

## The genetic liability to stress and postweaning isolation have a competitive influence on behavioral organization in rats

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Received 29 June 1999; received in revised form 18 August 1999; accepted 28 September 1999

### Abstract

Rats housed in social isolation postweaning (isolates) show profound behavioral and neurobiological differences when compared to socially housed rats (socials). Fischer rats (F344) relative to Lewis rats are hyperresponsive and significantly more susceptible to stressful stimuli. This investigation tested the hypothesis that the behavioral effects of postweaning isolation are more pronounced in a strain of rats with high susceptibility to stress compared to a strain with low susceptibility to stress. Seventy male Sprague–Dawley, Lewis, and F344 rats were housed individually or in groups at weaning on Day 21 and tested on Day 85 in the Behavioral Pattern Monitor. There was no interaction between strain and postweaning isolation for measures of locomotor activity and exploratory behavior (holepoking). However, the postweaning isolation-induced increase in the frequency of repetitive straight movements, a measure of behavioral organization, was more pronounced in Lewis isolates compared to Sprague–Dawley and F344 isolates. These results do not support the hypothesis that rats with a higher susceptibility to stress show more pronounced changes in behavior following postweaning isolation; instead, increased susceptibility to stress may counteract the repetitive movement patterns induced by social isolation. © 2000 Elsevier Science Inc. All rights reserved.

**Keywords:** Development; Schizophrenia; Locomotor activity; Stress; Strain differences; Isolation rearing

### 1. Introduction

Postweaning isolation housing is a nonpharmacological developmental manipulation that results in complex neurobiological and behavioral changes in rodents. The behavioral effects of postweaning isolation have been conceptualized as consisting of hyperactivity, ambivalence, cognitive impairment, and overresponsiveness to predictors of reinforcement [1]. The disruption of prepulse inhibition induced by postweaning isolation has been proposed as a nonpharmacological animal model for related behavioral deficits in schizophrenic patients [2]. Schizophrenia is a complex syndrome involving many neural systems, and is thought to emerge from interactions between genetic liability, developmental perturbations, and environmental insults [3]. The behavior of schizophrenic patients is characterized by a more rigid and perseverative response set [4], the inability to plan actions [5], and information-processing deficits characterized by diminished sensorimotor gating [6] and reduced suppression of irrelevant information [7].

Unconditioned motor behavior consists of a complex combination of locomotor, investigatory, and exploratory behaviors that are highly organized and change dynamically over time. Behavioral organization has been introduced as a concept to quantify the extent to which animals select and sequence different behavioral responses over time [8]. For example, a high degree of behavioral organization in rats is characterized by a combination of straight, meandering, and circumscribed movements to explore a novel environment. In contrast, disturbances in behavioral organization are characterized by the predominance of straight, meandering, or circumscribed movements. Using factor analysis, measures of behavioral organization were found to be independent of the amount of locomotor activity or the number of investigatory responses such as holepokes or rearings [8].

Several investigators have reported that postweaning isolation substantially affects unconditioned motor behavior. Specifically, increases in locomotor activity [9], decreases in habituation of activity over time [10], and increases in repetitive straight movement sequences [11] have been reported. Thus, the behavior of isolation-housed rats in a novel environment supports the notion that these animals exhibit a more rigid behavioral repertoire. An increase in stereotypic

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response patterns by schizophrenic patients has been reported in a number of neuropsychological [12] and behavioral tasks [13], indicating that behavioral organization is also affected in these patients. If changes in behavioral organization in isolation-housed rats parallel the behavioral changes in schizophrenic patients, then experimental manipulations of factors that have been implicated in the exacerbation of schizophrenic behavior should potentiate the effect of postweaning isolation on behavioral organization. For example, the effects of stress have been implicated in the exacerbation of symptoms in schizophrenic patients [14]. Therefore, manipulating the degree of stress and investigating the effect of postweaning isolation on behavioral organization may provide further construct validity for the conceptual approach of using measures of behavioral organization as target variables in assessing the behavior of schizophrenic patients and animal models relevant to schizophrenia.

Several strategies have been used to investigate the interaction between stress and the behavioral effects of postweaning isolation. One may induce an acute or chronic predictable or unpredictable stressor in the environment. Different experimental lighting conditions when exploring a novel environment is an example of an acute unpredictable stressor. In contrast to the hypothesized increased responsiveness to a stressful environment, exploratory behavior in different lighting conditions differed less in postweaning isolation rats than in socially housed rats [15]. This finding suggests that changing the stressful characteristic of the environment does not result in an increased behavioral effect in postweaning isolation rats compared to socially housed animals. Here, a strain-related strategy was pursued. Histocompatible Fischer 344 (F344) and Lewis rats differ in a wide range of biochemical [16–20], electrophysiological [21], immunological [22], and behavioral responses to stressors [23, 24]. These animals have been used to discern the influence of genetic background on immune responses, hypothalamo–pituitary–adrenal (HPA) axis regulation [25], the susceptibility to a neonatal lesion [26], and the susceptibility to drug dependence [27–30]. Lewis rats are hyporesponsive to inflammatory stimuli, novel situations, and have a greater propensity to self-administer drugs of abuse. Sprague–Dawley (SD) rats typically show an intermediate response to stressors. Thus, Lewis, SD, and F344 rats can be viewed as existing along a continuum of behavioral and immunological responsiveness.

This investigation tested the hypothesis that the behavioral effects of postweaning isolation are more pronounced in a strain of rats with high susceptibility to stress compared to a strain with low susceptibility to stress. Specifically, when housed in social isolation postweaning, F344 rats should show an augmented behavioral response characterized by a more rigid behavioral profile of repetitive straight movements when exposed to a novel environment. Alternatively, if stress-induced behavioral changes compete with the behavioral effects of postweaning isolation, then rats with a higher susceptibility to stress may overcome the iso-

lation-housing–induced behavioral deficit when exploring a novel environment.

## 2. Materials and methods

For the experiment, 70 male rats of three different strains (Sprague–Dawley: SD, Fisher 344: F344, Lewis all Harlan Laboratories, San Diego, CA) were obtained 1 day postweaning and separated into two different housing groups. Postweaning isolation rats (isolates) were subsequently housed singly in plastic cages for 64 days, whereas socially housed rats (socials) were housed in groups of three animals. Isolates were able to hear, see, and smell the other animals, but did not have any physical contact with other animals. These rats were on a reverse 12-h dark–light cycle, and handling was kept at a minimum, restricted to regular health checks and bedding changes. After 8 weeks of isolation or social housing, the animals were brought to the laboratory 1 h before testing. Each animal was tested during its first exposure to the Behavioral Pattern Monitor (BPM) for 60 min. The statistical analyses of the within-subjects ANOVA for the 60-min session were characterized by a substantial and strain-selective attrition due to habituation and subsequent inactivity. To minimize a bias due to selective attrition of one group of animals, only the first 40 min were used for statistical analyses comparing the following groups: 12 SD socials; 12 SD isolates; 12 F344 socials; 13 F344 isolates; 11 Lewis socials; 10 Lewis isolates. After testing in the BPM, these rats were tested in a startle paradigm to assess sensorimotor gating changes due to postweaning isolation. The results of that experiment are reported elsewhere [31].

A detailed description of the data acquisition system can be found in Geyer et al. [32]. The BPM comprises eight chambers, each enclosed within a ventilated wooden box. Each chamber consists of a 30.5 × 61.0 × 38.0 cm Plexiglas holeboard that is equipped with three floor holes in the front, middle, and rear part of the floor, six wall holes, three along either side of the long walls, and a hole in the back of each chamber. The location of the rat in the BPM chambers was obtained from a grid of 4 × 8 photobeams 2 cm above the floor in each chamber. Each hole is also equipped with a photobeam. The information about the status of the photobeams was transmitted with a frequency of 18 Hz to a PC-compatible computer. A change in the status of photobeams triggered the storage of the information in a binary data file together with the duration of the photobeam status. Subsequently, the raw data files were transformed into ASCII data files comprised of the (x,y) location of the rat in the BPM chamber with a resolution of 3.8 cm (7 × 15 different possible positions), the duration of each event (*t*), and whether a hole was poked.

Previous studies of large groups of control rats using a factor analytic approach demonstrated that the amount of locomotor activity, the geometric patterns of activity, and measures of exploratory behavior describe three indepen-

dent aspects of unconditioned motor behavior [8]. Therefore, three different categories of measures were assessed. First, the amount of locomotor activity was measured by the number of counts, i.e., the total number of microevents defined by a change in photobeam status. Second, the geometric patterns of locomotor activity were quantified by the spatial scaling exponent,  $d$ , that has been described in detail elsewhere [33, 34]. Briefly, the spatial scaling exponent,  $d$ , quantifies the extent to which a sequence of movements is along a straight line ( $d = 1$ ) or within a circumscribed area ( $d = 2$ ) according to the formula [average distance traveled]  $\approx$  [number of movements] $^{(2-d)}$ . Third, exploratory activity was quantified by the number of holepokes during a specified time interval.

Based on the above hypotheses, a repeated-measure analysis of variance (ANOVA) was computed for each measure. Specifically, a two between-factor (strain, housing condition) and one within-factor (time in enclosure) ANOVA was used to determine the effects of strain, housing conditions, and time in the chamber. Greenhouse–Geisser (GG) corrections were used for within-subjects statistics to account for violations of sphericity. Based on a positive mean effect of strains, *post hoc* analyses were carried out for strain for counts,  $d$ , and holepokes. The calculations were performed using the SPSS multivariate software package [35].

### 3. Results

#### 3.1. Effects of strain and postweaning isolation on the amount of locomotor activity

Lewis, SD, and F344 rats differed significantly in levels of locomotor activity,  $F(2, 65) = 34.27, p < 0.001$ . Isolates exhibited significantly increased levels of locomotor activity,  $F(1, 65) = 5.32, p < 0.05$ . However, there was no interaction between strain and housing condition,  $F(2, 65) = 1.10, NS$ . *Post hoc* Scheffe tests of homogenous subsets revealed that SD rats were more active during the first 10 min than both Lewis and F344 animals. As indicated by a significant interaction between time and strain,  $F(5.1, 167.4) = 2.35, p < 0.05$ , both SD rats and Lewis rats habituated more quickly than F344 rats, such that SD and F344 rats showed similar and higher levels of activity than Lewis rats during the fourth 10-min block. The increased locomotor activity of isolates, irrespective of strain, was most pronounced during the fourth 10-min time block, as shown in Fig. 1a and b resulting in a significant interaction between housing condition and time,  $F_{GG}(2.57, 167.4) = 3.43, p < 0.05$ . This result agrees with previous findings [11], and indicates that isolates exhibit an attenuated habituation.

#### 3.2. Effects of strain and postweaning isolation on geometric patterns of activity

Strain,  $F(2, 64) = 18.64, p < 0.001$ , housing condition,  $F(1, 64) = 7.26, p < 0.01$ , and the interaction between

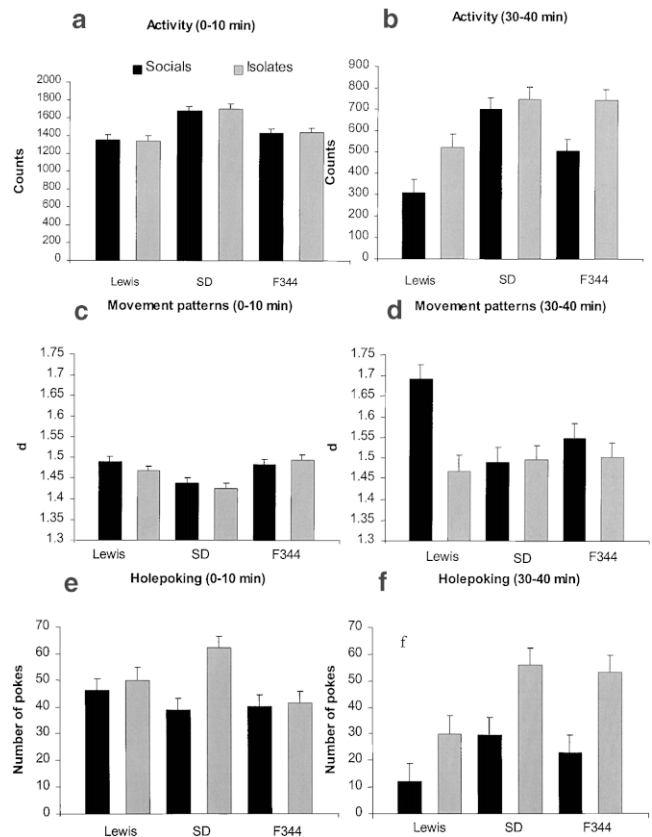


Fig. 1. Averages and SEM for activity (a and b), spatial scaling exponent,  $d$  (c and d), and hole poking (e and f) for socials (solid bars) and isolates (hatched bars) for the three strains show a significant disruption of habituation, an increase in hole poking in isolates across strains and a strain-specific increase in straight movements for Lewis rats during the third 10-min block.

strain and housing condition,  $F(2,64) = 6.26, p < 0.01$ , significantly affected movement patterns as measured by  $d$ . In addition, movement patterns changed significantly over time,  $F_{GG}(2.3, 151.2) = 12.66, p < 0.01$ , an effect that differed between strains,  $F_{GG}(2.3, 151.2) = 4.41, p < 0.01$ , and between isolates and socials,  $F_{GG}(2.3, 151.2) = 3.36, p < 0.05$ . The complex effects of strain and housing condition with time can be explained by examining the marginal averages for the different groups. Specifically, *post hoc* Scheffe tests of homogenous subsets revealed that movement patterns of F344 and Lewis rats were more circumscribed during the first 10 min than those of SD rats. During the last 10-min time block, Lewis socials showed the most circumscribed movement patterns, with F344 socials being intermediate, and SD socials showing significantly straighter movement patterns. Postweaning isolation did not affect these strain differences during the first 10-min block (Fig. 1c). During the last 10-min time block, Lewis, but not F344 or SD, isolates exhibited significantly straighter movement patterns than Lewis, F344, or SD socials, respectively (Fig. 1d). To summarize, both Lewis and F344 rats exhibited more circumscribed movements when

compared to SD rats. All strains exhibited more circumscribed movements with increasing time in the enclosure. Lewis socials showed the most substantial increase in circumscribed movements. In comparison, Lewis isolates failed to exhibit the significant change from straight to circumscribed movement patterns and were thus significantly straighter during the fourth 10 min block than Lewis socials.

### 3.3. Effects of strain and postweaning isolation on exploratory activity

The frequency of holepoking was affected by both strain,  $F(2, 64) = 10.32$ ,  $p < 0.001$ , and housing condition,  $F(1, 64) = 31.57$ ,  $p < 0.001$ , but not by the interaction between strain and housing condition,  $F(2, 64) = 1.05$ , NS. *Post hoc* Scheffe tests of homogenous subsets revealed that all strains exhibited similar levels of holepoking during the first 10-min block. During the fourth 10-min block, Lewis rats showed fewer holepokes than both SD and F344 animals, as supported by a significant interaction between time and strain,  $F(5.7, 183.2) = 2.94$ ,  $p < 0.05$ . Postweaning isolation significantly increased holepoking irrespective of strain and time (Fig. 1e and f), as supported by the lack of a significant interaction between housing condition and time,  $F(2.86, 183.2) = 2.67$ , NS.

## 4. Discussion

This investigation yielded three main results. First, rats housed in social isolation postweaning, irrespective of strain and, therefore, independent of the susceptibility to stress, show a disruption in habituation to a novel environment resulting in increased locomotor activity over time relative to socially housed rats. Second, rats housed in social isolation as weanlings show a strain-dependent increase in straight repetitive movements during the fourth 10-min block when tested as adults. In contrast to predictions, this increase was inversely related to the strain's susceptibility to stress. Third, rats housed in social isolation exhibited increased levels of holepoking independent of strain.

We have previously shown that unconditioned locomotor behavior reflects at least three independent dimensions, which include the amount of locomotor activity, the degree of behavioral organization, and the frequency of exploratory behaviors as measured by rearing or holepoking [8]. This investigation shows the importance of assessing these dimensions separately. Although there was no interaction between strain and rearing condition for locomotor activity, habituation, and exploratory behavior (holepoking), measures of behavioral organization revealed that postweaning isolation has a more pronounced effect in rat strains characterized by a low susceptibility to stress. This result does not support the hypothesis that rats with a higher susceptibility to stress show a more pronounced behavioral response to postweaning isolation. Instead, these results support the hypothesis that stress susceptibility and postweaning isolation

are competitive or unrelated with regard to their effects on behavioral organization. Specifically, rats with high susceptibility to stress housed in isolation postweaning show less change in behavioral organization relative to socially housed controls than rats with low susceptibility to stress.

Others have investigated the effects of acute stress manipulations on the behavioral effects on postweaning isolation and reported results that are consistent with the notion that stress and postweaning isolation have potentially competitive influences on behavior. For example, Hall et al. [15] reported that isolates exhibit a reduced behavioral difference in light versus dark open-field environments, which was interpreted to suggest that these animals are less responsive to changes in stress levels. Moreover, rats housed in isolation from the time of weaning enter a novel area more frequently under low-stress conditions [15], but show higher levels of avoidance behaviors in a novel and presumably high-stress environment [36]. The observation that Lewis rats show lower levels of stress hormones than F344 rats when exposed to a novel environment [37], suggests that the exposure to a novel environment is less stressful to Lewis rats than to F344 rats. Specifically, Lewis rats relative to F344 rats exhibited lower ACTH and corticosterone responses during exposure to an open field, swim stress, restraint, or ether [38]. Thus, rats that are less stressed when exposed to a novel environment when housed in isolation fail to show a substantial change of movement patterns from repetitive straight to highly circumscribed movements over time. Therefore, a blunted stress response is associated with an attenuated transition from repetitive straight to circumscribed movements over time.

The surprising finding that postweaning isolation affected the behavioral organization of movements most strongly in Lewis rats, which are characterized by a lower susceptibility to stress than F344 rats, raises several possibilities. These behavioral results are in contrast to anatomical findings, indicating that F344 rats showed more extensive neuroanatomical changes than Lewis rats [26] in a neurodevelopmental animal model of schizophrenia. We have previously shown that repetitive straight movement patterns in isolates occur after puberty, and thus follow a developmental course similar to that of schizophrenia [39]. Thus, whereas the emergence of repetitive straight movement patterns has some construct validity relevant to the emergence of perseverative behaviors in schizophrenic patients, the current results suggest that using rats with varying susceptibility to stress may not be analogous to the stress-diathesis model of schizophrenia. This model suggests that the clinical phenotype of schizophrenia results from an interaction between a genetic liability to develop schizophrenic symptomatology and stressful environmental factors. The current results would suggest that the genetic liability may not involve an increased susceptibility to stress. Indeed, schizophrenic patients show a blunted stress response in a challenging situation [40, 41]. Moreover, psychophysiological findings indicate a lower stress reactivity

in schizophrenic patients having more psychiatric symptoms [42]. Finally, while stress mechanisms have been implicated in the etiology of schizophrenia, recent investigations have failed to link increased stress and relapse or increased stress reactivity and exacerbation of symptoms [43]. Therefore, it appears that the blunted stress response found in Lewis rats and the similarly blunted stress response in schizophrenic patients may ultimately result in an inadequate behavioral response to a novel or challenging environment. In the BPM, this behavioral response is characterized by a disruption of habituation, which has been noted as a key characteristic of information processing deficits in schizophrenic patients [6], and particularly, an increase in repetitive movements.

Unconditioned motor behavior in a novel environment is highly dynamic, changes over time, and functions primarily to increase familiarity and reduce uncertainty [44]. The decreased frequency of behavior over time and the increased engagement in circumscribed movements over time may represent the effect of habituation. The disruption of this behavioral adjustment in rats housed in social isolation leads to a higher level of locomotor activity, with more repetitive straight movements and an increased frequency of exploratory behaviors throughout the session. To summarize, a higher level of susceptibility to stress is not synergistic with the change in movement patterns in a novel environment. Instead, the current results suggest that mounting a stress response in a novel environment may overcome the increase in repetitive straight movement patterns induced by postweaning isolation, which has been shown to have some construct validity with the perseverative behaviors in schizophrenic patients.

## Acknowledgments

We acknowledge the invaluable help of Virginia Masten, Darlene Giracello, and Barbara Carasso. This work was supported by grants from the National Institute of Mental Health to M.A.G. (MH52885) and the National Institute on Drug Abuse to M.P.P. (DA11277), and by the U.S. Veterans Affairs VISN 22 Mental Illness Research, Education, and Clinical Center.

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