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Brain Research 1028 (2004) 75–82
BRAIN RESEARCH
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Research report

Contrasting grooming phenotypes in C57Bl/6 and 129S1/SvImJ mice

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Accepted 8 September 2004
Available online 3 October 2004

Abstract

Since C57 and 129 mice are the commonly used background strains, a better knowledge of all their behavioural characteristics is important in neuroscience research. Grooming is a complex and essential ritual in the rodent behavioural repertoire, normally proceeding in a cephalocaudal progression (paws–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 in detail. Although strain differences between C57BL/6 and 129S1/SvImJ substrains have been assessed in many studies, no ethological analyses of their grooming have been performed. Here we show strain differences between these mice in spontaneous (novelty-induced) and artificial (water-induced) grooming. Overall, 129S1/SvImJ mice demonstrated less grooming activity, more interrupted and incomplete bouts, and more incorrect transitions (contrary to the cephalocaudal rule) between patterns, accompanied by lower vertical activity and higher defecation/urination in both tests. These results are consistent with general hypoactive anxious phenotype in 129S1/SvImJ mice and suggest that ethological analysis of mouse grooming may be used in neurobehavioural stress research, including behavioural phenotyping of both mutant and background mice.

Theme: Neural basis of behaviour
Topic: Neuroethology

Keywords: Grooming behavior; 129S1/SvImJ mouse; C57BL/6 mouse; Behavioral phenotype

1. Introduction

Genetically targeted animals are extensively used in behavioural neuroscience [17,48]. Mutant mouse strains are typically produced by injecting a genetically modified embryonic stem cell derived from the 129 inbred strain into a C57 blastocyst [9,50]. It has long been known that a phenotypic change due to a mutation may vary with the type of mouse strain [31,47,50]. The increased use of transgenic and null mutation techniques in the development of animal models of behavioural disorders underlines the importance of selecting the appropriate genetic background [18,31,33,40].

129 and C57 mouse stains are most commonly used background strains in behavioural research [12,41]. These mice are genetically different, demonstrating marked polymorphism in their genetic markers [45]. In addition, both strains are very different behaviourally, including marked strain differences in tests of learning, memory, anxiety, pain responsivity, olfactory discrimination and sensitivity to psychotropic drugs [13,22,29,39]. Overall, C57 mice are non-anxious, more active and good learners [6,31,40]. In contrast, although numerous 129 mouse substrains show substantial genetic and phenotypic variation [12,40], these mice are generally much less active, display more anxiety and their learning varies widely depending on the nature of the task [5,8–10,41,56].

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doi:10.1016/j.brainres.2004.09.001

Notably, while the literature on strain behavioural differences between C57 and 129 mice is vast [11,22,23,36,40], relatively few studies have assessed their grooming activity [23,41,48]. Although this behaviour is frequently displayed by mice, it has been addressed only cursorily among other measures. Surprisingly, there are no grooming data in the extensive Mouse Phenome database (http://www.jax.org/phenome) [20,26,51,54], indicating that this behaviour has still merited little scrutiny in behavioural genetics.

Why are grooming behaviours so essential? Firstly, grooming is an ancient innate behaviour that is represented across most animal species, and has long been known as a particularly important part of rodent behavioural repertoire [1,3,4,7,21,25,37]. In rodents, a cephalocaudal progression is normally observed: paw licking, nose and face wash, head wash, body wash and fur licking, leg licking, tail/genitals licking and wash [2–4]. 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 [7,14,16,34]. In addition, grooming and its patterning are very sensitive to various exogenous and endogenous factors, including stress, psychotropic drugs and genetic manipulations [15,24,25,46,49]. Since genetically targeted mice retain a large portion of background genes, especially around the ablated target, some behavioural characteristics usually attributed to the ablated locus may, in fact, be due to these "passenger" background genes [12]. Since various mutant mice often display altered grooming phenotypes [14,21,46,57], ethological dissection of the background vs. mutation-induced effects on grooming may be a necessary task. Therefore, a complex analysis of mouse grooming, including both mutant and background mice, represents an important part of behavioural neurogenetics.

C57Bl/6 (B6) and 129S1/SvImj (S1) mice are the most commonly used C57 and 129 mouse background substrains [8,33,53]. As such, a better knowledge of all behavioural profiles of B6 and S1 mice allows better distinction between mutation vs. background-dependent behavioural phenotypes. While the literature on B6 and S1 mouse behaviours is extensive (Table 1), there have been no studies analyzing grooming in these strains in detail. Thus, the goal of the present study was to dissect ethologically different types of grooming activity and define behavioural differences in grooming between B6 and S1 mice.

In general, behavioural analysis of mouse grooming is a complex task. On one hand, the latency of onset, the number of bouts and the duration are robust measures traditionally used as behavioural indices of grooming [24,25]. On the other hand, since grooming in rodents can be increased by different opposite factors, such as stress and comfort [24,37,38], these traditional "cumulative" measures may be insufficient for correct data interpretation and analysis. As such, there is a great need to use additional behavioural characteristics of grooming, including its organization or patterning [24,25,27,28].

For this, we used the approach based on differential registration of grooming patterns and quantifying the sequential domain of this behaviour [24,25]. In addition to measuring traditional "cumulative" grooming parameters, the percentages of incomplete and interrupted grooming bouts, and incorrect transitions (contrary to the cephalocaudal rule) were used in the present study to

Table 1
A brief summary of some behavioural strain differences between B6 and S1 mice

Behavioural tests/models	Measure	Strain ranking	Ref.
Social interaction	Grooming frequency	B6>S1	[23]
Home cage	Horizontal activity (daily, light, dark)	B6>S1	[44]
	Vertical activity (daily, light, dark)	B6>S1	[44]
Grid test	Horizontal activity	B6>S1	[13]
Open field	Horizontal activity	B6>S1	[11,12,20,53]
	% time in the center	B6>S1	[11,12,20]
	Stops (number, duration)	S1>B6	[20]
	Number of stops per excursion	S1>B6	[20]
	Number of exploratory excursions	B6>S1	[20]
	Time to reach half-maximal speed	S1>B6	[20]
	Recovery of horizontal activity next day	B6>S1	[53]
	Number of stereotypic behaviours	B6>S1	[12]
Elevated zero maze	Latency to enter open quadrant	S1>B6	[11,12]
	% time in open quadrant	B6>S1	[11,12]
	% time in closed quadrant	B6>S1	[11,12]
	Defecation	S1>B6	[11,12]
Y-maze	Horizontal activity	B6>S1	[53]
	Recovery of horizontal activity next day	B6>S1	[53]
Rotoroid	Latency to fall	B6>S1	[12]
	Missteps crossings	S1>B6	[13]
Fear conditioning	Baseline horizontal activity	B6>S1	[5,12]
	Altered context horizontal activity	B6>S1	[5,12]
	Conditioning response (%)	B6=S1	[5,12]
Accoustic startle	Acoustic startle response amplitude	S1>B6	[54,55]
Light–dark paradigm	Transitions frequency	B6>S1	[6]
	Time in the dark	S1>B6	[6]
Hyperthermia	Stress-induced temperature increase	B6=S1	[6]
Hot plate	Latency to nociceptive stimuli	B6>S1	[26]
Wildness assessment	Wildness	B6≥S1	[51]

analyse the behavioural microstructure of mouse grooming. To allow better generality of inter-strain comparison, two ethologically different types of grooming activity—spontaneous (novelty-induced) and artificial (water-induced)—were assessed in this study. Here we show that B6 and S1 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 B6 and S1 mice (25–30 g, n=32; University of Tampere, Finland) aged 20–24 weeks were maintained in a virus/parasite-free facility under conditions of controlled temperature (22±2 °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 06:00 h. The animals were experimentally naïve and housed in fours, with food and water freely available.

2.2. Procedure

Behavioural 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 3 h prior to testing. To induce spontaneous novelty-induced grooming, the mice were placed individually in a clean unfamiliar plastic box (30×30×30 cm), Experiment 1. To induce artificial grooming, the mice were misted with water (25 °C) using a hand spray and placed individually in the clean plastic observation box (30×30×30 cm), Experiment 2. Between subjects, each apparatus was thoroughly cleaned (wet and dry cloths). In all experiments, the animals were observed by an experienced investigator for a period of 5 min. During the testing sessions, the experimenter remained standing in front of (and 2 m away from) the testing boxes recording mouse grooming using specially designed register. 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

2.3.1. Non-grooming measures

Defecation and urination index (vegetative behaviours; the number of boli deposited and urination spots) was scored as the conventional emotionality index in all tests. In addition, we also assessed general vertical activity-vertical rears (the number of times an animal stood erect on its hind legs with forelegs in the air or against the wall) and the latency to the first vertical rear (s)—as conventional behavioural measures of exploratory motor activity.

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, according to Kalueff and Tuohimaa [24,25], with some modifications: paw 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), 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), paw licking (1), nose/face/head wash (2), body grooming (3), leg licking (4) and tail/genitals grooming (5). Grooming behavioural microstructure was assessed using the grooming analysis algorithm as described earlier [24,25], with some modifications. Complete grooming bouts adhered to the cephalocaudal pattern as follows: 0–1–2–3–4–5–0. Incomplete bouts included all other grooming bouts registered. A grooming bout was considered "interrupted" if at least one interruption was recorded within its stages; interruptions greater than 6 s determined separate grooming bouts. The percentage of incomplete and interrupted bouts, and the percentage of incorrect transitions were calculated for both mouse stains. Transitions between grooming patterns were assessed using the grooming analysis algorithm. 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 between grooming patterns. Correct/incorrect grooming transitions were analysed using the transition matrix and the percentages of incorrect transitions were calculated for both strains.

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. A probability of less than 0.05 was considered statistically significant.

3. Results

3.1. Experiment 1 (spontaneous grooming)

As can be seen in Fig. 1, non-grooming behaviours were different in both groups, including fewer vertical rears, longer latency to the first rear and more urination/defecation

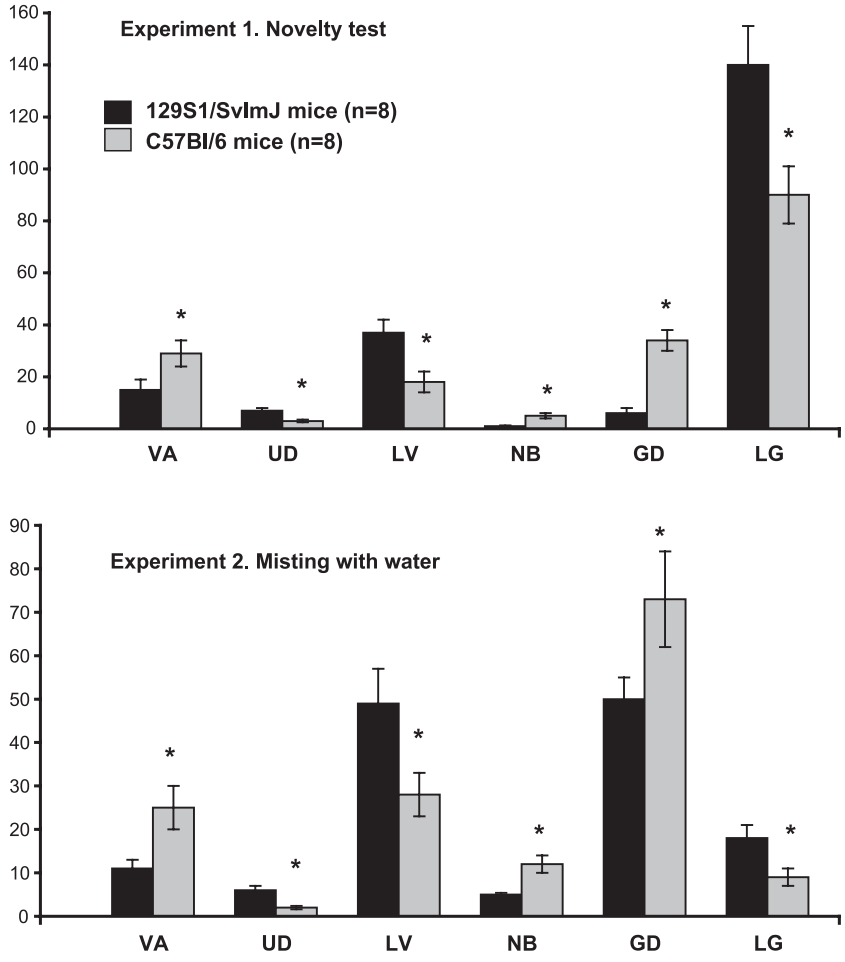

Fig. 1. Behavioural scores of B6 and S1 mice recorded in the actimeter test for 5 min. Data are expressed as mean±S.E.M. *P<0.05 difference between the stains (U-test). VA—vertical activity (number of rears), UD—urination spots and defecation boli deposited, LV—latency to the first vertical rear (s), NB—number of grooming bouts, GD—total duration of grooming activity (s), LG—latency to start grooming (s).

scores in S1 mice, compared to their B6 counterparts. Figs. 1 and 2 show spontaneous grooming activity of both groups of mice. In the observation box, the B6 mice demonstrated shorter latency to onset, more bouts and spent more time grooming than did the S1 mice (latency: 90±11 s (B6), 145±15 s (S1), P<0.05, U-test; bouts: 5±1 (B6); 1±0.3 (S1), P<0.05, U-test; grooming duration: 34±4 s (B6), 6±2 s (S1), P<0.05, U-test), while average duration of a single bout remained unaltered in both strains (6.8±1 s (B6), 6±0.4 s (S1), NS). Furthermore, the behavioural microstructure of grooming activity in these two mouse strains was also significantly different (Fig. 2). A detailed ethological analysis shows that the B6 mice generally displayed a wide spectrum of grooming patterns (involving all six patterns) with more total transitions (43±5 (B6), 3.5±0.8 (S1), P<0.05, U-test) and a tendency toward more transitions per bout (8±2 (B6), 4±1 (S1), NS). As can be seen in Fig. 2, B6 mice also showed lower percentages of interrupted (46±8% (B6), 96±3% (S1), P<0.05, U-test) and incomplete grooming bouts (24±4% (B6), 58±7% (S1), P<0.05, U-test). In contrast, the S1 mice demonstrated more stereotypic grooming activity which consisted predominantly of paw licking and nose wash (stages 0–1–2, only 2–4 transitions/bout), also showing higher percentages of incomplete, interrupted bouts (Fig. 2) and incorrect transitions between patterns (39±5% (B6), 61±7% (S1), P<0.05, U-test).

3.2. Experiment 2 (artificial grooming)

As can be seen in Fig. 1, non-grooming behaviours diminished in the water-misting test but consistently differed between strains, including less vertical activity, longer latency to the first rear and more urination/defecation scores in S1 mice, compared to their B6 counterparts.

Figs. 1 and 2 present data on artificial water-induced grooming activity in both strains. In this experiment, both groups displayed predictably more grooming, compared to the novelty-induced grooming test. Overall, the B6 mice demonstrate shorter latency to start grooming, more bouts and more time spent in artificial grooming than did the S1 mice (latency: 9±2 s (B6), 18±3 s (S1), P<0.05, U-test; bouts: 12±2 (B6), 5±0.4 (S1), P<0.05, U-test; grooming

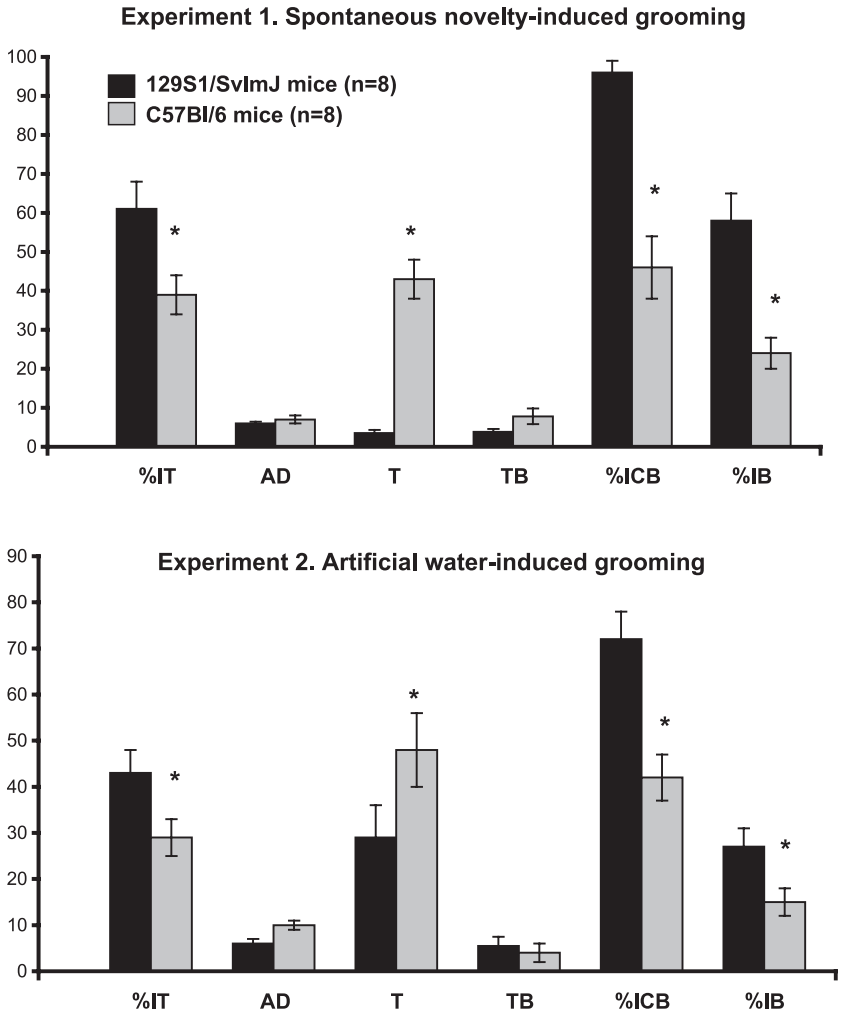

Fig. 2. Behavioural microstructure of spontaneous and artificial grooming in the B6 and S1 mice tested in the actimeter test for 5 min. Data are expressed as mean±S.E.M. *P<0.05 difference between the stains (U-test). %IT—percentage of incorrect transitions between patterns (contrary to the cephalocaudal progression), AD—average duration of a single grooming bout (s), T—number of transitions between grooming stages, TB—average number of transitions per bout, %ICB—percentage of incomplete bouts, %IB—percentage of interrupted bouts.

duration: 73±11 s (B6), 50±5 s (S1), P<0.05, U-test). Also there was no statistically significant difference in average duration of a single bout in both strains, although the S1 mice showed a tendency toward longer duration of a single bout (6±1 s (B6), 10±1 s (S1), NS).

Fig. 2 shows that the behavioural microstructure of grooming in this experiment also differed in both groups. Compared to the S1 group, the B6 mice tended to display more transitions between patterns (48±8 (B6) vs. 29±7 (S1), NS) but slightly fewer transitions per bout (4±2 (B6), 5±2 (S1), NS). Overall, the B6 mice also demonstrate significantly fewer incomplete (42±5% vs. 72±6% (S1), P<0.05, U-test) and interrupted grooming bouts (15±3% vs. 27±4% (S1), P<0.05, U-test). In contrast, the S1 mice showed more stereotypic grooming activity with fewer transitions between stages and higher percentages of incomplete and interrupted bouts (Fig. 2), also demonstrating more incorrect transitions between patterns (29±4% (B6), 43±5% (S1), P<0.05, U-test).

4. Discussion

There have been remarkably few studies comparing grooming in C57 and 129 mice. Rodgers et al. [41] showed that in the light–dark test some 129 substrains display lower grooming activity compared to B6 mice (tendency in 129/SvEm mice, a significant decrease in 129/SvHsD mice), while Van der Meer et al. [48] found no strain difference between daily grooming activity in B6 and 129/Ola mice. There has been only one study comparing grooming in B6 and S1 mice and showing the significant strain difference in grooming frequency (B6>S1) in the social interaction test [23]. To the best of our knowledge, this is the first ethological study focusing on detailed analyses of grooming behaviours in B6 and S1 mouse strains.

Our findings show that mice from S1 and B6 strains exhibit contrasting behavioural patterns of both spontaneous and artificial grooming. Overall, S1 mice demon-

strated altered cumulative measures of grooming (fewer bouts, longer latency to start grooming, and less time spent grooming) as well as abnormal behavioural microstructure of grooming (fewer transitions between grooming stages and higher percentages of incomplete and interrupted grooming bouts). Predictably, these behavioural differences between strains were more robust for more flexible spontaneous novelty-grooming compared to stereotypic artificial water-induced grooming (Fig. 2). However, the consistent and marked strain differences observed for both types of grooming activity in our experiments underline the generalizability of our observations.

Although our data showing more grooming activity in B6 mice are in line with similar findings in these mice subjected to the social interaction test [23], we note that the two strains markedly differ in their general motor activity (Table 1), see also Fig. 1. Therefore, it was possible to assume that low grooming scores in S1 strain may be due to low activity in these mice, compared to their active B6 counterparts. However, although hypolocomotion may explain low grooming activity measures seen in S1 mice in the present study (Fig. 1), grooming sequencing was also significantly impaired in these mice (Fig. 2). Given earlier findings that the organization of behaviour in C57 and 129 mice varies independently of the amount of activity [40], our results suggest that hypoactivity per se may not be the main reason for the strain differences in grooming patterning in S1 and B6 mice.

Importantly, grooming has long been known as a behavioural marker of stress in rodents [25,27,28,37,38], raising the possibility that more grooming in B6 mice may be due to more anxiety in this strain. However, this hypothesis clearly contradicts earlier findings [11,12,41], and our non-grooming data (Fig. 1), demonstrating more anxiety behaviours in S1 mice compared to B6 mice. Taken together, this indicates that stress or anxiety cannot be responsible for the strain differences in the amount of grooming in B6 and S1 mice.

As already mentioned, since rodent grooming is increased in both high and low stress situations, its cumulative measures may not reflect the level of stress, if taken alone [24,25]. Indeed, various manipulations, including genetic targeting, may lead to increased or decreased grooming phenotypes regardless the level of anxiety per se. For example, higher grooming scores have been reported for more anxious vitamin D receptor mutant mice or less anxious B6 mice, compared to S1 controls [25]. In contrast, the behavioural analysis of grooming microstructure shows consistent increase in abnormalities in more anxious strains (e.g. vitamin D receptor null mutants vs. S1 mice, stressed vs. non-stressed B6 mice [25], anxious S1 mice vs. non-anxious B6 mice; as reported here). Taken together, these data support our hypothesis [24,25] that shifts in the behavioural microstructure of grooming (the percentages of incomplete, interrupted bouts and incorrect transitions between patterns) are more reliable behavioural markers of stress than the traditional cumulative grooming measures. Thus, a dramatic difference between B6 and S1 mice in their grooming patterns (Fig. 2) 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 [24,25,27,28]. Indeed, our findings that S1 mice generally display extra-short (1–2 patterns) incomplete and frequently interrupted grooming bouts with more incorrect transitions (Fig. 2) are in line with recent data showing increased anxiety in mice of this strain (Table 1). Consistent with the idea that anxiety differentially affected B6 and S1 mouse behaviours in this study, vertical activity was lower, while defecation and urination scores were higher in more anxious S1 mice (Fig. 1). Overall, our grooming results are in line with general strain differences in anxiety levels (Table 1), suggesting that anxiety may determine the contrasting grooming phenotypes seen in this study (Figs. 1 and 2).

In addition, a probable factor underlying the behavioural findings in this study is the difference in brain anatomy reported for B6 and S1 strains. Overall, 129 mice, including S1, suffer from agenesis and dysplasia of the corpus callosum (CC) [31,32,43,51,53], compared to B6 mice with normal CC. The CC is a structure connecting the two brain hemispheres and integrating motor, sensory and cognitive functioning [36,42]. Interestingly, humans with abnormal CC may develop mental retardation and various cognitive, visual and motor coordination impairments (although this defect does not necessarily impede behaviours due to extracallosal compensatory pathways) [35,42], see also Ref. [32] for discussion. Likewise, some impairments in motor coordination have already been reported in mice with callosal dysfunctions [30,31,43]. Thus, 129 mice with this brain dysfunction may display abnormal behaviour due to loss of communication between brain hemispheres, as has been speculated [18]. Since the CC may be crucial for transcallosal passage of motor signals and feedback sensory signals controlling movements [19,30,42], callosal anomalies in S1 mice may be one of the reasons for the specific grooming phenotype seen in our study. Moreover, S1 mice have been reported to have reduced anterior comissure and slightly reduced hippocampal comissure [51,52], additional brain inter-hemispheric channels for sensory and mnemonic information [32]. Collectively, it is possible to assume that both trans- and extracallosal pathways are impaired in S1 mice, and that these differences in brain anatomy between B6 and S1 mice may underlie contrasting grooming phenotypes reported in the present study.

In general, the substantial difference observed here in both the amount and organization of self-grooming behaviours between the two background strains commonly used

in behavioural neuroscience represents an important aspect of neurobehavioural research, with several 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 S1 strain is used as a genetic background, abnormal grooming behaviours in mutant mice may be due to S1 background influence. Moreover, the fact that grooming microstructure is highly sensitive to stress [24,25], 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 both mutant and background 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. For example, given our data on impaired patterning of grooming in S1 mice, it can be suggested that B6 mice are a better choice to study the effects of mutations or drugs likely to affect motor coordination and patterning of complex behaviours. On the other hand, S1 background strain may be useful to assess genetic or other manipulations likely to improve such performance. Moreover, since general behavioural patterns of grooming are similar in rodents [2,3], we can suggest that a similar approach may be used to analyse grooming behavioural phenotypes of various background and mutant rats and other small laboratory rodents. Finally, our results, establishing contrasting grooming behavioural phenotypes in B6 and S1 mice, provide valuable information for discriminating between the effects of ablated or targeted gene and the effects of genetic background.

In summary, our data reveal different behavioural patterning of grooming in B6 and S1 strains, including less grooming activity and impaired grooming patterning in S1 mice. Our data provide evidence that altered grooming patterns observed in these mice may be attributed to a high anxiety phenotype of S1 mice, compared to non-anxious B6 mouse strain. Overall, the results of the present study emphasise the importance of understanding the differences between grooming patterns in the parental mouse strains for correct ethological analyses of behavioural phenotypes.

Acknowledgements

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

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