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Exploration, Emotionality, and Hippocampal Mossy Fibers in Nonaggressive AB/Gat and Congenic Highly Aggressive Mice

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ABSTRACT: AB/Gat mice and congenic mice bred for high aggressiveness (CS/ag) were tested for exploratory behavior in novel situations and anxiety-related behavior, using an open-field test and the elevated plus-maze test. Subsequently, the size of hippocampal mossy fiber terminal fields was evaluated. Considerably higher exploratory activity was found in nonaggressive mice, whereas aggressive mice exhibited more anxiety-related behavior. Larger intra- and infrapyramidal mossy fiber terminal fields (IIP-MF) and a larger hilus were found in the highly aggressive strain. Within the nonaggressive AB/Gat strain, larger IIP-MF were correlated with higher exploratory behavior and lower anxiety in the plus-maze test. Within the aggressive strain, no individual correlations between hippocampal morphometry and behavior were found. The results corroborate the "ecotype hypothesis," which suggests that mice of subpopulations with highly aggressive males tend to display reduced exploratory behavior. The findings support the view that genetic factors involved in aggressive behavior also affect hippocampal connectivity. However, our results do not support the hypothesis that a higher level of aggressiveness is necessarily related to smaller IIP-MF. © 2003 Wiley-Liss, Inc.

KEY WORDS: aggressiveness; exploration; anxiety; mossy fibers; AB/Gat; congenic mice

INTRODUCTION

Studies in mice selected for short and long attack latencies suggest a bimodal distribution of individual mice within populations, in that subgroups of individuals belong to either an ecotype characterized by low aggressiveness, behavioral flexibility, and good spatial learning, or to an ecotype that displays high aggressiveness, poorer spatial learning, and more routine-like behavior (Benus et al., 1987, 1991; Koolhaas et al., 2002). Several studies indicate that one of the neuronal factors correlated with these behaviors is the extent of hippocampal mossy fiber terminal fields. Intra- and infrapyramidal mossy fiber terminal fields (IIP-MF) have been reported to be comparatively smaller in mice of the aggressive type (Guillot et al., 1994; Sluyter et al., 1994). In addition, their extent was correlated with maze learning (Crusio et al., 1987; Schwegler et al., 1990, 1993; Schwegler and Lipp, 1995). However, the relationship between the genes selected for, their subsequent effects on brain function, and the behavioral pattern is far from clear. Congenic strains of mice, which differ in only one or a few genes, are a useful tool with which to resolve this issue.

We therefore tested nonaggressive AB/Gat mice and congenic mice (CS/ag) bred for high aggressiveness (Schneider-Stock and Epplen, 1995) in tests for exploratory activity in novel situations and emotionality. These strains of mice have been bred for differences in aggressiveness using the following approach. Mice of the highly aggressive strain ABH have been backcrossed on the nonaggressive strain AB/Gat. The relevant trait for "isolation-induced aggression" is determined by one major or only a few genes (Schicknick et al., 1993) exhibiting autosomal dominant inheritance (Schneider et al., 1992; Schneider-Stock and Epplen, 1995). Through backcrossing of the ABH strain on the background of the nonaggressive AB/Gat strain for at least 10 generations and subsequent brother-sister mating, differences between the aggressive and nonaggressive congenic lines should be reduced to only one or very few relevant genes (Schneider-Stock and Epplen, 1995). A pilot study on exploratory behavior in these strains (Marashi et al., 1998), using the open-field test, pointed to differences in exploratory behavior in that nonaggressive mice showed a higher inclination to explore. A first aim of the present study was to test further as to whether, in accordance with the "ecotype hypothesis," selection for high aggressiveness had led to marked reduction in exploratory behavior. The second aim was to test whether selection for aggressiveness had affected hippocampal morphology, particularly the infra- and intrapyramidal mossy fiber terminal fields (IIP-MF). IIP-MF are reported to be smaller in aggressive strains of several models, namely, SAL vs LAL mice (Sluyter et al., 1994), C57BL/6JNmg vs C57BL/6J//Kun mice (Sluyter et al., 1999), as well as seven inbred strains (Guillot et al., 1994). In addition, IIP-MF were found to be both larger (Hausheer-Zarmakupi et al., 1996) and smaller (Crusio et al., 1989a,b) in mice showing high open-field exploration. Third, we wanted to test whether there was a link between IIP-MF and anxiety as studies in DA rats and BDE rats had suggested that larger IIP-MF might be related to lower anxiety (Prior et al., 1997) and as the level of anxiety represents the internal state related to risk-averse behaviors in an ecological context.

With regard to earlier findings, our predictions were that nonaggressive AB/Gat mice should explore more

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than aggressive CS/ag mice, should be less anxious, and should have larger IIP-MF terminal fields in the hippocampus.

MATERIALS AND METHODS

Animals and Maintenance

The subjects were 21 adult mice bred at the Institut für Neuro- und Verhaltensbiologie at Münster University from parents belonging to the strains bred and kept by Schneider-Stock and Epplen (1995). There were six males and five females of the AB/Gat strain and five individuals of each sex from the CS/ag strain. Animals were transferred to Bochum University by car 3 weeks before the tests started. They were housed singly in standard laboratory cages [Makrolon type III, 37 (L) × 21 (W) × 15 (H) cm] in a keeping facility with a temperature of 21 ± 1°C and a 12:12 h light/dark cycle with lights on at 7:00 AM. Food (Altromin 1324) and tap water were always available ad libitum. During the behavioral tests, the mice were about 6 months of age. Before the beginning of the behavioral tests, the animals were handled. The animals were taken from their cages and were kept on the hands of the experimenter for 3 min on 5 consecutive days.

Experimental Room and Apparatus

Experimental room

Both tests took place in the same experimental room, which measured 550 (L) × 350 (W) × 400 (H) cm. The room was kept at a temperature of 21 ± 1°C. Part of the room (350 × 150 cm) was separated by a wooden partition. The open-field and the elevated plus-maze tests, respectively, were located in the center of the larger part of the room and were monitored and controlled via a video system in the smaller part of the room.

Open-field test

The open-field test was an 80 × 80-cm wooden arena with 40-cm-high walls. The bottom was marked off in 16 equal squares. The field was dimly illuminated, with 15 ± 2 lux brightness at the floor level.

Elevated plus-maze test

The maze was cross-shaped with two opposing arms surrounded by 30-cm-high walls (closed arms) and two opposing arms without walls (open arms). The walls were removable to facilitate cleaning of arms and walls between trials. The arms were 10 cm wide and 50 cm long. The maze was illuminated without shadows. The brightness at the arms was 15 ± 2 lux.

Procedure

Behavioral tests

The animals were brought from the keeping facility to a room adjacent to the experimental room about 30 min before a test. Following Pellow et al. (1985) and Prior and Sachser (1995), we used a protocol with an exploration test preceding the plus-maze test. At the beginning of a test each mouse was taken by hand from its cage and placed into the open-field through a small door (10 × 10 cm) in one of the sidewalls. After a 5-min test in the open-field, the animal was taken up again and placed in the center of the elevated plus-maze facing randomly one of the arms. A plus-maze trial was finished after 5 min. Trials were videotaped. After a trial, the number of feces was counted, and the open-field and elevated plus-maze were thoroughly cleaned. The mice were given a second test in the open-field and on the elevated plus-maze tests, 10 days later. All procedures were the same as on the first test.

Hippocampal morphometry

Timm's silver sulfide staining for heavy metals was applied (Danscher and Zimmer, 1978). The mice were sacrificed by an overdose of Nembutal and were transcardially perfused with a 1.17% solution of phosphate-buffered sodium sulfide (pH 7.4) for 1 min, followed by a phosphate-buffered solution of 3% glutaraldehyde for 5 min. They were then rinsed for 5 min with the sodium sulfide solution. After removal, the brains were postfixed in a buffered sucrose solution containing 3% glutaraldehyde and were then cut into 40-μm horizontal sections, using a cryostat. Sections were mounted on glass slides, dried, and developed for 60 min in Timm's solution containing arabic gum, hydroquinone, citrate buffer, and silver nitrate. For morphometry, 10 sections per animal were sampled immediately below the ventralmost part of the septal pole of the hippocampus. Taking every other one, five sections either from the left or the right hippocampus were analyzed per animal.

For morphometry, outlines and distribution of Timm-stained bands and patches were drawn using a projection microscope and measured with a graphics tablet connected to a PC in order to assess the size of the hilus, the suprapyramidal mossy fiber terminal fields (SP-MF), and the intra- and infrapyramidal mossy fiber terminal fields (IIP-MF). The area of the scattered IIP-MF projection was measured by overlaying the drawings with a point grid and counting the number of points coincident with the Timm reaction product.

Data Analysis and Statistics

Based on videotapes, the following behaviors were subjected to quantitative analysis. Concerning the open-field test, the number of entries into peripheral fields (n = 12) and central fields (n = 4) was counted, and the number of total field entries and of proportion of central field entries was calculated. Regarding the elevated plus-maze test, the number of open and closed-arm entries as well as the time spent in the open and closed arms were assessed. An arm entry was defined as entering the arm with all four paws. The time spent in the central square of the maze was recorded separately. The tendency to enter the open arms, which is the measure of anxiety (Pellow et al., 1985), was calculated as the percentage of open arm entries with regard to total arm entries as well as the proportion of time spent on open arms. The data of the behavioral scores were subjected to analysis of variance (ANOVA), with strain and sex as independent factors and first versus second test as a repeated measure. Significant overall ANOVA was followed by planned pairwise comparisons (Fisher's LSD) of the strains for each test. As there were no sex differences in any of the behavioral measures and no interactions of sex with the other factors, males and females were combined in descriptive statistics (mean and SEM) and for the calculation of correlations.

Anatomical data on mossy fiber terminal fields (hilus, SP-MF, IIP-MF) were analyzed by ANOVA, with strain and sex as independent factors and size of total regio inferior as a covariate. This controls for possible differences in the size of mossy fiber terminal fields, which are due to general differences in brain or hippocampus size. As there were no sex differences in any of the morphometric measures and no sex × strain interactions, males and females were combined in descriptive statistics (mean and SEM) and for the calculation of correlations. For evaluation of a possible relationship between behavioral scores and morphometric measures (hilus, SP-MF, IIP-MF), residuals from linear regression on regio inferior size were correlated with behavioral scores (Pearson's product moment correlation). Regarding the open-field test, the mean scores of overall open-field activity and the proportion of central field entries were considered. With regard to the elevated plus-maze test, morphobehavioral correlations were calculated for the number of closed-arm entries, the proportion of open arm entries and the proportion of time spent in the open arms.

RESULTS

Open-Field Test

The results of the open-field test are shown in Figure 1. AB/Gat mice showed considerably higher overall exploratory activity (total number of field entries; Fig. 1a) than did CS/ag mice ($F_{1,17} = 15.04$, $P < 0.002$). There was a difference between the first and second test ($F_{1,17} = 32.23$, $P < 0.0001$). As a measure of anxiety, the tendency to explore the center was calculated as the proportion of central exploration with regard to total exploration. Central area exploration (Fig. 1b) was lower in CS/ag mice ($F_{1,17} = 38.44$, $P < 0.0001$).

Elevated Plus-Maze Test

With regard to the number of closed-arm entries as a measure of locomotor activity (Fig. 2a), there was no main effect of strain ($F_{1,17} = 2.98$, $P > 0.1$), but a significant strain × test interaction ($F_{1,17} = 6.16$, $P < 0.05$). Pairwise comparisons demonstrated a significant strain difference on the first ($P < 0.005$), but not on the second test ($P > 0.4$). The tendency to enter the open arms expressed as the proportion of open arm entries of total arm entries did not differ between the strains ($F_{1,17} = 1.05$, $P > 0.3$). There was a difference between the first and second test ($F_{1,17} = 11.34$, $P < 0.005$). In AB/Gat mice, the percentage was 47.1 ± 2.8 on the first and 50.7 ± 2.0 on the second test; in CS/ag mice, the respective values were 39.6 ± 5.4 and 48.6 ± 3.8. Similarly, the proportion of time spent in the open arms (Fig. 2b) did not differ between strains ($F_{1,17} = 0.10$, $P > 0.7$). Again, there was a difference between the first and second test ($F_{1,17} = 12.98$, $P < 0.005$).

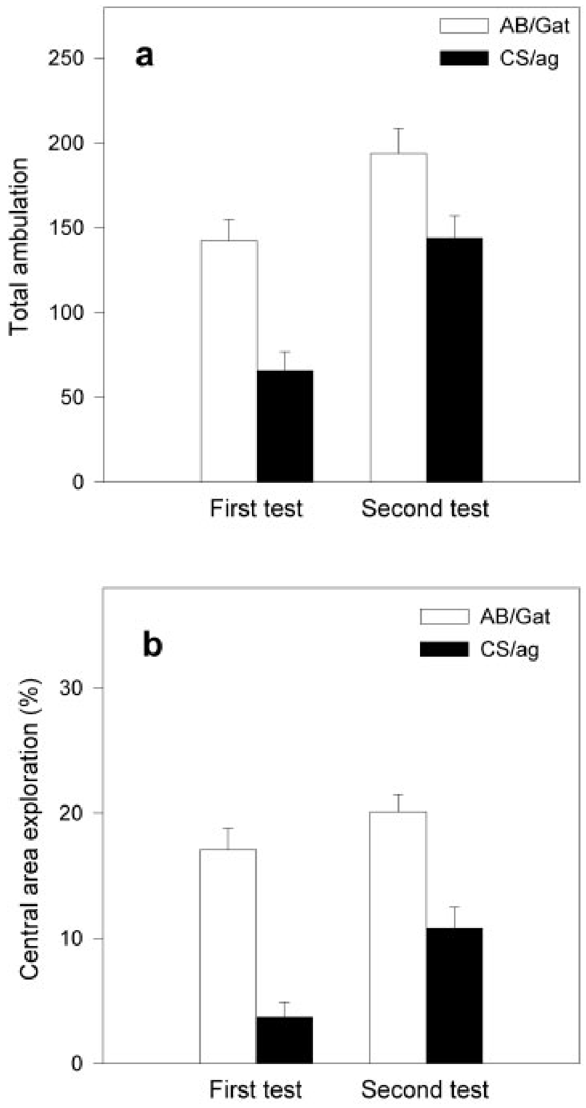

FIGURE 1. **Open-field exploration. Overall exploratory activity (a, top) as indicated by the total number of square entries/5 min was considerably higher in the AB/Gat strain (open bars) than in congenic mice bred for high aggressiveness (CS/ag) (filled bars) ($P < 0.005$). The tendency to explore the center of the open-field expressed as the proportion of central square entries (b, bottom) was also higher in the AB/Gat strain ($P < 0.0001$) indicating higher anxiety in CS/ag mice.**

Hippocampal Morphometry

The results from hippocampal morphometry are given in Table 1. Size of the total regio inferior (hilus + CA3) did not differ between the strains ($F_{1,17} = 0.26$, $P > 0.6$). Relative size of the hilus was larger in CS/ag mice ($F_{1,16} = 9.20$, $P < 0.01$). Size of the suprapyramidal mossy fiber terminal fields (SP-MF) did not differ between the strains ($F_{1,16} = 0.00$, $P > 0.95$). Size of intra- and infrapyramidal mossy fiber terminal fields (IIP-MF; Fig. 3a) was larger in CS/ag than in AB/Gat mice (+37%, $F_{1,16} = 5.88$, $P < 0.05$).

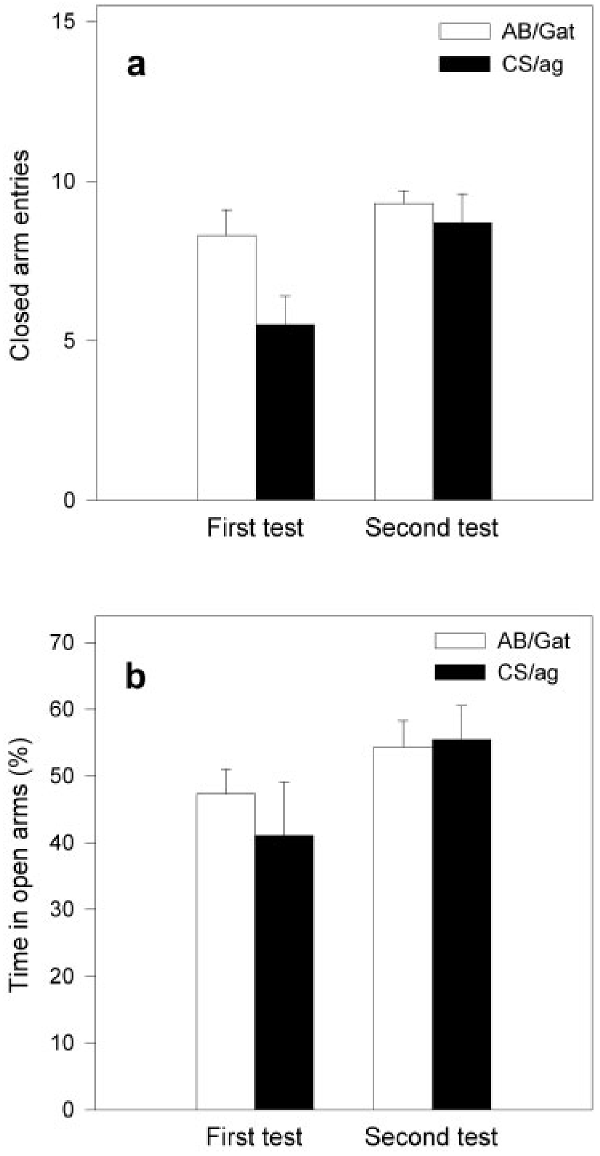

FIGURE 2. **Elevated plus-maze test. Overall exploratory activity (a, top) as indicated by the number of closed-arm entries/5 min was higher in the AB/Gat strain in the first ($P < 0.0005$), but not the second test ($P > 0.4$). The proportion of time spent on the open arms, a measure of anxiety, did not differ between the strains (b, bottom).**

Individual Morphobehavioral Correlations

For assessment of individual morphobehavioral correlations within each strain, the mean scores from both behavioral tests were correlated with residual size of the hilus, the SP-MF, and IIP-MF. For the open-field test, the total number of field entries and the proportion of central fields entered the analysis, for the elevated plus-maze test the number of closed-arm entries, the proportion of open entries and the proportion of time spent on the open arms were considered. Thus, within each strain and for each hippocampal measure two correlations were calculated regarding general exploratory activity and three correlations regarding anxiety (center exploration in the open-field, proportion of open arm entries and time on open arms in the plus-maze). In AB/Gat mice, there was a positive correlation between IIP-MF size and exploratory activity in the open-field (Fig. 3) as indicated by total field entries ($r = 0.80$, $df = 10$, $P < 0.01$). In CS/ag mice, this correlation was not significant ($r = -0.09$, $df = 9$, ns). Furthermore, there was a correlation between IIP-MF size and the proportion of time spent on open arms in AB/Gat mice ($r = 0.67$, $df = 10$, $P < 0.025$). There were no other significant correlations.

TABLE 1.

Results From Hippocampal Morphometry

Hippocampal subfield	Strain	
	AB/Gat	CS/ag
RI ($\mu^2 \times 10^3$)	674.4 ± 11.4	687.2 ± 22.0
Hilus (% of RI)	9.6 ± 0.2	11.0 ± 0.5*
SP-MF (% of RI)	9.1 ± 0.3	9.2 ± 0.2
IIP-MF (% of RI)	0.90 ± 0.07	1.24 ± 0.12*

CS/ag, congenic mice bred for high aggressiveness; RI, regio inferior; SP-MF, suprapyramidal mossy fiber; IIP-MF, intra- and infrapyramidal mossy fiber.
*Significant difference between strains, $P < 0.05$.

DISCUSSION

Our results can be summarized as follows. First, exploratory activity was higher in nonaggressive AB/Gat mice than in congenic

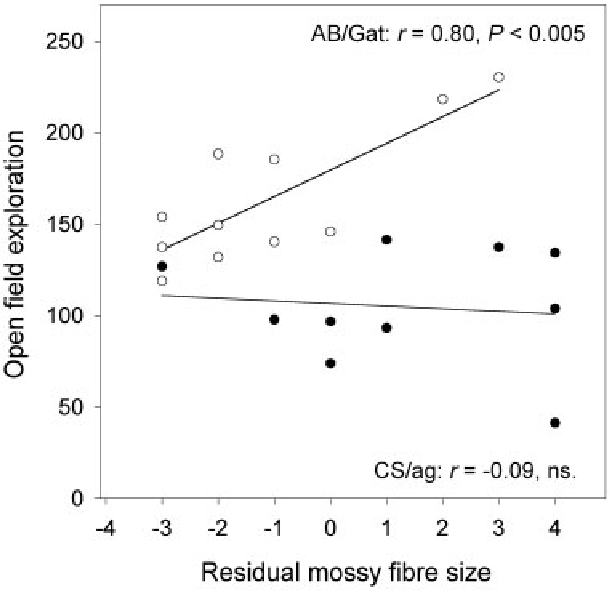

FIGURE 3. **Morphobehavioral correlations. In nonaggressive AB/Gat mice, but not in congenic mice bred for high aggressiveness (CS/ag), size of intra- and infrapyramidal mossy fiber terminal fields (IIP-MF) was correlated with exploratory activity. Calculations are based on the mean score from the first and second open-field test (y-axis) and residuals from linear regression of IIP-MF size on regio inferior size (x-axis).**

aggressive CS/ag mice. While this difference was profound in the open-field test, it was smaller and transient in the elevated plus-maze test. Second, anxiety levels were higher in aggressive CS/ag mice, indicated by a lower proportion of central area exploration in the open-field. Strain differences in the elevated plus-maze were in the same direction, but they were small and not significant. Third, there were two main findings of hippocampal morphometry, which both concerned the intra- and infrapyramidal mossy fiber terminal fields (IIP-MF): (1) the size of IIP-MF correlated strongly with exploratory activity and to a smaller degree with low anxiety in the AB/Gat strain, but not in the CS/ag strain; and (2) in the strain comparison, IIP-MF were smaller in nonaggressive AB/Gat mice. Overall, the results show that breeding for differences in aggressiveness between AB/Gat and CS/ag mice based on only one or very few genes has led to profound differences in exploratory behavior as well as to differences in hippocampal mossy fiber terminal fields. The pattern of differences was more complex, however, than predicted.

Regarding their ecological function, exploration and anxiety are related, in that the individual level of exploratory activity reflects a tradeoff between maximizing the use of environmental resources and reducing risks, e.g., from predators (Wall and Messier, 2000, Crusio, 2001). Since the tests used in the present study capitalize on this tradeoff (central area exploration vs "wall clinging" in the open-field, open vs closed-arm preference in the plus-maze), rather than evaluating one of the factors in isolation, it is possible that both the correlation of IIP-MF size with open-field exploration and of IIP-MF size with the proportion of time spent in open arms in the elevated plus-maze represent two sides of the same coin.

At the behavioral level, results are in full agreement with predictions from the "ecotype hypothesis" (Benus et al., 1991; Koolhaas et al., 2002), as aggressive CS/ag mice explored less than nonaggressive AB/Gat mice. This corroborates findings in LAL/SAL mice (Benus et al., 1991) and C57BL/6J/Nmg/Kun mice (Sluyter et al., 1999). It also confirms and extends findings from a pilot study on exploration in AB/Gat and CS/ag mice (Marashi et al., 1998). In addition to reduced exploration, CS/ag mice were more fearful than AB/Gat mice. Quantitatively, the link between aggressiveness and overall exploration appears to be stronger than the link between aggressiveness and fear or anxiety. Interestingly, Sluyter et al. (1999) found no significant difference between more aggressive C57BL/6J/Nmg and less aggressive C57BL/6J/Kun mice in a test for anxiety in a light/dark box (Sluyter et al., 1999). However, in this case, all measures showed a tendency toward higher anxiety in aggressive mice. Because the proportion of open arm entries and of time spent on open arms in the present study was close to 50%, one might ask whether aspects of the experimental environment, e.g., the width of the maze arms, might have contributed to behavioral scores typical for low anxiety levels. The results from other experiments with the same maze and exactly the same protocol, however, do not support this possibility. For example, in a recent study with four lines of mice derived from the C57/BL/6 and the 129Sv strain, the proportion of open arm entries was in the range from 5% in the most anxious line to 22% in the least anxious line (L. Lewejohann, H. Prior, N. Sachser, C. Prehn, P. Heiduschka, S. Thanos, U. Jordon, A.L. Vyssotski, M.G. Pleskacheva, H.-P. Lipp, H. Tiedge, B. Skryabin, J. Brosius, unpublished observation). Also, the presence of a correlation between the time spent on open arms and IIP-MF in AB/Gat mice showed that individual mice did differ in their level of anxiety.

Consistent with the predictions, larger IIP-MF were correlated with higher exploratory activity and lower anxiety within the AB/Gat strain. As no individual morphobehavioral correlations were found in the CS/ag strain, the question arises as to whether selection for aggressiveness could have interfered with the "normal" modulating role of the IIP-MP. Such a disruption of normal function might provide one possible explanation of why, contrary to our predictions and to earlier studies (Guillot et al., 1994; Sluyter et al., 1994, 1999), CS/ag mice had larger rather than smaller IIP-MF than AB/Gat mice. Although it has to be taken into account that both the AB/Gat and the CS/ag strain have fairly small IIP-MF, particularly when compared with the widely used C3H and C57/BL strains, and thus the possible range of variability is smaller than in other models of aggressiveness, the present findings suggest that the possible link between aggressiveness and mossy fiber size requires further study.

Hippocampal morphometry also demonstrated a strain difference in the hilus. We had no predictions, however, with regard to this hippocampal subfield, and earlier studies do not suggest a role of the hilus in aggressive behavior (e.g., Sluyter et al., 1994).

Taken together, our results confirm the "ecotype hypothesis" by showing that aggressive mice explored less than nonaggressive mice. In addition, findings indicated a higher level of fear in aggressive mice. A clear correlation with hippocampal connectivity, in particular the size of IIP-MF, was found only within the nonaggressive strain, and not in the strain bred for high aggressiveness. By contrast to earlier models, aggressive mice had comparatively larger IIP-MF. The results confirm that selection for aggressiveness affects hippocampal connectivity, but it is also shown that the role of variability in hippocampal structure for the modulation of aggressive behavior requires further clarification.

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