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Behavioural Brain Research 160 (2005) 1–10
BEHAVIOURAL BRAIN RESEARCH
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Research report

Contrasting grooming phenotypes in three mouse strains markedly different in anxiety and activity (129S1, BALB/c and NMRI)

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Received 9 September 2004; received in revised form 5 November 2004; accepted 11 November 2004
Available online 16 December 2004

Abstract

129S1/SvImJ (129S1), NMRI and BALB/c mice are widely used in behavioural research, demonstrating marked strain differences in their behavioural phenotypes. Grooming is a complex and essential ritual in the rodent behavioural repertoire with a general cephalocaudal progression (forepaws–nose–face–body–legs–tail and genitals). Various stressors as well as genetic manipulations have been reported to alter mouse grooming and its patterning, underlying the importance of analysis of grooming behaviours. Although strain differences between these mice have been assessed in many studies, no comparative analyses of their grooming have been performed. Here we show strain differences in spontaneous (novelty-induced) grooming between 129S1, NMRI and BALB/c mice. Overall, 129S1 mice demonstrated lower grooming activity and impaired microstructure (more interrupted bouts and incorrect transitions contrary to the cephalocaudal rule), accompanied by lower vertical exploration. In contrast, BALB/c and NMRI mice showed high vertical activity and unimpaired grooming microstructure, also exhibiting different grooming levels (BALB/c > NMRI). Our study suggests that contrasting grooming phenotypes in these mice may not be due to the strain differences in their sensory abilities, general activity levels, brain anatomy or aggressiveness, but rather reflect a complex interplay between anxiety, motor and displacement activity in these strains (hypoactive anxious phenotype in 129S1 mice, active anxious phenotype in BALB/c and non-anxious high displacement phenotype in NMRI mice). We suggest that ethological analysis of mouse grooming, such as that reported here, may be a useful tool in neurobehavioural research.

Keywords: Grooming behaviours; 129S1/SvImJ mice; BALB/c mice; NMRI mice; Behavioural phenotype; Grooming microstructure

1. Introduction

129S1/SvImJ (129S1), BALB/c and NMRI mouse stains are commonly used in neurobehavioural research [1,2,6–10,23,32,33,46,48]. These mice are genetically different and demonstrate marked strain differences in various behavioural tests (Table 1). For example, NMRI mice display low anxiety and high activity [2,17,45], while BALB/c and 129S1 mice are anxious, have abnormal corpus callosum (CC) [10,17,27,47,48] and markedly differ in their motor activity (high: BALB/c; low: 129S1) [5,9,18,48]. BALB/c mice are aggressive, neophobic and very sensitive to open light aversive stimuli, but show moderate anxiety in the elevated plus maze [1,10,17,30], while anxious 129S1 mice often display freezing behavioural response to aversive stimuli [18,48]. NMRI mice are good learners [45], BALB/c mice show impaired spatial and shock avoidance learning [7,30] (but [45]), while 129S1 mouse performance in memory tests is limited by locomotor factors, and varies widely depending on the nature of the task [7,48]. There are many other behavioural strain differences reported for these three strains in the literature (Table 1), underlining the importance of their further in-depth comparative ethological analysis.

Notably, although grooming is frequently displayed by mice, there have been no studies comparing grooming activity in these mouse strains. Moreover, there are no grooming data in the extensive Mouse Phenome Database [30],

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doi:10.1016/j.bbr.2004.11.010

Table 1
A brief summary of some neurobehavioural strain differences between 129S1, BALB/c and NMRI mice

Functions tested	Parameters	Strains	Reference
Grooming	Frequency in social interaction test	Very low: 129S1	[18]
	Duration in actimeter and open field	High: BALB/c	[37]
	Activity, sequencing	Low, impaired: 129S1	[19,20]
	Social grooming	Low: BALB/c	[30]
Brain anatomy	Abnormal corpus callosum	129S1, BALB/c	[27,47,48]
	Retarded hippocampal commissure	129S1, BALB/c	[27,47]
Sensory abilities	Olfactory sensitivity (urine)	BALB/c > 129S1	[23]
	Progressive hearing loss	129S1, BALB/c	[48,49,50]
	Visual impairment	BALB/c	[7] but [35]
Learning	Good performance in Morris maze	BALB/c	[45]
	Impaired spatial learning	BALB/c	[7]
	Performance varies widely depending on the nature of the task	129S1	[7,48]
	Conditioning altered context activity	BALB/c > 129S1	[5]
	Contexual memory (day 2 response)	129S1 > BALB/c	[5]
	Y-maze habituation next day	High: 129S1	[48]
	Open field habituation next day	High: 129S1	[48]
Anxiety and activity	Free exploration neophobia	BALB/c > NMRI	[2]
	Free exploration horizontal activity	NMRI ≈ BALB/c	[2]
	Free exploration vertical activity	NMRI ≫ BALB/c	[2]
	Cat and cat feces-induced vertical activity drop	NMRI > BALB/c	[2]
	Freezing response	Common: 129S1	[18][a]
	Actimeter horizontal activity	BALB/c > 129S1	[5]
	Horizontal activity after saline	BALB/c > 129S1	[30]
	Defensive burying	Very low: BALB/c	[51]
	Open field distance travelled	NMR ≫ BALB/c > 129S1	[26]
	Open field vertical activity	NMRI ≫ BALB/c ≫ 129S1	[26]
	Open field time in center	NMRI > BALB/c	[26]
	Open field defecations and urinations	NMRI > BALB/c	[26,30][a]
	Stress-induced hyperthermia	NMRI ≈ BALB/c	[32]
	EPM % open entries	NMRI ≈ BALB/c	[17]
	EPM open, closed entries	NMRI ≈ BALB/c	[17,51]
	EPM total entries	NMRI > BALB/c	[17]
	EPM defecations, urinations	BALB/c ≫ NMRI	[51]
	Light-dark transitions	NMRI ≫ BALB/c	[17,26]
	Light-dark time in light	NMRI ≫ BALB/c	[17,26]
Startle	Fear-potentiated response	NMRI ≈ BALB/c	[51]
	Defecations, urinations	NMRI ≈ BALB/c	[51]
	Accoustic startle response	NMRI ≫ BALB/c ≫ 129S1	[30,41,51]
Sensory gating	Pre-pulse inhibition response	BALB/c > 129S1	[30,41]
Depressiveness	Frequency of passive floating	High: 129S1, BALB/c	[35,41]
	Tail suspension immobility	BALB/c > NMRI	[26]
Diazepam sensitivity (0.5–3 mg/kg)	Light-dark test transitions	BALB/c ≫ NMRI	[17]
	Light-dark test time in light	BALB/c ≫ NMRI	[17]
	EPM % open entries	BALB/c ≫ NMRI	[17]
Aggression	Inter-male fight	BALB/c > 129S1 > NMRI	[30][b]
Strength	Maximal peak tension	BALB > 129S1	[30]
Nociception	Latency to respond (hot plate)	BALB/c > 129S1	[30]
	Hind-leg response (hot plate)	129S1 > BALB/c	[30]
Other behaviours	Tail rattling activity	High: BALB/c	[30][a]
	Overall wildness	129S1 > BALB/c> NMRI	[b]
	Homecage burying activity	129S1>BALB/c»NMRI	[b]
	Male copulatory behaviour	Low: BALB/c	[10]

EPM: elevated plus maze test.
[a] Own unpublished open field data.
[b] Own unpublished homepage observations.

indicating that this behaviour has still merited little scrutiny in behavioural genetics [19]. However, there are several important reasons to focus on grooming phenotypes in mice. First, grooming is an ancient innate behaviour that is represented across most animal species, including mammals [12,41]. Second, grooming is a particularly important part of rodent behavioural repertoire, representing a substantial portion of their waking behaviour [3,4,12,43]. Third, rodent grooming is a rich source of behavioural and biological information [12,36] and a complex, hierarchically organised ritual with robust cephalocaudal progression (forepaw licking, nose and face wash, head wash, body wash and fur licking, hind-leg licking, tail/genitals licking and wash) [3,4,11,19]. Grooming may serve a variety of adaptive functions, including body care, dearousal, stress reduction, social communication, thermoregulation, pain relief and self-stimulation [12,13,31,36,41]. Many neuromediators and hormones as well as multiple regions in the brain appear to be involved in the regulation of both normal and pathological grooming [3,4,11,29,41,44]. In addition, grooming and its patterning are very sensitive to various exogenous and endogenous factors, including stress, psychotropic drugs and genetic manipulations [19,20,21,22,29]. Since various mutant mice often display altered grooming phenotypes [16,20,42], ethological dissection of the strain versus mutation-induced effects on grooming may be a necessary task. Therefore, a complex analysis of mouse grooming represents an important part of behavioural neurogenetics.

Since 129S1, BALB/c and NMRI mice are widely used in behavioural research, a better knowledge of all behavioural profiles of these strains is necessary to distinguish between the effect in question versus strain-dependent behavioural phenotypes. Thus, the goal of the present study was to define behavioural differences in grooming activity and its organisation between 129S1, BALB/c and NMRI mice. For this, we subjected mice to novelty stress in a confined observation box, known to activate grooming behaviour in rodents [13,20,29,33], and assessed their grooming using the approach based on differential registration of its patterns and quantifying both the amount of activity and the sequential domain of this behaviour [20]. Here we show that 129S1, BALB/c and NMRI mice demonstrate contrasting grooming phenotypes, including both quantitative (activity) and qualitative (behavioural patterning) measures of grooming.

2. Materials and methods

2.1. Animals

Adult male 129S1, BALB/c and NMRI mice (25–30 g, $n = 10$ in each group; University of Tampere, Finland) aged 20–24 weeks were maintained in a virus/parasite-free facility under conditions of controlled temperature ($22 \pm 2\,^{\circ}C$), humidity (60%), and exposed to a 12 h light, 12 h dark cycle. Lights were turned off at 18.00 h and on at 6.00 h. The animals were experimentally naïve and housed 3–4 per cage, with food and water freely available (except food finding experiments, when in order to increase hunger, animals were food deprived for 14 h prior to testing).

2.2. General procedure and non-grooming tests

Behavioural testing was always conducted between 14.00 and 18.00 h. The following battery of tests was used in this study: actimeter (novelty-induced grooming test); novel sphere test (visual and motor coordination test); vertical screen and horizontal rod tests (motor and vestibular function tests); food and fecal boli finding tests (olfactory function tests). On the first day of the experiments, animals were transported to the dimly lit room and left undisturbed for 3 h prior to testing. To induce spontaneous novelty-induced grooming, the mice were placed individually in a clean unfamiliar plastic actimeter box (30 cm × 30 × 30 cm) for 10 min. In all experiments, the animals were observed by an experienced investigator (inter-rater reliability > 0.9). During the testing sessions, the experimenter remained standing in front of (and 2 m away from) the testing boxes scoring mouse grooming and non-grooming behaviours using a specially designed register.

One week later, the visual sensory abilities and motor coordination of the mice were analysed in a novel object-finding test for 5 min. The animals were placed in a plastic box (50 cm × 50 cm × 50 cm) and after a 5 min acclimation time, the novel object (5 cm metal sphere) was introduced in the diagonally opposite corner of the box. The latency (s) of finding the sphere was used as a measure of the animals' visual abilities. The number of approaches (<2 cm) was used as a measure of animal exploratory activity, and the number of physical contacts (the number of times an animal stood on its hind-legs with forepaws placed on the sphere) was used as a measure of animal motor coordination/manipulatory activity. One week later, the motor performance of mice was assessed in the vertical screen test for 5 min. Each mouse was placed on the centre of the screen consisting of a plastic frame (30 cm high and 15 cm wide, with 10 cm top and side walls) covered by a plastic net (2 mm mesh) elevated to a height of 60 cm from the floor. The screen was turned immediately to the vertical position with the mouse facing the upper end, and the retention time (the latency to fall off from the screen, s) was measured. To avoid any harm to the animals caused by falling from the screen, a thick cloth was placed underneath it. In addition, emotional reactivity was assessed by the number of defecation boli deposited, the latency to the first bolus (s) and the number of urination episodes. One day later, the vestibular functions of mice were assessed on the horizontal rod balancing test, a 1 m wooden bar 1 cm in diameter fixed to a platform elevated 30 cm from the floor. The mice were tested for 5 min and the latency to fall (s) was measured. We also measured the latency to leave the central zone (a virtual 20 cm zone around the placement point; four-paw criterion) as an index of locomotor activity. In addition, emotional reactivity was assessed by the number of defecation boli deposited, the latency to the first bolus (s) and the number of urination episodes.

One week later, the olfactory abilities of food-deprived mice were tested in the food finding test for 2 min. The animals were placed in the actimeter box and the food (cheese, 2 cm × 1 cm × 0.5 cm) was introduced in the diagonally opposite corner of the box. The latency of finding food (s) and the number and the duration (s) of contacts with food (including sniffing and physical contacts: touching, eating, biting, licking), were used as

measures of olfactory functions. In addition, the average duration of a single contact (s; calculated as total time spent contacting the food divided by the number of contacts) and the percentages of physical contacts and time spent in physical contacts (of total number and duration of contacts with food) were calculated for all three groups. One day later, the olfactory abilities of mice were tested in the fecal boli finding test for 1 min. The animals were placed in the actimeter box and five fresh fecal boli obtained from the same unfamiliar male mouse of a neutral (C57BL/6) strain were introduced in the diagonally opposite corner of the box. The latency (s) of finding the boli, the number, the duration (s) of sniffing episodes and the average duration of a single contact (s; calculated as total time spent sniffing divided by the number of contacts) were used as measures of olfactory functions in mice. We also measured vertical activity (the number of vertical rears) during these two tests. In addition, emotional reactivity of mice was assessed by the number of defecation boli deposited and the number of urination episodes in these tests. In all these tests, the latency measures were reckoned as total observation time (60, 120, 300 or 600 s, depending on the test) in the mice not showing the respective behaviours. Between subjects, the apparatus was thoroughly cleaned (wet and dry cloths). 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 University of Tampere.

2.3. Behavioural analysis of novelty-induced behaviours in the actimeter test

2.3.1. Non-grooming measures

Vegetative behaviours (the number of fecal boli deposited and the number of urination spots) were scored as the conventional emotionality indices in the present study. We also assessed general vertical activity (vertical rears; the number of times an animal stood erect on its hind-legs with forepaws in the air or against the wall) and the latency to the first vertical rear (s)—as conventional behavioural measures of exploratory motor activity. Additional non-grooming behavioural parameters were displacement activity, including the number of jumping, tail-rattling episodes and manipulatory activity directed at the fecal boli (touching, pushing, lifting with the forepaws, eating and relocation by mouth).

2.3.2. Grooming activity measures

Four ethological measures of grooming activity were evaluated in all these tests: latency to start grooming (s); frequency (the number of grooming bouts); total time (s) spent grooming, and average duration of a single grooming bout (s) calculated as total time spent grooming divided by the number of bouts.

2.3.3. Analysis of grooming behavioural microstructure

The following patterns of grooming activity were recorded for each individual bout, as described earlier [20]: forepaw licking, nose/face grooming (strokes along the snout), head washing (semicircular movements over the top of the head and behind ears), body grooming/scratching (body fur licking and scratching the body with the hind paws), hind-leg licking and tail/genitals grooming (licking of the genital area and tail). The following scaling system was used in the present study: no grooming (0), forepaw licking (1), nose/face wash (2), head wash (3), body grooming (4), hind-leg licking (5), and tail/genitals grooming (6); see [19,20] for details. Grooming behavioural microstructure was assessed using the grooming analysis algorithm [20], and the percentages of interrupted bouts and incorrect transitions were calculated for all mouse stains. A grooming bout was considered "interrupted" if at least one interruption was recorded within its stages; interruptions >6 s determined separate grooming bouts. Transition between grooming patterns were analysed using the transition matrix [20]: correct transitions adhered to the cephalocaudal progression as follows: (0–1), (1–2), (2–3), (3–4), (4–5), (5–6), and (6–0); incorrect transitions included all other possible transitions. In addition, the occurrence of atypical "vertical grooming" (the number and duration of episodes when an animal self-groomed standing *erect*/*semi-erect* on its hind-legs) was analysed in this study. This displacement behaviour included forepaw grooming bouts frequently seen in NMRI mice following vertical rears. Notably, this specific grooming pattern differed markedly from more common "non-vertical" forepaw grooming (displayed by all mouse strains and characterised by a typical *flexed* body position).

2.4. Data analysis

All results are expressed as means ± S.E.M. Behavioural data were analysed by Mann–Whitney *U*-test for independent samples. To evaluate differences between strains in the actimeter test, analysis of variance (one-way ANOVA) was performed with the post-hoc *U*-test. A probability of less than 0.05 was considered statistically significant in all tests.

3. Results

3.1. Non-grooming behaviours

Table 2 summarizes non-grooming behavioural data obtained in NMRI, BALB/c and 129S1 mice in a battery of tests. Overall, all three strains demonstrated unimpaired visual abilities, as assessed in the novel object finding test. The latency to find sphere, the number of approaches and contacts, and the duration of contacts were unaltered in all these mice. In contrast, vertical activity was significantly higher in the NMRI versus 129S1 mice (23 ± 4 versus 11 ± 2, $P < 0.05$, *U*-test). The BALB/c group showed intermediate level of vertical activity in this test (16 ± 2), although this did not reach statistical significance. Urination and defecation scores were similar in all mouse strains subjected to this test (Table 2).

Table 2 shows that all three groups have unimpaired olfactory function, as assessed in the food and fecal boli finding tests. The mice demonstrated similar latencies to find cheese and fecal boli, also showing unaltered number of contacts and average duration of a single contact in both tests (Table 2). However, the 129S1 mice spent significantly more time contacting the cheese (but not the fecal boli) compared to both NMRI and BALB/c groups (22 ± 4 s versus 10 ± 2 s and 9 ± 2 s, $P < 0.05$, *U*-test; respectively). Correspondingly, the 129S1 group displayed higher percentages of physical contacts and time spent touching, licking or biting food, compared to both NMRI and BALB/c mice. Unlike other strains, neophobic BALB/c mice showed no physical contacts with

Table 2
Non-grooming behaviours in NMRI, BALB/c and 129S1 mice subjected to a battery of behavioural tests

Tests and behaviours	129S1	BALB/c	NMRI
Novel object finding test (5 min)			
Latency to find sphere (s)	26 ± 4	20 ± 4	17 ± 3
Number of approaches	5 ± 1	5 ± 1	6 ± 1
Number of physical contacts (touching)	4 ± 0.5	6 ± 1	7 ± 1
Total duration of contacts (s)	16 ± 3	23 ± 4	24 ± 5
Average duration of a contact (s)	4 ± 1	3.8 ± 1	3.4 ± 1
Vertical activity	11 ± 2 a	16 ± 2	23 ± 4 a
Defecation boli deposited	5 ± 1	7 ± 2	6 ± 1
Urination	0.2 ± 0.1	0.4 ± 0.1	0.4 ± 0.1
Food finding test (2 min)			
Latency to find cheese (s)	16 ± 3	22 ± 4	18 ± 4
Number of contacts with cheese	5 ± 1	3.5 ± 0.5	4 ± 0.6
Total duration of contacts (s)	22 ± 4 ab	9 ± 2 a	10 ± 2b
Average duration of a single contact (s)	4.4 ± 0.8	2.7 ± 0.6	2.4 ± 0.5
% physical contacts (touching, biting, licking)	48 ± 7 a	0 ab	30 ± 5 b
% time in physical contacts	57 ± 8 a	0 ab	42 ± 5 a
Vertical activity	8 ± 1 a	7 ± 1 b	13 ± 1.5 ab
Defecation boli deposited	4 ± 0.5	4 ± 1	3 ± 0.5
Urination	0.2 ± 0.1	0.4 ± 0.1	0
Defecation boli finding test (1 min)			
Latency to find defecation boli (s)	11 ± 2	19 ± 4	10 ± 4
Number of contacts with boli	5 ± 0.5	6 ± 1	5.5 ± 1
Total duration of contacts (s)	11 ± 2	9 ± 1.5	11 ± 2
Average duration of a contact (s)	2.3 ± 0.4	1.5 ± 0.5	2 ± 0.4
Vertical activity	6 ± 1 a	6 ± 0.5 b	8 ± 0.5 ab
Defecation boli deposited	1.2 ± 0.2 a	2.8 ± 0.3 ab	0.8 ± 0.1 b
Urination	0.2 ± 0.1	0.4 ± 0.1	0.2 ± 0.1
Vertical screen retention test (5 min)			
Latency to fall (s)	300 ± 0	253 ± 23	300 ± 0
Defecation boli deposited	3 ± 0.4 a	7 ± 1 a	5 ± 0.3
Latency to the first bolus (s)	56 ± 6 a	62 ± 6 b	106 ± 11 ab
Urination	0.2 ± 0	0.8 ± 0.1	0.4 ± 0.1
Horizontal rod balancing test (5 min)			
Latency to fall (s)	240 ± 27 ac	153 ± 22 ab	55 ± 6 bc
Latency to leave central zone (s)	153 ± 12 ac	115 ± 10 ab	30 ± 2 bc
Defecation boli deposited	5 ± 1	6 ± 1	NA[a]
Latency to the first bolus (s)	29 ± 7	38 ± 5	NA
Urination	0	0	NA
Actimeter novelty test (10 min)			
Between-groups difference was analysed by one-way ANOVA test (factor: strain)			
Vertical activity $F(2,27) = 10.44$; $P < 0.0004$	43 ± 6 a	61 ± 4 b	78 ± 6 ab
Latency to the first vertical rear (s) $F(2,27) = 9.6$; $P < 0.001$	32 ± 5a	40 ± 6 b	12 ± 2 ab
Number of tail rattling episodes $F(2,27) = 123.45$; $P < 0.0001$	0 a	2 ± 0.2 ab	0 a
Manipulations with own fecal boli[b] $F(2,27) = 100$; $P < 0.0001$	0 a	0 b	10 ± 1 ab
Defecation boli deposited $F(2,27) = 9.14$; $P < 0.001$	4 ± 0.5 ab	12 ± 2 a	8 ± 1b
Urination $F(2,27) = 1,23$; $P < 0.28$ (NS)	0.4 ± 0.1	0.4 ± 0.1	0.2 ± 0.1
Number of jumping episodes $F(2,27) = 100$; $P < 0.0001$	1 ± 0.1 ab	0 a	0 b

Data are expressed as mean ± S.E.M. Strains sharing common letters are statistically different ($P < 0.05$, U-test). NS—non-significant difference (ANOVA test).
[a] Data not available
[b] Touching, lifting, eating, moving with forepaws, relocating by with mouth.

food, despite their hunger (14 h food deprivation). Vertical activity was significantly higher in the NMRI mice in the food finding test (13 ± 1.5 versus 8 ± 1 (129S1; $P < 0.05$, U-test) and 7 ± 1 (BALB/c; $P < 0.05$, U-test), but remained unaltered in the fecal boli finding test (Table 2). Urination and defecation scores were similar in all three mouse strains tested in both olfactory tests (Table 2).

Motor coordination abilities of mice were assessed in the vertical screen retention test and the horizontal rod balancing tests. In addition, we also assessed emotional reactivity (defecation and urination scores) during these tests. In the vertical screen test, all mice showed similar retention time and urination scores, while the 129S1 group demonstrated significantly less defecation, compared to the BALB/c (3 ± 0.4

versus 7 ± 1, $P < 0.05$, *U*-test) but not NMRI mice (5 ± 0.3; NS), Table 2. In addition, both BALB/c and 129S1 mice showed shorter latencies to the first fecal bolus compared to the NMRI group (56 ± 6 s and 62 ± 6 s versus 106 ± 11 s, respectively; $P < 0.05$, *U*-test for both strains). In the horizontal rod test, all groups demonstrated significant differences in the latency to fall (129S1: 240 ± 27 s; BALB/c: 153 ± 22 s; NMRI: 55 ± 6 s; $P < 0.05$, *U*-test for each group). Notably, the NMRI mice, showing minimal retention time in this test, also demonstrated the shortest latency to leave the central zone (30 ± 2 s versus 153 ± 12 s (129S1; $P < 0.05$, *U*-test) and 115 ± 10 s (BALB/c; $P < 0.05$, *U*-test, also versus 129S1 mice), respectively). Defecation and urination scores were similar in the BALB/c and 129S1 mice (however, these measures were not taken in the NMRI group due to their poor performance in this test).

Finally, using one-way ANOVA to compare behaviours of mice tested in the actimeter test, we found significant strain differences for all non-grooming measures except urination (Table 2). Further analysis using *U*-test revealed that the NMRI mice displayed maximal vertical activity scores (78 ± 6 versus 43 ± 6 (129S1) and 61 ± 4 (BALB/c); $P < 0.05$) and the shortest latency to the first vertical rear (12 ± 2 s versus 32 ± 5 s (129S1) and 40 ± 6 s (BALB/c); $P < 0.05$). In contrast, the 129S1 mice deposited significantly fewer boli (4 ± 0.4) compared to both BALB/c (12 ± 2) and NMRI (8 ± 1) groups, while no changes were seen in the number of urination episodes in this test (Table 2). Another striking finding, as can be seen in Table 2, was that all mouse groups markedly differed in their strain-specific displacement activity, including tail rattling (BALB/c), jumping activity (129S1) and manipulations with own fecal boli (NMRI).

3.2. Novelty-induced grooming behaviours

Table 3 shows grooming activity of mice tested in the actimeter test. Using one-way ANOVA test, we found significant strain differences in the following grooming measures: time spent grooming; average duration of a single bout; percent of incorrect transitions, number of interruptions of grooming activity, percent of interrupted bouts; number and duration of vertical grooming episodes. Further analysis using post-hoc *U*-test showed that the BALB/c mice spent significantly more time grooming (34 ± 4 s) than did their 129S1 (19 ± 2 s) and NMRI (23 ± 3 s) counterparts. The number of grooming bouts in all three strains was similar, although the 129S1 mice showed a tendency to display more bouts. The average duration of a single bout was significantly longer in the BALB/c group (8.1 ± 1 s) compared to the 129S1 (3.2 ± 0.3 s) and NMRI (5.2 ± 2 s) groups. As can be seen in Table 3, the latency to start grooming was not statistically different in all three mouse strains, although the NMRI mice showed a clear tendency to earlier onset of grooming, compared to both 129S1 and BALB/c strains.

Analysis of grooming behavioural microstructure in these strains (Table 3) shows that 129S1 mice tend to display fewer transitions between patterns but show significantly higher percentages of incorrect transitions (64 ± 5% versus 43 ± 4% (BALB/c) and 47 ± 5% (NMRI) and interrupted grooming bouts (28 ± 5% versus 5 ± 1% (BALB/c) and 10 ± 2% (NMRI). The average number of transitions per bout was similar in all groups, while the NMRI mice displayed specific vertical grooming activity completely lacking in the BALB/c and 129S1 groups (Table 3).

4. Discussion

To the best of our knowledge, this is the first ethological study comparing grooming behaviours in 129S1, NMRI and BALB/c mouse strains. These mice were chosen for their importance in genetic and behavioural research, and for their marked strain differences in several features that might be related to grooming (Table 1). This situation, when one strain is always different from the other two (activity: 129S1; anxiety: NMRI; aggression: BALB/c; brain anatomy: NMRI; dis-

Table 3
Grooming behaviours in NMRI, BALB/c and 129S1 mice tested in a 10 min actimeter test

Grooming behaviours/*F* (one-way ANOVA) test	129S1	BALB/c	NMRI
General cumulative measures			
Number of bouts $F(2,27) = 0.91$; $P < 0.41$ (NS)	5.8 ± 1	4.2 ± 1	4.4 ± 0.7
Time spent grooming (s) $F(2,27) = 6.24$; $P < 0.006$	19 ± 2 a	34 ± 4 ab	23 ± 3 b
Latency to start grooming (s) $F(2,27) = 1.38$; $P < 0.27$ (NS)	130 ± 23	146 ± 19	100 ± 17
Average duration of a single bout (s) $F(2,27) = 11.52$; $P < 0.0002$	3.2 ± 0.3 a	8.1 ± 1 ab	5.2 ± 0.7 b
Behavioural microstructure of grooming			
Total number of transitions between patterns $F(2,27) = 1.34$; $P < 0.28$ (NS)	14 ± 2	16 ± 4	21 ± 3
% Incorrect transitions $F(2,27) = 5.65$; $P < 0.008$	64 ± 5 ab	43 ± 4 a	47 ± 5 b
Number of interruptions $F(2,27) = 54.32$; $P < 0.0001$	1.4 ± 0.1 ab	0.2 ± 0 ac	0.7 ± 0.1 bc
Average transitions per bout $F(2,27) = 2.85$; $P < 0.07$ (NS)	2.4 ± 0.5	3.8 ± 1	4.7 ± 0.4
% Interrupted bouts $F(2,27) = 14.63$; $P < 0.0001$	28 ± 5 ab	5 ± 1 a	10 ± 2 b
Number of vertical grooming episodes $F(2,27) = 891.00$; $P < 0.0001$	0 a	0 b	2 ± 0 ab
Time spent vertical grooming (s) $F(2,27) = 25.00$; $P < 0.0001$	0 a	0 b	5 ± 1 ab

Data are expressed as mean ± S.E.M. Between-groups difference was analysed by one-way ANOVA test (factor: strain) followed by a post-hoc *U*-test. Strains sharing common letters are statistically different ($P < 0.05$, *U*-test). NS—non-significant difference (ANOVA test).

placement activity: NMRI; Tables 1 and 2) allows pair-wise comparisons between the strains and one-by-one dissection of possible factors influencing their grooming. Here we show that mice from these strains exhibit contrasting behavioural patterns in their spontaneous (novelty-induced) grooming (Table 3).

Analysing behavioural profiles of 129S1, BALB/c and NMRI mice, we first noted that these strains differ markedly in their baseline activity (Table 1). Thus, it was possible to assume that the strain differences in grooming seen in the present study may be merely due to different levels of activity in these strains. However, analysis of grooming and motor activity shows no clear correlation between these behaviours (Tables 2 and 3). Indeed, the two strains with low-grooming phenotypes show markedly different activity profiles (low: 129S1; high: NMRI, Table 2) while both active strains show different grooming activity (low: NMRI; high: BALB/c, Table 3). Finally, grooming sequencing was also different in the 129S1 versus BALB/c and NMRI mice (Table 3), consistent with earlier findings showing that the organisation of behaviour in mice varies independently of the amount of activity [34]. Taken together, these findings suggest that the contrasting grooming phenotypes reported here are not determined by different levels of activity in these three mouse strains.

Notably, 129S1, BALB/c and NMRI male mice differ markedly in their aggressiveness (BALB/c > 129S1 ≫ NMRI). Since grooming is often seen as a part of agonistic behavioural repertoire in mice [41], it was possible to assume that the strain differences in grooming reported here may be due to different levels of aggression. However, our data show no clear correlation between grooming and aggression. Indeed, while both non-aggressive strains (NMRI, 129S1) show markedly different patterning of grooming, the strains with different levels of aggression (BALB/c and NMRI) show similar unimpaired grooming microstructure (Table 3). Collectively, these observations negate the idea that the contrasting grooming phenotypes reported in the present study are due to different aggressiveness of these mouse strains.

Another potential explanation for our data could be that all three mouse strains may differ in their major sensory abilities, such as vision, olfaction and vestibular system. Disturbances in these systems are known to lead to particularly marked abnormalities in grooming behaviour, and this possibility is therefore to be examined in detail. Indeed, some visual problems have been suggested for albino BALB/c mice [7,10] but not NMRI and 129S1 strains (see, however [35] reporting unimpaired vision in BALB/c mice). In contrast, olfaction has been reported to be better in BALB/c than in 129S1 mice [23]. In the present study, we demonstrated that all three strains have unimpaired olfactory system, as assessed in the food and fecal boli finding tests (Table 2). In addition, all three strains appear to have unimpaired vision, as assessed in the novel object-finding test (Table 2, see also [35]). Although in the horizontal rod test, vestibular functions appear to be unimpaired in the BALB/c and 129S1, but not NMRI mice (Table 2), we speculate that poorer performance of the NMRI group in this test may be probabilistic in nature, merely reflecting their hyperactive phenotype (active uncautious behaviour—more chances of falling from the rod), rather than impaired vestibular functions per se. In line with this, motor coordination and manipulation activity were unimpaired in all three strains subjected to the vertical screen and the novel object test (Table 2). Finally, NMRI mice generally display high vertical activity (Table 1) inconsistent with impaired vestibular system. Furthermore, the 129S1 mice exhibited the poorest grooming performance and the best horizontal rod retention (Table 2). Collectively, these findings allowed us to rule out any possible role of motor-sensory disturbances in the markedly different grooming activity demonstrated by the 129S1, BALB/c and NMRI mice in the present study.

Another probable factor underlying our behavioural findings may be the difference in brain anatomy reported for these mouse strains. It has long been known that 129S1 and BALB/c mice suffer from agenesis and dysplasia of the CC [25,27,30,47,48], a structure connecting the two brain hemispheres and integrating motor, sensory and cognitive functioning [15,28,38,39]. Notably, humans with abnormal CC may develop mental retardation and various cognitive, visual and motor coordination impairments [15,28,38,39]. Likewise, some impairments in motor coordination have been reported in mice with abnormal CC [24,25,39]. Thus, acallosal mice may display abnormal behaviour due to loss of communication between brain hemispheres, as has already been speculated [14]. Since the CC may be crucial for transcallosal passage of motor signals and feedback sensory signals controlling movements [15,28,38], it was possible to assume that callosal anomalies may affect mouse grooming phenotypes [19]. However, both “acallosal” BALB/c and 129S1 strains performed well in the horizontal rod and the vertical screen tests (Table 2), thus showing no overt motor and coordination deficits. Furthermore, we found markedly different levels of grooming activity and its behavioural organisation in the two strains (129S1 and BALB/c) sharing the same brain dysfunction (Table 3). Collectively, this negates the idea that the strain differences in the CC determine contrasting grooming phenotypes reported in the present study. Clearly, further comparative studies may be necessary to assess more fully other possible brain differences between 129S1, BALB/c and NMRI mice.

Finally, all three strains have been reported to possess different baseline levels of anxiety (Table 1). Grooming has long been known to be a behavioural marker of stress in rodents [20,22,31], raising the possibility that more grooming in BALB/c mice may be due to more anxiety in this strain, compared to low-grooming NMRI and 129S1 mice. The fact that defecation scores – a traditional marker of stress in rodents – were maximal in the BALB/c and minimal in the 129S1 mice (Table 2) seems to support this notion. However, this hypothesis clearly contradicts numerous earlier findings [2,5,17,26,40] and our present data (Table 2), demonstrat-

ing more anxiety in 129S1 compared to BALB/c and particularly NMRI mice. The fact that non-anxious NMRI mice also showed high defecation levels indicates that defecation index is only one of several types of stress measures, and different mouse strains display some but not all stress-related behaviours. For example, although anxiety strain difference may indeed explain high grooming in BALB/c and low grooming in NMRI mice (Table 2), the fact that different strains display stress in different ways may underlie low grooming duration in anxious 129S1 mouse strain seen in this and other studies [19,20].

Importantly, it has long been recognised that the interaction of grooming and anxiety is rather complex, and that rodent grooming is increased in both high and low stress situations [13,20]. Therefore, its cumulative measures may not reflect the level of stress, if taken alone [19,20]. Indeed, various manipulations, including genetic targeting, may lead to increased or decreased grooming phenotypes regardless of the level of anxiety per se [13,19,20]. For example, both activation and inhibition of grooming was seen after anxiolytic and anxiogenic drugs [13]. Higher grooming scores have been reported for both anxious Vitamin D receptor mutants [21] and non-anxious C57BL/6 [19,20] versus 129S1 mice. Consistent with this, anxious BALB/c mice showed more grooming than non-anxious NMRI mice, while low grooming levels were seen in both anxious 129S1 and non-anxious NMRI mice (Table 3). Given the low-anxiety profile of NMRI mice, we can suggest that their non-grooming behaviours (such as high vertical activity) may confound their grooming, thus, showing a clear low-anxiety low-grooming response. Moreover, grooming may represent a displacement activity and/or a "self-directed form of coping" in these mice, serving to alleviate anxiety, as has already been suggested for NMRI mice [33]. Indeed, grooming is a common displacement activity in rodents, including mice [12,33]. In line with this, our NMRI mice frequently displayed displacement "vertical" grooming and another interesting displacement activity—manipulations with fecal boli (behaviour that cannot be expected in high-anxiety states and, predictably, was not seen in anxious 129S1 and BALB/c mice) (Tables 2 and 3). Some other strain-specific non-grooming behaviours may also explain the low grooming activity of 129S1 mice seen in the present study. For example, these mice frequently display anxiogenic-like "freezing" behavioural response to stressors [18,48] as well as a tendency to more escape-like behaviours (jumping, Table 2). It is therefore possible that these behaviours may affect the grooming phenotypes reported here (see similar results in [19]).

In contrast to cumulative measures of grooming, its behavioural microstructure shows consistent increase in abnormalities in more anxious strains (e.g. 129S1 < Vitamin D receptor null mutant mice [21]; non-stressed < stressed C57BL/6 mice [20]; C57BL/6 < 129S1 mice [19], NMRI < BALB/c < 129S1 mice; as reported here). Taken together, these data support our hypothesis that shifts in the behavioural microstructure of grooming (the percentages of interrupted bouts and incorrect transitions between patterns) are highly sensitive behavioural markers of stress [20]. Thus, a dramatic difference between non-anxious NMRI, moderately anxious BALB/c and anxious 129S1 mice in their grooming microstructure (Table 3) may be explained by different levels of anxiety in these strains. Moreover, the behavioural microstructure of rodent grooming is very sensitive to the level of stress, known to disrupt its cephalocaudal pattern and increase the percentage of interrupted and incomplete bouts [19,20,22]. Indeed, our observations that 129S1 mice generally display extra-short (one to two patterns) incomplete and frequently interrupted grooming bouts with more incorrect transitions (Table 3) are in line with our non-grooming data (Table 2) and previously published studies (Table 1) describing the anxious behavioural phenotype of this strain.

Overall, the substantial difference observed here in both the amount and organisation of self-grooming behaviours between the three strains commonly used in behavioural neuroscience represents an important aspect of neurobehavioural research, with several additional important implications. First, the phenotypic features of grooming in background strains have to be taken into account when interpreting the behavioural phenotypes of mutant mice. For instance, it can be suggested that, if 129S1 strain is used as a genetic background, abnormal grooming behaviours in mutant mice may be due to 129S1 background influence. Moreover, the fact that grooming microstructure is highly sensitive to stress [19,20,22], indicates good predictive validity for the use of grooming ethological analysis as an additional tool to assess the level of stress in laboratory animals, including NMRI, BALB/c and 129S1 mice. For example, this may be important for screening the effects of mutations or psychotropic drugs with unclear or mild stress-tropic effects, i.e. in situations when the effect in question is difficult to detect by simply measuring locomotion and exploration.

Furthermore, understanding strain differences in the patterning of complex behaviours, such as grooming, may assist us in the search for better animal models of specific behavioural disorders. Given our data on impaired patterning of grooming in 129S1 mice, it can be suggested that BALB/c mice are a better choice to study the effects of mutations or drugs likely to impair motor coordination and patterning of complex behaviours. In contrast, 129S1 mice may be useful to assess genetic or other manipulations likely to improve such performance. Overall, our results, establishing contrasting grooming behavioural phenotypes in NMRI, 129S1 and BALB/c mice, may provide valuable information for discriminating between the effects in question and the effects of mouse strain-specific phenotypes.

In summary, our data reveal different grooming profiles in 129S1, BALB/c and NMRI mouse strains in novelty stress (Table 4), which appear to be unrelated to the strain differences in general activity levels, sensory abilities, brain anatomy or aggressiveness. The results of this study suggest that the strain differences in grooming may

Table 4
Summary of behavioural strain differences in the novelty situation between NMRI, BALB/c and 129S1 mice

Behaviour	129S1	BALB/c	NMRI
General activity	Low	High	High
Anxiety	High	High	Low
Self-grooming activity	Low	High	Low
Grooming patterning (sequencing)	Impaired	Unimpaired	Unimpaired
Vertical (displacement) grooming	None	None	High
Non-grooming displacement activity	None	Low[a]	High[a]

[a] Tail rattling (BALB/c mice) and manipulations with own fecal boli (NMRI mice), see Table 2 for details.

be a result of complex interplay between anxiety, motor and displacement activity (Table 4), perhaps reflecting different behavioural stress-coping strategies in these mice. We suggest that contrasting grooming phenotypes may be attributed to a high anxiety low activity phenotype of 129S1 mice, compared to anxious BALB/c and non-anxious NMRI active mouse strain. In addition, NMRI mice showed frequent displacement behaviours, including specific manipulatory activity and "vertical" grooming, suggesting that animals of this non-anxious strain make extensive use of displacement activity as an effective stress-coping strategy (see also [33]). Given the increasing use of NMRI, BALB/c and 129S1 mice in behavioural research, the results of the present study emphasise the importance of understanding the differences between grooming patterns in these mouse strains for correct ethological analyses of behavioural data. Thus, an in-depth analysis of mouse grooming, such as reported here, may contribute to our understanding of some human behavioural disorders, as has already been speculated [12].

Acknowledgements

This research was supported in part by grants from the University of Tampere, EVO (Medical Research Council of Tampere University Hospital) and the Academy of Finland.

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