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Research report

Influence of paternal genotypes on F1 behaviors: Lessons from several mouse strains

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Abstract

F1 and F2 mouse hybrids derived from different parental strains are becoming a useful tool in behavioral research, underlining the importance of their in-depth behavioral phenotyping. 129S1/SvImJ (S1), C57BL/6 (B6), NMRI (N) and BALB/c (BC) mice are commonly used in behavioral neuroscience, demonstrating marked behavioral differences. Here, we assess behavioral phenotypes of male mice of S1 and several hybrid strains (S1B6, S1N, S1BC) in a battery of behavioral tests, including the open field, novel odor exposure, novelty-induced grooming, horizontal rod (Suok) and the elevated plus maze tests. In addition, we assessed aggression and social barbering in these strains. Overall, the substantial differences observed here between these strains allow us to determine the influence of different genetic backgrounds on mouse behaviors, and more fully understand how different strain-specific behaviors overlap in the F1 progeny. Our results imply complex interplay between parental genotypes in anxiety, activity, grooming, aggression and barbering of their F1 progeny, further confirming the utility of F1 hybrids in behavioral neurogenetics.

Keywords: Behavioral phenotypes; F1 hybrid mice; 129S1; BALB/c; NMRI; C57BL/6 strains; Paternal genotype

1. Introduction

The increased use of various mouse strains and genetically modified (transgenic or mutant) mice in the development of animal behavioral models [6,16–18,39,52] underlines the importance of our understanding of how different genotypes determine various behaviors [1–3,5,14,40,41,49,50,55]. Multiple behavioral tests enables a high-throughput mouse behavioral phenotyping, including an in-depth assessment of animal activity, emotionality, cognitive, sensory, and neurological functions [7,13–15,19,20,24,26,28,38,44,45,54].

C57, 129, BALB and NMRI strains are currently widely used in behavioral neuroscience research [2,3,12,14,34,40,49,58]. While they differ markedly in activity and emotionality (e.g. high activity: C57, NMRI, BALB; high anxiety: 129, BALB) [25–27], there are many other behavioral differences reported for these strains in the literature [1,22,42,45,47,56,57,59].

As hybrid mice derived from different parental genotypes are an useful tool in behavioral research [4,10,29,30], the growing use of F1 and F2 hybrids [18,34,43,46,53] implies the importance of their further in-depth ethological investigation. 129S1/SvImJ (S1), C57B/6J (B6), BALB/cJ (BC) and NMRI (N) mouse sub-strains are commonly used in behavioral neuroscience [3,23,25–30,34,52]. Numerous recent studies have performed their detailed comparative phenotypical analyses (Table 1), enabling the assessment of the impact of parental genotypes on the F1 behavioral domains.

The main aim of the present study was to examine how different paternal genotypes (S1, B6, BC and N) influence specific behaviors of F1 mice. The same maternal genotype (S1) was used to minimize potential epigenetic influences, such as known strain differences in mothering styles [11,16,17]. The following battery was used in this study: open field and elevated plus maze (activity and anxiety tests [16,20,48]), novelty-induced grooming test (anxiety and grooming test [25–27]), unfamiliar odor test (olfaction and anxiety test [9,27]), and horizontal rod Suok test (balancing and anxiety test [28]). Since mice

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Table 1
A brief summary of main behavioral differences between 129S1 (S1), C57Bl/6 (B6), BALB/c (BC) and NMRI (N) mouse strains

Functions, parameters	Strain ranking	References
Sensory		
Olfactory sensitivity	BC > B6, S1	[31]
Progressive hearing loss	S1, B6	[41]
Vestibular/motor coordination	N, B6 > S1 > BC	[15,28,32]
Anxiety		
Freezing responses	S1 ≫ N, BC, B6	[24]*
Novel food/odor neophobia	BC > B6, N, S1	[27,45]
Open field horizontal, vertical activity	N > BC, B6 > S1	[5,27,34,41]
Defecations, urinations	N, BC > S1, B6	[11,25,27,41]
Horizontal rod activity	N > BC > B6 > S1	[28,32]
Stress-evoked motorisensory deficits	S1, BC > N; BC > B6	[28,32]
Light–dark transitions	N ≫ BC > B6 > S1	[6,34]*
Time in light (aversive) part	N ≫ BC; B6 > S1	[6,34]*
Aggression		
Inter-male aggression	BC ≫ S1, B6 > N	[27,41]*
Barbering		
Occurrence	B6, N > S1 ≫ BC	[30,51]*
Overall severity	N > B6 > S1 ≫ BC	
Grooming		
Frequency in social interaction	Very low: S1	[23]
Frequency in open field	B6 > S1 ≈ N ≈ BC	[25–27]
Duration in open field	BC > N > S1; B6 > S1	[25–27]

* Also own unpublished open field, light–dark box or homecage observations.

often demonstrate marked strain differences in their aggression [16,41] and behavior-associated hair loss (barbering) [36,37,51], these behaviors were also assessed in the present study.

2. Materials and methods

2.1. Animals

Subjects were adult male S1 mice and F1 hybrid mice (S1BC, S1B6, S1N) bred and maintained in a virus/parasite-free facility (University of Tampere, Finland) under conditions of controlled temperature (22 ± 2 °C), humidity (60%), and a 12-h light, 12-h dark cycle. Lights were turned off at 18.00 h and on at 6.00 h. The animals (n = 7–8 in each group) were experimentally naïve at the beginning of the study, and housed 3–4 per cage, with food and water freely available. Aggression and hair barbering phenotypes were assessed in a separate group of adult male mice housed socially (6 cages, 3–4 mice per cage, n = 20 for each genotype) for 4 weeks.

2.2. Behavioral testing and apparatus

Behavioral testing was always conducted between 14.00 and 18.00 h. On the day of the experiments, animals were transported to the dimly lit room and left undisturbed for 1 h prior to testing. In all tests, the animals were observed by experienced investigators (intra-rater reliability >0.9, established prior to testing) unaware of genotypes, except in the case of S1BC mice (where coat color was lighter). The observers sat in front of (and 2 m away from) the testing boxes and scored mouse behaviors using specially designed registers. Between sessions, each apparatus was cleaned with 70% ethanol and swept by paper towels.

On the first testing day, the olfactory abilities and neophobic responses were assessed in the novel odor test. Each mouse was placed individually in the actimeter box (30 cm × 30 cm × 30 cm) with 5–6 red ants (*Formica rufa)* immobilized by a 1.5-cm scotch tape in the diagonally opposite corner. The latency (s) of finding the odor (formic acid), and the number and the duration (s) of approaches (<2 cm) were measured for 3 min. The average duration of a single sniffing episode (total time spent sniffing divided by the number of approaches) was also calculated for all genotypes. We also assessed vertical activity (the number of wall leanings, unsupported and total vertical rears) in this test, as additional indices of exploration.

One day later, the animals were exposed to the open field test (Plexiglas 50 cm × 50 cm × 50 cm box) divided into nine sectors by line drawing. Horizontal activity (sectors visited with four paws), defecation boli, urination episodes and vertical activity (wall leaning, unsupported vertical rears and total rears) were assessed in this test for 5 min.

Two days later, the mouse exploration and vestibular functions of mice were assessed on the horizontal rod Suok test, a 2-m aluminium bar 1.5 cm in diameter (fixed to a platform elevated 30 cm from the floor and divided into 10-cm sectors by line marking) [28]. The mice were placed in the middle of the bar (facing either end) and tested for 5 min. The latency (s) to leave the central zone (a virtual 20-cm zone around the placement point; 4-paw criterion), horizontal activity (sectors visited with 4 paws), the number of falls, defecation boli and urination episodes were measured in this test, as described previously.

Three days later, we subjected the mice to the grooming test. To evoke spontaneous novelty-induced grooming, the mice were placed individually in a clean unfamiliar glass cylinder (20 cm in diameter and 30 cm in height) for 5 min. The latency to start grooming (s), the number and total duration (s) of bouts and the average bout duration (total duration divided by the number of bouts) were assessed in this test. In addition, we analyzed preliminary grooming episodes (grooming-like forepaw movements not touching the body) and total vertical rears (as a conventional behavioral measure of vertical exploration).

The final test was the elevated plus maze, performed one week later. The maze was made from Plexiglas and consisted of two open arms (30 cm × 10 cm) and two enclosed arms (30 cm × 10 cm × 10 cm) extending from a common central region (10 cm × 10 cm), elevated to a height of 60 cm. In this test, each mouse was placed in the center of the apparatus, facing the open arm, and observed for 5 min. Conventional measures were the number of open-, closed-arm and total arm entries (4-paw criterion), vertical rears and head dips (looks down) from the open arms of the maze. In addition, the ratios of open:closed and open:total arm entries were calculated for each mouse group in this test.

2.3. Barbering and aggression analysis

Barbering phenotypes were assessed in adult male mice housed socially (3–4 animals per cage). Hair loss was recorded by an experienced observer. Each mouse was visually inspected on both the dorsal and ventral surfaces for at least 2 min. Hair loss was scored as barbering if the hair lesion was non-puritic, there was no scarring or scabbing around the lesion, and the animal was otherwise in good health and the fur (where present) was in good conditions [21]. For each genotype, we analyzed the number (%) of cages in which the barbering occurred, and the percentages of barbers and barbered animals (of total animals of each genotype). Barber animals were identified as the single intact mouse in the cage [30].

Inter-male aggression was assessed by recording % of animals with scars on the hind limbs, base of the tail and rear flanks [21] in the groups used to assess barbering. Each mouse was assessed individually for 2–4 min by the same experienced observer. All experimental procedures were conducted in accordance with the European legislation (86/609/EEC) and the guidelines of the National Institutes of Health. All animal experiments reported here were approved by the Ethical Committee of the Medical School of the University of Tampere.

2.4. Statistical analysis

All results are expressed as means ± S.E.M. To evaluate differences between genotypes, analysis of variance (one-way ANOVA; factor: genotype) was performed followed by the post hoc Tukey's test. A probability of less than 0.05 was considered statistically significant in all tests.

3. Results

Table 2 summarizes data obtained in these mice in a battery of behavioral tests. Overall, all four groups have unimpaired olfactory function, as assessed in the novel odor exposure test. The mice demonstrated similar latencies to find odor, the duration of sniffing and the number of approaches (Table 2), but showed significant genotype differences in grooming frequency and the average duration of a single contact. The S1BC mice spent significantly less time contacting the odor (compared to the S1N mice). In addition, there was a significant genotype effects on unsupported vertical rears (S1BC ≫ S1, S1N), with a similar (but not-significant) trend for the total number of rears but not wall leanings in this test.

Data on the mouse open field and Suok test behaviors are summarized in Table 2. Overall, there were significant genotype differences in the number of open filed wall leanings (S1N > S1B6), unsupported rears (S1BC > S1N; S1 > S1N) and defecation boli (S1BC > S1, S1B6). In contrast, horizontal, total vertical activity and urination scores did not differ significantly across the genotypes. In the Suok test, there was a similar (but non-significant) tendency to altered horizontal activity (S1BC > S1, S1N, S1B6), whereas the latency to leave the center and the number of falls were unaltered in all four genotypes.

In the novelty-induced grooming test (Table 2), there were significant genotype differences in the number and duration of bouts (S1 > S1B6), vertical activity (S1BC ≫ S1B6, S1N, S1) and the occurrence of pre-grooming episodes (seen only in S1BC). There were no significant genotype differences in the latency to start grooming and the average duration of a single bout in this test.

In the elevated plus maze, there were no strain effects for some anxiety-related measures (open arm entries, open:total entries ratio and head dips, Table 2), although mice demonstrated significant genotype differences for the number of closed, total arm entries and vertical rears (S1N > S1B6), as well as for open:closed entries ratio (S1BC > S1N, S1B6).

Table 2
Behavioral performance of 129S1 (S1) and F1 hybrid strains S1-BALB/c (S1BC), S1-NMRI (S1N) and S1-C57Bl/6J (S1B6) subjected to a battery of behavioral tests ($n = 7$–8 in each group)

Test and behaviors	S1BC	S1N	S1B6	S1	$F(3,29)$	P
Novel odor test						
Wall leaning	11 ± 2.1	13 ± 1.4	12 ± 1.5	7 ± 1.2		NS
Vertical rears	13 ± 4.8 ab	2.2 ± 0.9 a	4 ± 1.8	2 ± 1.0b	3.87	0.025
Total vertical rears	24 ± 6.2	15 ± 1.9	16 ± 3.3	9 ± 2.2		NS
Latency to approach (s)	35 ± 5.4	31 ± 5.7	62 ± 26.0	41 ± 6.1		NS
Number of approaches	6 ± 0.6	5 ± 0.8	5 ± 1.2	5 ± 1.1		NS
Duration of investigation (s)	8 ± 1.0	14 ± 1.6	15 ± 3.2	12 ± 2.9		NS
Single contact duration (s)	1.4 ± 0.1 a	3 ± 0.3 a	2.3 ± 0.5	2.3 ± 0.3	3.56	0.033
Open field test						
Horizontal activity	76 ± 3.9	79 ± 7.3	63 ± 6.9	84 ± 10.6		NS
Wall leaning	17 ± 3.1	28 ± 4.4 a	12 ± 1.3 a	22 ± 4.4	3.70	0.025
Vertical rears	27 ± 6.3 ab	6 ± 1.5 a	11 ± 2.5	18 ± 3.3 b	5.13	0.007
Total vertical activity	44 ± 8.5	34 ± 5.3	23 ± 3.2	40 ± 6.9		NS
Defecation boli	5 ± 1.1 ab	3.1 ± 0.9	0.6 ± 0.2 a	1.7 ± 0.8 b	5.20	0.006
Urination	0.4 ± 0.3	0 ± 0	0 ± 0	0.1 ± 0.1		NS
Suok test						
Horizontal activity	75 ± 22.2	21 ± 14.0	14 ± 8.5	26 ± 17.9		NS
Latency to leave center (s)	96 ± 51.1	197 ± 53.0	210 ± 54.1	244 ± 40.6		NS
Falls from the rod	0.3 ± 0.3	0.6 ± 0.2	0.4 ± 0.3	0.7 ± 0.3		NS
Grooming test						
Latency to start (s)	59 ± 15.2	77 ± 21.2	66 ± 27.0	48 ± 14.7		NS
Grooming bouts	5 ± 0.3	4 ± 0.8	3 ± 0.4 a	5.5 ± 0.8 a	3.18	0.041
Grooming duration (s)	16 ± 1.9	15 ± 3.0	10 ± 1.5 a	22 ± 2.4 a	4.26	0.014
Average bout duration (s)	3.5 ± 0.4	4 ± 0.4	4 ± 0.5	4.5 ± 0.5		NS
Pre-grooming episodes	3 ± 1.3 abc	0 ± 0 a	0 ± 0 b	0 ± 0 c	4.83	0.0083
Total vertical rears	30 ± 2.4 abc	13 ± 2.0 a	12 ± 1.4 b	14 ± 2.1 c	16.95	0.0001
Elevated plus maze						
Open arm entries	1.5 ± 0.5	2.7 ± 1.0	0.9 ± 0.5	2.0 ± 1.2		NS
Closed arm entries	8 ± 1.7	11 ± 1.5 a	5 ± 0.6 a	6 ± 1.4	3.40	0.033
Total arm entries	9.5 ± 2.0	13.7 ± 2.0 a	5.9 ± 0.9 a	8 ± 2.5	2.29	0.036
Open:closed entries ratio	0.67 ± 0.06 ab	0.24 ± 0.1 b	0.15 ± 0.10 a	0.33 ± 0.20	3.21	0.039
Open:total entries ratio	0.16 ± 0.05	0.19 ± 0.07	0.18 ± 0.08	0.25 ± 0.15		NS
Vertical rears	17 ± 2.0	22 ± 3.3 a	9 ± 1.6 a	11 ± 3.8	4.79	0.009
Head dips	12 ± 2.0	19 ± 3.3	8 ± 2.0	13 ± 3.3		NS

Data are expressed as mean ± S.E.M.; F values are given for significant ANOVA data. Strain scores sharing common letters are statistically different (Tukey's post hoc test for significant ANOVA data).

Table 3
Aggression and barbering profiles in 129S1 (S1) and F1 hybrid strains S1-BALB/c (S1BC), S1-NMRI (S1N) and S1-C57Bl/6J (S1B6)

Behaviors	S1BC	S1N	S1B6	S1	$F(3,23)$	P
Barbering activity						
% Cages with barbering	0 ± 0 ab	100 ± 0 a	83 ± 17 b	50 ± 22	10.04	<0.0003
% Barbered animals	0 ± 0 abc	70 ± 0 a	75 ± 10 b	85 ± 8 c	36.78	<0.0001
% Barbers	0 ± 0 ab	30 ± 0 abc	25 ± 10 b	15 ± 8 c	48.40	<0.00001
Aggressiveness						
% Cages with scarring	100 ± 0 a	0 ± 0 a	67 ± 21	50 ± 22	7.52	<0.0015
% Animals with scars	100 ± 0 ab	0 ± 0 acd	45 ± 11 bc	40 ± 11 bcd	27.93	<0.00001

Data are expressed as mean ± S.E.M. for six cages ($n = 20$) for each genotype. Strains sharing common letters differ statistically (Tukey's post hoc test for significant ANOVA data).

Finally, as can be seen in Table 3, there were marked genotype differences in barbering and aggressive behaviors, with S1N showing the highest barbering activity and the lowest aggression. In most cases, barbering targeted whiskers, face, head and body, and in all cages with barbering there was a single dominant animal whose fur and whiskers remained fully intact (data not shown). In a striking contrast, the S1BC mice displayed the highest aggression but no barbering activity.

4. Discussion

Performing comparative behavioral analyses of S1, S1BC, S1B6 and S1N mice, we first noted that these genotypes display generally unaltered open field horizontal activity (Table 2), differing from the reported ranking of their parental strain (Table 1). This suggests that activity levels in F1 mice may be determined by both parental strains, and that "inactive" S1 maternal genotype (due to floor effect) may contribute to reduced F1 differences in horizontal exploration of novel arenas. In contrast to horizontal activity, the mouse open field vertical activity differed across the F1 genotypes (Table 2), and was consistently higher in the S1BC (rears) and S1N (wall leanings) groups. Paralleling these data, vertical activity differed across strains in the elevated plus maze, with S1BC and S1N mice again showing more vertical rears than did S1 and S1B6 mice (Table 2). Collectively, these data suggest that horizontal and vertical exploration represents two distinct behavioral domains, differentially (and independently) controlled by paternal genotypes.

As all four parental genotypes have been reported to possess different baseline levels of anxiety (BC, S1 ≫ B6, N; Table 1), it was possible to expect that behavioral phenotypes of F1 hybrids in the present study would resemble parental anxiety phenotypes (S1BC, S1 ≫ S1B6, S1N). However, our results do not support this hypothesis, since the genotype ranking for anxiety was S1B6, S1 ≫ S1N, S1BC, as assessed by altered vertical exploration in the open field (Table 2). The elevated plus maze test produced similar results, with S1BC genotype showing less anxiety in some measures (higher open:closed entries ratio), and S1N mice showing more vertical exploration. The number of closed and total arm entries (reflecting both exploration and activity domains) also tended to differ across the genotypes (S1N > S1B6, S1). Taken together, these data support the notion that anxiety is a behavioral trait with complex polygenic nature in F1 mice, and not a mere combination of "anxiety" and "activity" profiles of the respective parental strains (see similar results in [56] showing close behavioral profiles in F1 129S2-B6 and anxious inactive 129S2 mice).

Interestingly, grooming activity was higher in S1 than S1B6 and other F1 mice (Table 1), generally inconsistent with the strain ranking previously reported for their parental genotypes: BC, N, B6 ≫ S1 [25,27]. This suggests that grooming may represent a behavioral domain sensitive to both activity and anxiety levels, and that F1 mouse grooming is the result of a complex interplay between these domains. Specific "preliminary" grooming, previously reported for BC mice [27], was also observed the S1BC group (Table 2). This observation suggests strong influences of the BC genotype on this behavior, and represents an example of how some rare behaviors (specific for the parental strains) can be inherited in F1 strains.

Although all four genotypes differed markedly in their aggressiveness (S1BC ≫ S1, S1B6 > S1N; Table 3), we noted that their ranking coincides with that of the paternal strains, previously reported in the literature (Table 1). Likewise, there were robust genotype differences in the mouse barbering behavior (S1N, S1B6 > S1 ≫ S1BC; Table 3), generally consistent with earlier reports on barbering phenotypes of their parental strains, including active barbering in B6 and N, and absent barbering in BC mice [30,51]. Taken together, these observations support the idea that strain aggression negatively correlates with barbering activity [30] (Tables 1 and 3), and that BC and N paternal genotypes strongly (although reciprocally) regulate both domains in their F1 progeny.

Another potentially important factor to consider here is sensorimotor abilities, as their disturbances are known to influence mouse behaviors [13,16]. All strains tested here (Table 2) have unimpaired olfaction, as assessed in the novel odor exposure test, and there were no differences in the Suok test balancing, implying relatively normal vestibular functions and motor coordination in all these mice. Collectively, these results indicate that sensorimotor deficits are unlikely to contribute to behavioral differences reported here.

Analysing defecation data in this study, we noted that BC and N parental strains are "high defecators", compared to B6 and S1 mice (Table 1). Negating simplistic views of defecation as an emotionality index, this measure appears to represent a complex trait which may (BC mice) or may not (N mice) reflect the strain

anxiety. In our study, we observed predictably high open field defecation activity in S1BC and S1N groups, and low defecation levels in S1 and S1B6 mice. The ethological interpretation of this measure is rather complex, and may involve several interplaying factors (such as emotionality- and genotype-related defecation activity). In contrast, urination scores did not differ significantly in our study, suggesting a relative weakness of this index in behavioral phenotyping of F1 mice.

In general, there were several limitations of the present study. Given the rich literature on behavioral profiles of parental strains consistently reported in various studies (Table 1), they were not included in this study. However, in the future experiments it may be interesting to compare both parental strains and their F1 progeny, also studying F1 mice produced by crosses with maternal strains beyond S1. Second, in order to obtain more information on the genetic contribution of the parental strains, further cross-breeding experiments (e.g. a diallel cross [18]) may be necessary. Collectively, this may help unravel further the underlying genetics of quantitative behavioral traits in these animals. Future experiments focusing on these and other F1 domains (e.g. depression-related, cognitive, parental, social, and sexual behaviors) are needed, also using other paradigms, different types of stressors, and test batteries.

Moreover, as this study was performed in male mice, and given known gender-specific strain differences in mouse behaviors [56], it will be interesting to assess behaviors of female F1 hybrid mice, also focusing on potential sex-linked traits. For example, it is possible that behavioral genetics and patterns of barbering or aggression in female F1 mice will differ from that of F1 males used here. It is also possible that some strain-specific behaviors (e.g. aggression in S1BC mice) and their interaction with environmental factors (e.g. social housing and laboratory environment [33]) may indirectly influence other domains assessed here, such as anxiety and activity. From this point of view, F1 mice may be a useful tool to assess both gene–gene and gene–environment interactions. Likewise, the role of epigenetic factors (such as maternal behavior [8]) merits in-depth studies in F1 mice, using other maternal strains and cross-fostering.

In conclusion, our study shows a substantial domain- and strain-specific contribution of paternal genotypes on behaviors of their F1 progeny. Several behaviors traits (e.g. aggression and barbering) were strongly influenced by paternal backgrounds in our F1 mice, whereas some other F1 behaviors (such as activity, anxiety, and grooming) appeared to be the result of a complex interplay between both parental genotypes (rather than a mere combination of their behavioral profiles). Overall, these results show complex interactions between parental genotypes and between different domains in F1 hybrid mouse behavior, further confirming the utility of F1 mice as a rich source of information [35,46] on behavioral genetics.

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