $p < 0.001$

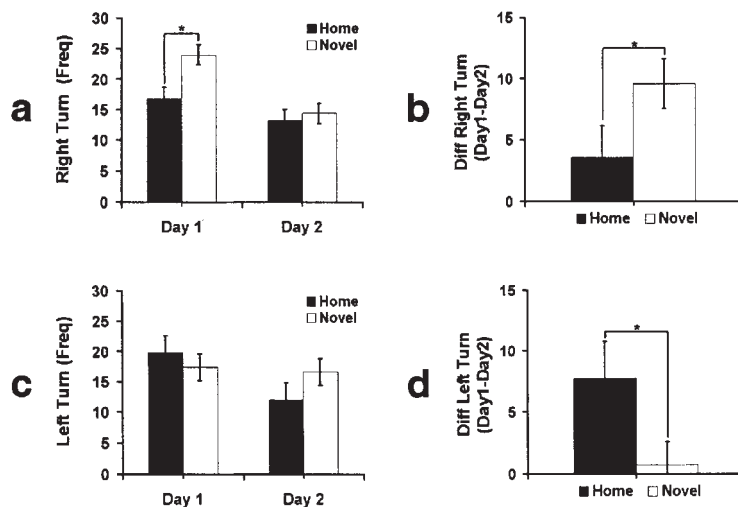


FIGURE 3 The effects of neonatal novelty exposure on the dynamics of left- and right-turn frequencies over 2 days of testing ($N_{Novel} = 12$; $N_{Home} = 12$). Right-turn frequencies on Days 1 and 2 (a). Dynamics of right-turn frequency: Day1 – Day 2 (b). Left-turn frequencies on Days 1 and 2 (c). Dynamics of left-turn frequency: Day 1 – Day 2 (d).

(Figure 3b), while Home rats significantly reduced their left turn frequency, $t = 2.543$, $df = 11$, $p < 0.05$ (Figure 3d). In comparison to the Home rats, Novel rats had a greater reduction in right-turn frequency, $t = -1.846$, $df = 22$, $p < 0.05$ (Figure 3b), and a smaller reduction in left-turn frequency, $t = 1.955$, $df = 22$, $p < 0.05$ (Figure 3d), over the 2 testing days. For descriptive statistics, see Table 1.

Turn Asymmetry

Of all four conditions (Day \times Treatment), only Novel rats showed a significant turn asymmetry (right bias) during the initial cage-habituation session on Day 1, $t = 2.550$, $df = 11$, $p < 0.05$ (Figure 4a). The changes in this L score over the 2 testing days differed significantly between Novel and Home groups, two-sample $t = -2.364$, $df = 22$, $p < 0.05$ (Figure 4b), with Novel rats showing a significant reduction in L score, one-sample $t = 3.181$, $df = 11$, $p < 0.01$, while Home rats showed no significant changes from Day 1, one-sample $t = -0.896$, $df = 11$, $p > 0.20$. For descriptive statistics, see Table 1.

Changes in Behavioral Asymmetry and Social-Recognition Memory

The reduction in right-turn frequency over the 2 testing days had a positive correlation with the subsequent short-term habituation of social investigation, $r_s = 0.480$, $p < 0.025$; partial $r = 0.379$, $p = 0.082$; $n = 23$, two tailed (Figure 5a). In contrast, the reduction in left-turn

Table 1. Descriptive Statistics

	Day 1	Day 2	Day 1–Day 2
Right-Turn Frequency			
Novel	23.92 ± 1.67	14.33 ± 1.74	9.58 ± 2.03
Home	16.75 ± 1.87	13.17 ± 1.69	3.58 ± 2.54
Left-Turn Frequency			
Novel	17.33 ± 2.24	16.58 ± 1.84	0.75 ± 1.84
Home	19.75 ± 2.77	12.00 ± 1.98	7.75 ± 3.05
L-Score			
Novel	18.35 ± 7.21	−7.46 ± 5.96	25.81 ± 8.11
Home	−5.32 ± 10.49	7.31 ± 11.26	−12.63 ± 14.09

frequency had a negative correlation with the habituation, $r_s = -0.523$, $p < 0.025$; partial $r = -0.349$, $p = 0.112$; $n = 23$, two tailed (Figure 5b). Finally, the changes in L score correlated positively with the short-term habituation of social investigation, $r_s = 0.547$, $p < 0.005$; partial $r = 0.385$, $p = 0.077$; $n = 23$, two tailed (Figure 5c).

Changes in Lateralization Expressed in an Alternative Index

The distribution of alternative L scores for the Novel and Home rats together are shown for Day 1 (Figure 6a) and Day 2 (Figure 6b). The peak of the Day-1 distribution is slightly positive while the peak for Day 2 is clearly negative, around -0.5 . Thus, consistent with the trend observed using the L score, there was an overall right shift in turn preference from Day 1 to Day 2. For the Novel rats, there was a large shift in z score from a peak slightly above 1.5 to a peak at -0.5 between Day 1 and Day 2 (Figure 6c). In contrast, the shape of the distribution changed very little for the Home rats (Figure 6d). These observations are again consistent with those made from L scores. These distributions appeared to be unimodal and skewed, with a majority of the observation falling within the intermediate range and a few taking on extreme values.

DISCUSSION

In this developmental study, we demonstrated the effects of neonatal novelty exposure on the dynamic aspect of turning asymmetry and the implications of such dynamics to social recognition memory. Turning bias was examined by calculating a lateralization score (L score) based on the relative frequency of right to left turns made during a cage habituation session immediately prior to the social exposure. The dynamic aspect of turning bias was measured by the change in the L scores between 2 consecutive days. Social recognition memory was measured by the

habituation of social investigatory behaviors between two 5-min social-exposure sessions with 10- and 2-min ITIs following the first cage habituation session. We found that turning asymmetry in a novel testing cage is not constant. Instead, it decreased as a result of increased familiarity to the testing environment and procedure. The direction and the amount of change in this asymmetry observed during adulthood can be modulated by temporally remote and brief neonatal environmental alterations. Furthermore, the change in lateralization correlated significantly with the measure for short-term social recognition memory, suggesting that the dynamic aspect of turning asymmetry and short-term social recognition memory may share common underlying mechanisms.

Dynamics of Functional Asymmetry

Patterns of brain asymmetry are generally considered stable over time. In this study, we found that neonatal novelty-exposed rats displayed a right-turn preference on the initial day of testing⁴ and that there was a significant reduction in this right preference 24 hr later on the second day of testing. This initially lateralized turning pattern appeared to have habituated over repeated testing; this habituation was observed only among neonatal novelty-exposed animals. This suggests that functional brain asymmetry may be more plastic and experience-dependent than what has been implicitly assumed. Furthermore, this short-term, experience-dependent plasticity adds to the long-term, experience-dependent plasticity previously reported for other aspects of brain lateralization (Denenberg et al., 1978; Rogers, 1982; Tang, 2003; Tang & Verstynen, 2002; Verstynen et al., 2001). Together, these findings offer converging evidence suggesting that asymmetric brain activation is no longer a constant state of mind but highly plastic, both sensitive to environmental influences during development and to novelty or familiarity of the immediate environment.

The dynamics of brain lateralization have not been used previously to predict other psychological measures, although lateralization of brain activation at one point in time has been used as a predictor for learning in animal models (Glick, Zimmerberg, & Jerussi, 1977; Vallortigara, 1992; Willar & Crowne, 1989) and for temperament (McManis, Kagan, Snidman, & Woodward, 2002) and affect (Davidson & Irwin, 1999) in humans. The finding that the reduction in right-turn bias (Figure 5c) was positively correlated with the habituation in social

⁴This study was not intended for determining statistical insignificance of individual lateralization. Instead, changes in the lateralization of a population-level asymmetry as a function of early stimulation and 2-day repeated testing was tested.

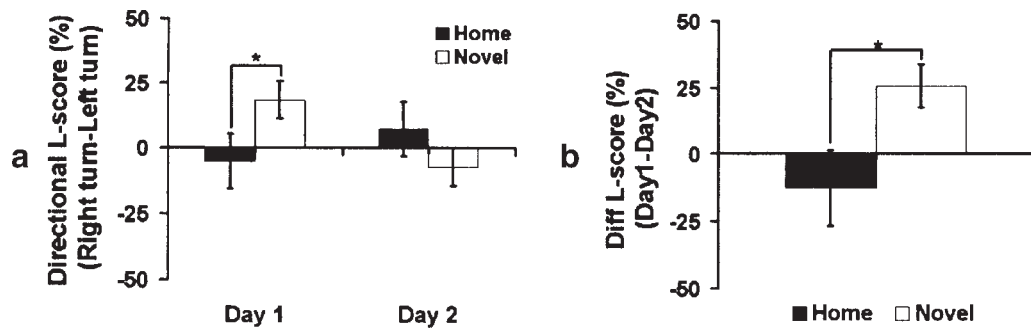


FIGURE 4 The effects of neonatal novelty exposure on the dynamics of brain asymmetry. Dominance measured by an L score = $(R - L)/(R + L) * 100\%$. L scores on Days 1 and 2 (a). Dynamics of L scores: Day 1 – Day 2 (b).

investigation suggests that dynamics of turning asymmetry may be associated with social cognitive capabilities; the greater the habituation of the right-turning dominance in response to repeated exposure to a novel testing cage, the greater the subsequent habituation in social investigation as well.

Measuring Turning Asymmetry in a Novel Environment

Our measure of asymmetry is novel in several aspects. First, frequency of rearing, the up–down movement, was used as a control variable to separately measure general activity levels as opposed to frequencies of turning behavior. Previously, we were able to demonstrate a dissociation between the frequencies of rearing and turning behavior (Tang et al., 2003). While both left- and right-turn frequencies and turning asymmetry differed significantly between Novel and Home rats, rearing frequency did not. Second, because the space in the testing cage was limited to approximately the animals' body length in the horizontal dimensions, to explore its environment the animal must make either right or left turns to move in the horizontal plane, thus maximizing the frequency of turning. Third, the asymmetry measure was derived from behaviors occurring immediately prior to the social recognition memory test and in the same testing environment as the social recognition memory test. This temporal and spatial proximity allows the relationship between functional asymmetry and social behavior to be studied with fewer added sources of variance. Finally, the testing cages and covers were transparent, allowing differential visual feedback after left and right turns were made. Thus, it is possible that the underlying neural pattern of activation during left versus right turns is different from those activated in the rotometer, which offers a homogeneous visual field in all directions and does not offer the normal proprioceptive and visual feedback (Ungerstedt & Arbuthnott, 1970).

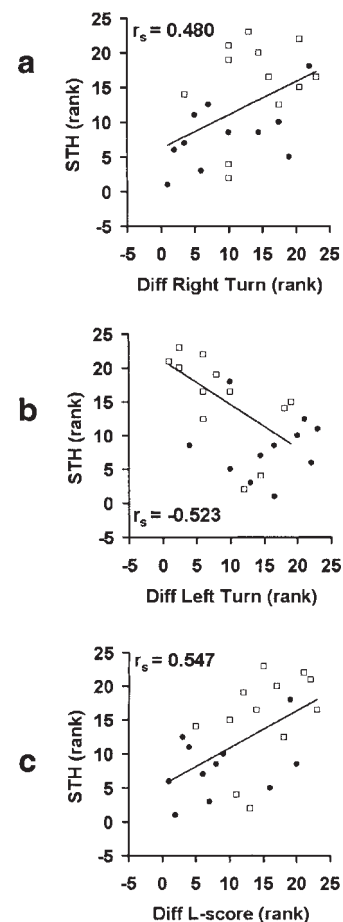


FIGURE 5 Relationship between the dynamics of brain asymmetry and short-term social-recognition memory. Novel rats: open square; Home rats: filled circle. Positive correlation between the *right*-turn frequency and short-term habituation (STH) (a). Negative correlation between the *left*-turn frequency and STH (b). Positive correlation between the *right*-turn bias (positive L score) and STH (c).

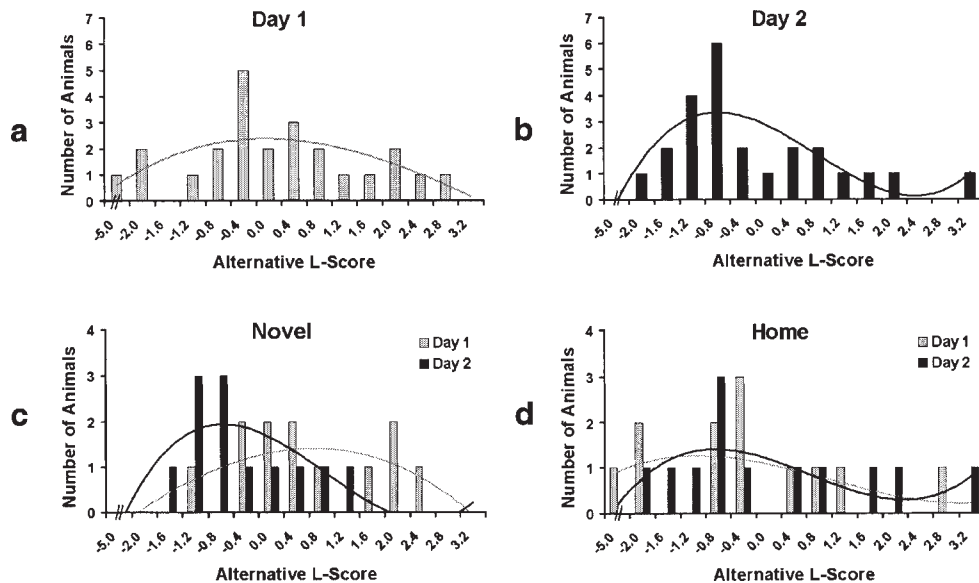


FIGURE 6 Changes in turn asymmetry expressed in an alternative lateralization measure. (a, b). The distribution of z scores of the alternative lateralization score for all rats on Days 1 and 2, respectively. The fitted curves (polynomial) show a peak shift from the more positive to more negative (from right to left turn) between Day 1 and Day 2. Distribution of the z scores for the Novel rats only. The fitted curves showed a much larger leftward peak shift, indicating a change in turn preference (c). Distribution of the z scores for Home rats only. The fitted curves showed no peak shift, indicating a lack of change in turn preference among the Home rats (d).

Direction of Brain Asymmetry Underlying Turning Asymmetry

The turns measured during the cage habituation in this study were often accompanied by a clear push of the contralateral forelimb. By examining how turns were made among neonates, it was clear that turns are initiated by a dominant force exerted by the contralateral forelimb in a direction away from the direction of turning. These observations from both adult (Figure 2a) and neonatal (Figure 2b) rats favor the interpretation that a *right* turn made in the horizontal plane is achieved at least initially by a push from the left forelimb, which in turn can be interpreted as a result of a net *right* hemisphere activation. This interpretation of right-brain dominance underlying a right turn is supported by the selective influence of neonatal novelty exposure on right hippocampal synaptic plasticity (Tang & Zou, 2002; Zou et al., 2002), neonatal novelty exposure-induced relative increase of the right hippocampal volume (Verstynen et al., 2001), and a left shift in paw preference in the reaching task (Tang & Verstynen, 2002). This set of consistent findings is in contrast to findings from earlier studies that suggest a greater hemispherical activation that is contralateral to the direction of rotation (Ungerstedt, 1971; Zimmerberg, Glick, & Jerussi, 1974). As reviewed by Hiscock and Kinsbourne (1995), asymmetric patterns of dopamine

activity were sometimes associated with ipsilateral and other times with contralateral turns (Shapiro, Glick, & Hough, 1986).

Two Mechanisms of Brain Asymmetry Revisited

Lateralization measures obtained from paw preference and turn preference appear to differ in at least two aspects. The turning asymmetry measured in this study is characterized by a rather smooth unimodal distribution and by its dynamic change in response to changing environmental familiarity. In contrast, the paw preference measures obtained from our previous study (Tang & Verstynen, 2002) were clustered into three discrete groups: strong right preference, strong left preference, and ambidextrous. Furthermore, the L scores computed for paw preference are highly stable not only over consecutive days but after delays of many months. The differences in plasticity over time and in the uni-versus multimodal distribution suggest that two different brain mechanisms may underlie these two forms of behavioral asymmetry in paw and turn asymmetry. These two forms of behavioral asymmetry may be two specific instantiations of the action versus activation-based systems proposed by Pribram and McGuinness (1975) and reviewed in Tucker and Williamson (1984).

Neonatal Novelty Exposure Enhances Plasticity in Brain Asymmetry

Our data demonstrated that only animals that experienced neonatal novelty exposure displayed experience-dependent changes in brain asymmetry while the matched control animals did not. In the Novel rats, the initial right-turn bias *decreased* when tested for a second time under identical conditions with a short ITI (Figure 4b). The lack of change in turning asymmetry among the Home rats suggests a lack of such plasticity under otherwise identical conditions. These contrasting findings from the Novel and Home rats suggest that the change in turning asymmetry between the 2 days is not random but systematic—reflecting a plasticity in functional lateralization. This plasticity is highly sensitive to early-life environmental differences even though the neonatal novelty exposure was very brief (3 min per day) and transient (first 3 weeks of life).

This enhanced plasticity in functional asymmetry in the neonatal novelty-exposed rats is paralleled by several other forms of plasticity at both the behavioral and synaptic level. We have previously shown that adult long-term potentiation in the CA1 region of the hippocampus can be enhanced by neonatal novelty exposure (Tang & Zou, 2002). More recently, we found that adult long-term depression, another important form of synaptic plasticity, is enhanced as well by the same neonatal treatment (Zou et al., 2002). In addition to these electrophysiological findings, greater plasticity has been found in behavioral tasks involving spatial and nonspatial memory, social and nonsocial memory, and tasks that involve positive and negative reinforcement (Reeb et al., 2001; Tang, 2001). Together, these findings indicate that neonatal novelty exposure creates individuals with greater experience-dependent plasticity in behavior and neural mechanisms as well as functional asymmetry.

Summary

We examined the change in the right and left turns, and in the lateralization scores based on these turns over 2 testing days. We investigated whether these measures were affected by mild early-life stimulation (neonatal novelty exposure) and whether these measures have any functional significance with respect to short-term social recognition memory, measured as habituation in social investigation. We found that changes in the pattern of left and right turns as well as the lateralization scores over 2 testing days were different for the Novel and Home rats, and the amount of change, or the plasticity of these measures, is associated with short-term social recognition memory. These results point to a dynamic aspect of brain lateralization and suggest

potential functional consequences from this dynamic brain asymmetry.

REFERENCES

- Agresti, A., & Finlay, B. (1997). Introduction to multivariate relationships. In A. Agresti & B. Finlay (Eds.), *Statistical methods for the social sciences* (3rd ed., pp. 91–94, 187–188). Upper Saddle River, NJ: Prentice Hall.
- Camp, D., Robinson, T., & Becker, J. (1984). Sex-differences in the effects of early experience on the development of behavioral and brain asymmetries in rats. *Physiology & Behavior*, 33, 433–439.
- Caplan, M., Reeb, B., & Tang, A. (2002). Neonatal novelty exposure attenuates the interfering effects of surprise/uncertainty on spatial working memory [Abstract]. *Developmental Psychobiology*, 41, 18.
- Caplan, M., Verstynen, T., & Tang, A. C. (2001). Neonatal novelty exposure modulates navigational strategies in the Morris water maze [Abstract]. *Journal of Cognitive Neuroscience*, 57C, 8, 79.
- Davidson, R., & Irwin, W. (1999). The functional neuroanatomy of emotion and affective style. *Trends in Cognitive Science*, 3, 11–21.
- Denenberg, V. (1964). Critical periods, stimulus input, and emotional reactivity: A theory of infantile stimulation. *Psychological Review*, 71, 335–351.
- Denenberg, V. (1981). Hemispheric laterality in animals and the effects of early experience. *Behavioral Brain Science*, 4, 1–21.
- Denenberg, V., Garbanati, J., Sherman, G., Yutzey, D., & Kaplan, R. (1978, September 2). Infantile stimulation induces brain lateralization in rats. *Science*, 201, 1150–1152.
- Glick, S., Zimmerberg, B., & Jerussi, T. (1977). Adaptive significance of laterality in rodent. *Annals of the New York Academy of Sciences*, 299, 180–185.
- Glick, S. D., Meibach, R. C., Cox, R. D., & Maayani, S. (1980). Phencyclidine-induced rotation and hippocampal modulation of nigrostriatal asymmetry. *Brain Research*, 196, 99–107.
- Glick, S. D., & Ross, D. A. (1981). Right-sided population bias and lateralization of activity in normal rats. *Brain Research*, 205, 222–225.
- Güntürkün, O., Diekamp, B., Manns, M., Nottelmann, F., Prior, H., Schwarz, A., & Skiba, M. (2000). Asymmetry pays: Visual lateralization improves discrimination success in pigeons. *Current Biology*, 10, 1079–1081.
- Hiscock, M., & Kinsbourne, M. (1995). Phylogeny and ontogeny of cerebral lateralization. In R. Davidson & K. Hugdahl (Eds.), *Brain asymmetry* (pp. 535–578). Cambridge, MA: MIT Press.
- Kosslyn, S., Sokolov, M., & Chen, J. (1989). The lateralization of BRIAN: A computational theory and model of visual hemispheric specialization. In D. Klahr & K. Kotovsky (Eds.), *Complex information processing: The impact of Herbert A. Simon* (pp. 3–29). Hillsdale, NJ: Erlbaum.
- Levine, S. (1957, August 30). Infantile experience and resistance to physiological stress. *Science*, 126, 405.

- Levitan, S., & Reggia, J. (2000). A computational model of lateralization and asymmetries in cortical maps. *Neural Computation*, 12, 2037–2062.
- Maier, S., Vandenhoff, P., & Crowne, D. (1988). Multivariate-analysis of putative measures of activity, exploration, emotionality, and spatial-behavior in the hooded rat (*Rattus norvegicus*). *Journal of Comparative Psychology*, 102, 378–387.
- McManis, M., Kagan, J., Snidman, N., & Woodward, S. (2002). EEG asymmetry, power, and temperament in children. *Developmental Psychobiology*, 41, 169–177.
- Meaney, M., Aiken, D., Bhatnager, S., Vanberkel, C., & Sapolsky, R. (1988, February 12). Effect of neonatal handling on age-related impairments associated with the hippocampus. *Science*, 239, 766–769.
- Michel, G. F. (1998). A lateral bias in the neuropsychological functioning of human infants. *Developmental Neuropsychology*, 14, 445–469.
- Michel, G. F., Sheu, C. F., & Brumley, M. R. (2002). Evidence of a right-shift factor affecting infant hand-use preferences from 7 to 11 months of age as revealed by latent class analysis. *Developmental Psychobiology*, 40, 1–13.
- National Institutes of Health. (1986). Guide for the care and use of laboratory animals. (DHEW Publication No. 86-23). Washington, DC: U.S. Government Printing Office.
- Pribram, K., & McGuinness, D. (1975). Arousal, activation, and effort in the control of attention. *Psychological Review*, 82, 116–149.
- Reeb, B., Brown, B., & Tang, A. (2001). Neonatal novelty exposure enhances social recognition memory in adult rats [Abstract]. *Developmental Psychobiology*, 41, 80.
- Reggia, J., Goodall, S., & Shkuro, Y. (1998). Computational studies of lateralization of phoneme sequence generation. *Neural Computation*, 10, 1277–1297.
- Rogers, L. J. (1982, May 20). Light experience and asymmetry of brain function in chickens. *Nature*, 297, 223–225.
- Rogers, L. J. (2000). Evolution of hemispheric specialization: Advantages and disadvantages. *Brain and Language*, 73, 236–253.
- Rogers, L. J., & Andrew, R. J. (2002). *Comparative vertebrate lateralization*. Cambridge, England: Cambridge University Press.
- Rothman, A. H., & Glick, S. D. (1976). Differential effects of unilateral and bilateral caudate lesions on side preference and passive avoidance behavior in rats. *Brain Research*, 118, 361–369.
- Shapiro, R., Glick, S., & Hough, L. (1986). Striatal dopamine uptake asymmetries and rotational behavior in unlesioned rats: Revising the model? *Psychopharmacology*, 89, 25–30.
- Tang, A. (2001). Neonatal exposure to novel environment enhanced hippocampal-dependent memory function during infancy and adulthood. *Learning & Memory*, 8, 257–264.
- Tang, A. (2003). A hippocampal theory of cerebral lateralization. In R. Davidson & K. Hugdahl (Eds.), *The asymmetrical brain* (pp. 37–68). Cambridge, MA: MIT Press.
- Tang, A., & Verstynen, T. (2002). Early life exposure to a novel environment modulates “handedness” in rats. *Behavioural Brain Research*, 131, 1–7.
- Tang, A., & Zou, B. (2002). Neonatal exposure to novelty enhanced long-term potentiation in CA1 region of the rat hippocampus. *Hippocampus*, 12, 398–404.
- Tang, A. C., Reeb, B. C., Romeo, R. D., & McEwen, B. S. (2003). Modification of social memory, hypothalamic–pituitary adrenal axis, and brain asymmetry by neonatal novelty exposure. *Journal of Neuroscience*, 23, 8254–8260.
- Tucker, D., & Williamson, P. (1984). Asymmetric neural control-systems in human self regulation. *Psychological Review*, 91, 185–215.
- Ungerstedt, U. (1971). Striatal dopamine release after amphetamine or nerve degeneration revealed by rotational behaviour. *Acta Physiologica Scandinavica*, 82 (Suppl.), 49–66.
- Ungerstedt, U., & Arbuthnott, G. (1970). Quantitative recording of rotational behavior in rats after 6-hydroxy-dopamine lesions of the nigro-striatal dopamine system. *Brain Research*, 24, 485–493.
- Vallortigara, G. (1992). Right hemisphere advantage for social recognition in the chick. *Neuropsychologia*, 30, 761–768.
- Verstynen, T., Tierney, R., Urbanski, T., & Tang, A. (2001). Neonatal novelty exposure modulates hippocampal volumetric asymmetry in the rat. *NeuroReport*, 12, 3019–3022.
- Willar, C., & Crowne, D. (1989). Circling, hemispheric asymmetry, and left–right discrimination. *Brain Research*, 500, 405–407.
- Whishaw, I. Q., Pellis, S. M., & Gorny, B. P. (1992). Skilled reaching in rats and humans: Evidence for parallel development or homology. *Behavioural Brain Research*, 47, 59–70.
- Zimmerberg, B., Glick, S., & Jerussi, T. (1974, August 16). Neurochemical correlate of a spatial preference in rats. *Science*, 185, 623–625.
- Zou, B., Reeb, B., & Tang, A. (2002). Neonatal novelty exposure induces long lasting enhancement in long term depression (LTD) in the right hippocampus of adult rats. *Society for Neuroscience Abstracts*, 648.17, 32, 16.