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ORIGINAL ARTICLE

Comparison of sex differences in motor activities of exploratory and spontaneous behaviour of laboratory CD1 mice (*Mus musculus)*

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ABSTRACT

Sex differences in exploratory and spontaneous behaviour were investigated in 65 male and 67 female control CD1 mice of F_1-generation in two-generation toxicity studies over a 6-year-period. Exploratory and spontaneous behaviour was measured using an animal movement analysing system (SCANET CV-40; Melquest Ltd.) consisted of two crossing sensor frames of 72 units of detectors of near-infrared photosensors for measuring motor activity. Exploratory behaviour of F_1-generation mice was investigated at 8 weeks of age. Adult females showed less activity in the rearing time and average rearing time than adult males in the 10-minute total. These variables indicated similar longitudinal patterns in male and female mice during the 10-minute observation period and indicated the significant distance between the male and female lines. Spontaneous behaviour of F_1-generation mice was investigated at 9–10 weeks of age. No significant differences were shown between male and female mice in all measured variables in the 120-minute total. The average rearing time indicated a similar longitudinal pattern between male and female mice during the 120-minute observation period. Other variables indicated a different longitudinal pattern between male and female mice. In the relationship between exploratory and spontaneous behaviour, most variables of males excluding the number of horizontal activities showed significant but weak correlations. In females, most variables excluding the number of horizontal activities and movement time showed significant but weak correlations between exploratory and spontaneous behaviour. In males, the activity levels of exploratory behaviour correlated with spontaneous behaviour levels, but females indicated lower correlations than males. From these results, it appears that female CD1 mice display shorter rearing time of exploratory behaviour than male CD1 mice, and the longitudinal patterns of spontaneous behaviour indicate sex differences.

Keywords: Exploratory behaviour, mice, motor activity, sex differences, spontaneous behaviour.

INTRODUCTION

Several studies have reported differences in nonsexual behaviour between male and female mammals. In particular, differences in emotional behaviour have been frequently observed in rodents. Valle (1970) reported that female rats were generally more active than male rats in the open field. Masur (1972) found that male rats displayed more defecation and less ambulatory behaviour than female rats in the open field.

Archer (1974, 1977) reported a lower latency time and more stationary sniffing among male rats and mice compared with those in female rats and mice. Archer (1975) suggested that male rats typically showed more defecation behaviour than female rats in the open field. However, among mice, neither sex can be said to typically defecate more than the other.

In general, in both rats and mice, males show fewer ambulatory movements than females in open-field tests; however, there have also been several cases where no significant differences between sexes have been observed. Gray (1979) suggested that similar to outbred rat strains, outbred mice strains exhibit the typical rat pattern of greater defecation and less activity among males. Nevertheless, few studies have examined sex differences in exploratory behaviour of outbred mice.

In reproductive and developmental toxicity studies, exploratory and spontaneous behaviour is usually measured as a neurobehavioural parameter, and it is an important variable for detecting neurobehavioural toxicity. At the Tokyo Metropolitan Institute of Public Health, several reproductive and neurobehavioural toxicity studies of agricultural and related chemicals have been performed on CD1 (ICR) mice (*Mus musculus*), and their results have been evaluated. Exploratory behaviour, motor activity in a novel environment including ambulatory and rearing movements, has been analysed in adult F_1-generation mice. Spontaneous behaviour, motor activity without external stimuli including ambulatory and rearing movements, has been analysed in adult F_1-generation mice. Chemical effects at times result in different patterns of exploratory and spontaneous behaviour in both sexes.

However, there have been very few reports on exploratory and spontaneous behaviour of control mice, in particular, in terms of sex-related differences. Tanaka (2015b) reported that female CD-1 mice display less exploratory behaviour measured by the previous apparatuses than male CD-1 mice. This study deals with sex differences in motor activities of exploratory and spontaneous behaviour of control CD1 (ICR) mice in two-generation toxicity studies performed in the current facility of animal experiments under similar conditions over a 6-year-period (Tanaka et al. 2014, 2018, 2020; Tanaka and Inomata 2015, 2016, 2017). Moreover, since the exploratory and spontaneous behaviour was measured using the same animal, the relationship between both behaviour was analysed by correlation analysis.

MATERIALS AND METHODS

Animals and maintenance. Male and female mice (Crl: CD1, 4 weeks of age) were purchased from Charles River Japan Inc., Kanagawa, Japan, for each study over a 6-year-period. They have housed individually in polycarbonate solid-floored cages with pulp chips made from alpha-cellulose (ALPHA-dri® or ALPHA-dri® + PLUS™; Shepherd

Specialty Papers Inc., Watertown, TN, USA), and kept in a temperature-controlled room maintained at 24.5°C ± 1°C at a relative humidity of 50% ± 5% on a 12-h light/dark cycle (6:00 a.m. –6:00 p.m.). They were given a controlled basal diet (CE-2; Clea Japan Inc., Tokyo, Japan) and water ad libitum.

Reproductive procedure. In six reproductive and neurobehavioural toxicity studies (2013–2018), male and female mice (n = 10 or 20 per study) were used as a control group. The F_0 generation mice were 5 weeks of age at the start of the study. At 9 weeks of age, each female mouse from the control group was mated with a male from the control group. After 5 days, the males were removed and the females were allowed to carry their litters to term, deliver and rear their offspring. Offspring were weaned at 4 weeks of age, and one male and one female mouse were randomly selected from each litter for the remaining experiment. They have housed individually in polycarbonate solid-floored cages with pulp chips after weaning. These procedures were the same in each study. A total of 885 offspring were born in 69 litters. After the lactation period, 67 litters were weaned at 4 weeks of age, and 65 males and 67 females were selected for the remaining experiment.

Exploratory behaviour. Exploratory behaviour of the mice was measured using an animal movement analysing system (SCANET CV-40; Melquest Ltd., Toyama, Japan) on distance (DT) mode at 8 weeks of age in the F_1 generation. The system consisted of two crossing sensor frames of 72 units of detectors of near-infrared photosensors for measuring motor activity (Mikami et al. 2002). The measuring cage was rectangular (300 × 202 × 208 mm) with transparent walls and lid made from acrylate resins. The measurements of behaviour were carried out by four sets of measuring units. The measuring cages of four sets each of male and female were used alternately and cleaned immediately during the next measurement. The illuminance inside the measuring cage was 330–380 lux at the bottom of the cage. Each sensor unit was scanned at a different height, and these steps were completed within 0.1 sec and repeated (Tanaka 2015a). The behavioural parameters were recorded (8:50–10:20 a.m.) for 10 min on all mice at 8 weeks of age in the F_1 generation. These procedures were the same in each study. The measured variables on DT mode were as detailed below (Tanaka 2015a):

1. Total distance (cm): Total distance covered by the animal after it moved from the central position.
2. Number of horizontal activities: Frequency at which the animal began moving from a stationary position.
3. Movement time (s): Total time for which the animal was moving.
4. Average speed (cm/s): (total distance/movement time).
5. Average movement time (s): (movement time/number of horizontal activities).
6. Number of rearing: Frequency of rearing (including jumping).
7. Rearing time (s): Total rearing time.
8. Average rearing time (s): (vertical time/number of vertical activities).

Spontaneous behaviour. Spontaneous behaviour of mice was measured in the animal movement analysing system SCANET CV-40 (Melquest Ltd.) on DT mode from 9 to 10 weeks of age in the F_1 generation. The behavioural parameters were measured in all mice for 120 min (male: 9:00–11:00 a.m.; female: 11:20 a.m. –1:20 p.m.) at an interval of 10 min after 10 min latency. As the measurement time for each of males and females, a time during which there was little variation among individuals in the preliminary test was selected.The measurement parameters were the same as those for exploratory behaviour.

Statistical analysis. Movement activity data related to exploratory and spontaneous behaviour of male and female mice were compared using Welch's t-test. Differences in the longitudinal patterns (during the 10- or 120-minute observation period) of exploratory and spontaneous behaviour between the sexes were assessed using profile analysis (test for equality of mean vectors, test for equality of covariance matrices and the parallelism hypothesis test). This longitudinal analysis is appropriate for a study that involves repeated observations of the same variables over long periods (Fujikoshi et al. 2008; Fujikoshi 2009). Differences between sexes at different time points were assessed using the Tukey–Kramer test. The relationship between exploratory and spontaneous behaviour was analysed by the Pearson product-moment correlation coefficient. After the correlation coefficient (r) of each variable was assessed by the test of no correlation, it was assessed by the test of the population correlation coefficient ($\rho > 0.7$).

Guidelines. The present study was conducted under guidelines set by the National Research Council (2010) and the Science Council of Japan (2006). Animal experiments conformed to the following Japanese laws and relevant regulations: 'Act on Welfare and Management of Animals' (Act No. 105 of 1 October 1973, revised on Act No. 46 of May 30, 2014); Notice No. 88 of 28 April 2006 and Notice No. 84 (revised) of August 30, 2013, of the Ministry of the Environment of Japan 'Standards Relating to the Care and Management of Laboratory Animals and Relief of Pain'; and Notification of 1 June 2006 (revised on February 20, 2015) of the Ministry of Health, Labour and Welfare of Japan 'Fundamental Guidelines for Proper Conduct of Animal Experiments and Related Activities in Research Institutions under the jurisdiction of the Ministry of Health, Labour and Welfare'.

Table 1. Comparison of exploratory behaviour in F_1-generation adult mice in the 10-minute total.

	Male	Female
No. of mice	65	67
Total Distance (cm)	1887.7 ± 50.2	1827.8 ± 52.3
No. of horizontal activities	128.3 ± 1.5	126.1 ± 1.4
Movement time (s)	387.6 ± 4.5	377.5 ± 4.8
Average speed (cm/s)	4.84 ± 0.09	4.79 ± 0.09
Average movement time (s)	3.05 ± 0.05	3.01 ± 0.05
No. of rearing	132.0 ± 4.2	123.3 ± 3.9
Rearing time (s)[b]	250.4 ± 7.5	216.4 ± 6.6
Average rearing time (s)[a]	1.93 ± 0.05	1.79 ± 0.05

Each value represents the mean ± SE. Significant differences between male and female mice: [a]$p < 0.05$, [b]$p < 0.001$.

Table 2. Summary of profile analysis of exploratory behaviour between F_1-generation adult male and female mice during the 10-minute observation period.

	***p*-value**			
	Equality of mean vectors	Equality of covariance	Parallelism	Distance between lines
Total distance (cm)	< 0.001	0.223	0.449	0.351
No. of horizontal activities	< 0.001	0.195	0.357	0.117
Movement time (s)	< 0.001	0.521	0.781	0.221
Average speed (cm/s)	< 0.001	0.582	0.118	0.370
Average movement time (s)	< 0.001	< 0.001	0.230	0.683
No. of rearing	< 0.001	0.109	0.185	0.113
Rearing time (s)	< 0.001	0.931	0.085	< 0.001
Average rearing time (s)	< 0.001	0.044	0.374	0.045

RESULTS

Exploratory behaviour. At 8 weeks of age, exploratory behaviour of 65 males and 67 females was examined. Female mice showed less activity than male mice in terms of the following variables (Table 1): rearing time and average rearing time ($p < 0.001$ and 0.05, respectively). These variables were parallel (similar longitudinal pattern without qualitative changes) in longitudinal analysis in male and female mice (Table 2), and the parallel lines between males and females indicated the significant distance ($p < 0.001$ and 0.05, respectively). The rearing time was significantly different at the 1 and 4 min ($p < 0.001$ and 0.05, respectively) between male and female mice (Fig. 1). The other variables were not significantly different between male and female mice (Table 1) and were parallel in longitudinal analysis in male and female mice (Table 2).

Spontaneous behaviour. At 9–10 weeks of age, spontaneous behaviour of 65 males and 67 females were examined. No significant differences showed between male and female mice in all measured variables (Table 3). The average rearing time was parallel in longitudinal analysis in male and female mice (Table 4). Any other variables were not parallel (different longitudinal pattern with qualitative change) according to longitudinal analysis in male and female mice (Table 4). No significant difference between males and females was observed for any variable at different time points in the longitudinal pattern (Fig. 2).

Table 3. Comparison of spontaneous behaviour in F_1-generation adult mice in the 120-minute total.

	Male	**Female**
No. of mice	65	67
Total distance (cm)	8922.9 ± 456.5	9030.0 ± 470.3
No. of horizontal activities	1006.2 ± 33.6	1028.9 ± 38.1
Movement time (s)	2443.9 ± 97.8	2462.2 ± 103.3
Average speed (cm/s)	3.56 ± 0.06	3.59 ± 0.06
Average movement time (s)	2.40 ± 0.03	2.37 ± 0.03
No. of rearing	710.0 ± 49.2	775.3 ± 52.9
Rearing time (s)	1865.9 ± 112.6	2070.4 ± 128.8
Average rearing time (s)	2.78 ± 0.10	2.76 ± 0.08

Each value represents the mean ± SE.

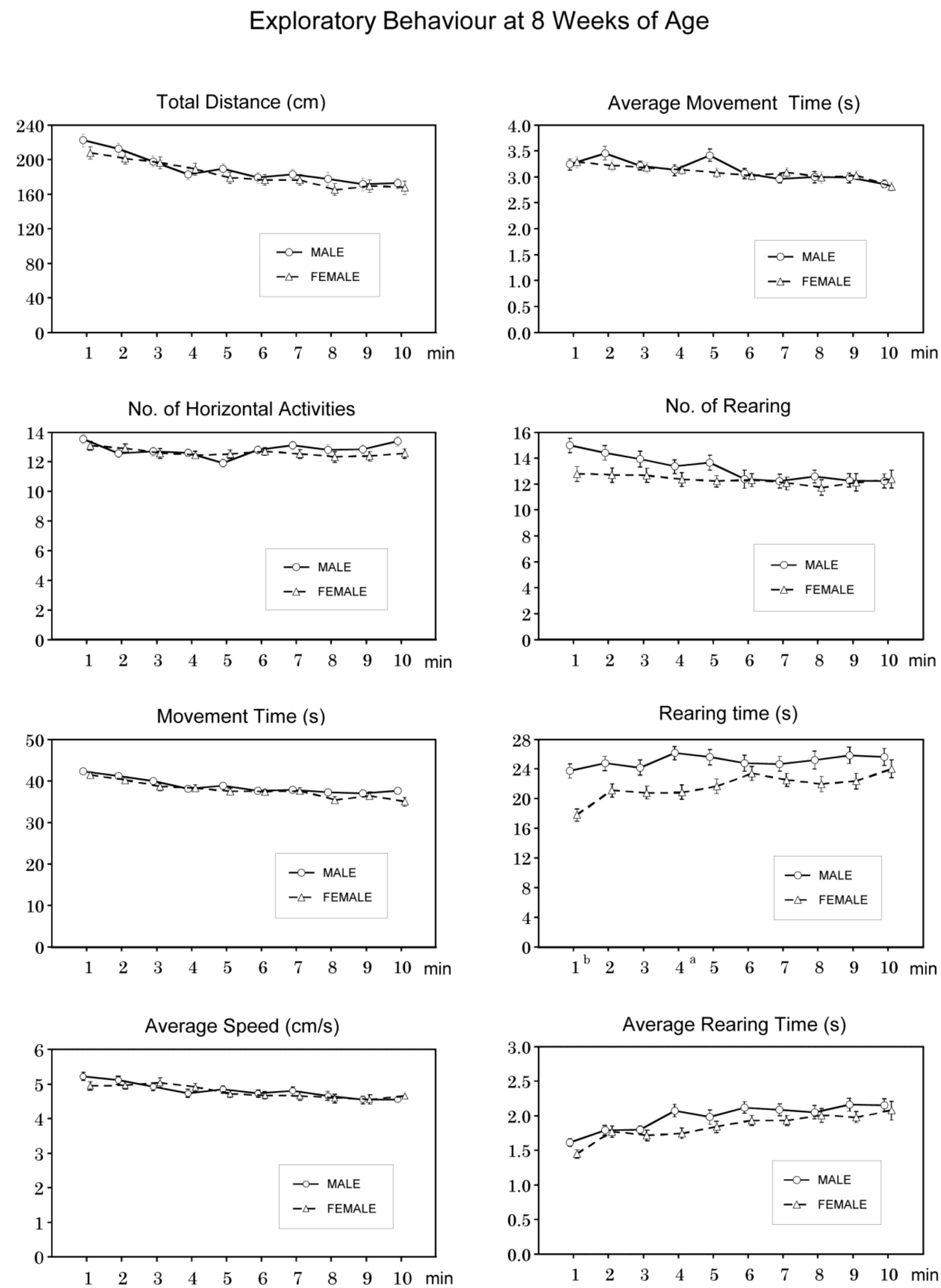

Figure 1. Longitudinal pattern of sex differences in exploratory behaviour at 8 weeks of age in F_1-generation mice. Each value represents the mean ± SE. Significant differences between sexes at different time points: $^{a}p < 0.05$, $^{b}p < 0.001$.

Table 4. Summary of profile analysis of spontaneous behaviour between F_1-generation adult male and female mice during the 120-minute observation period.

	***p*-value**			
	Equality of mean vectors	Equality of covariance	Parallelism	Distance between lines
Total distance (cm)	< 0.001	< 0.001	0.008	0.656
No. of horizontal activities	< 0.001	< 0.001	0.012	0.280
Movement time (s)	< 0.001	< 0.001	0.0021	0.005
Average speed (cm/s)	< 0.001	0.005	0.036	0.817
Average movement time (s)	< 0.001	< 0.001	0.008	0.247
No. of rearing	< 0.001	0.047	0.023	0.894
Rearing time (s)	< 0.001	0.001	0.013	0.657
Average rearing time (s)	< 0.001	< 0.001	0.242	0.410

Dispersion of behavioural variables. The dispersion (extent of variation) of measured variables was similar between the sexes in exploratory behaviour (Table 1). In spontaneous behaviour, the dispersion of all variables was similar between the sexes (Table 3). In total, 6.2% and 7.5% of male and female mice, respectively, were hyperactive in both of exploratory and spontaneous behaviour (determined by the total distance moved, >2,500 cm and >15,000 cm, respectively).

Relationship between exploratory and spontaneous behaviour. In the relationship between exploratory and spontaneous behaviour, most variables of males excluding the number of horizontal activities showed significant ($p < 0.01$) but weak ($r < 0.7$) correlations (Table 5). Nevertheless, the population correlation coefficients (ρ) of the average speed, average movement time, number of rearing, and average rearing time were similar to 0.7. In females, most variables excluding the number of horizontal activities and movement time showed significant ($p < 0.05$) but weak ($r < 0.7$) correlations between exploratory and spontaneous behaviour (Table 5). Nevertheless, the population correlation coefficient (ρ) of the average speed was similar to 0.7.

Table 5. Relationship between exploratory and spontaneous behaviour in F_1-generation adult male and female mice.

	Male	**Female**
Total distance (cm)	0.543[b]	0.281[a]
No. of horizontal activities	-0.104	-0.022
Movement time (s)	0.409[b]	0.125
Average speed (cm/s)	0.696[b, c]	0.556[b, c]
Average movement time (s)	0.583[b, c]	0.406[b]
No. of rearing	0.601[b, c]	0.493[b]
Rearing time (s)	0.496[b]	0.477[b]
Average rearing time (s)	0.621[b, c]	0.509[b]

Each value represents the correlation coefficient (*r*). Significance of the correlation coefficient: [a]$p < 0.05$, [b]$p < 0.01$. [c]No significant difference from population correlation coefficient (ρ) = 0.7: $p \geq 0.05$.

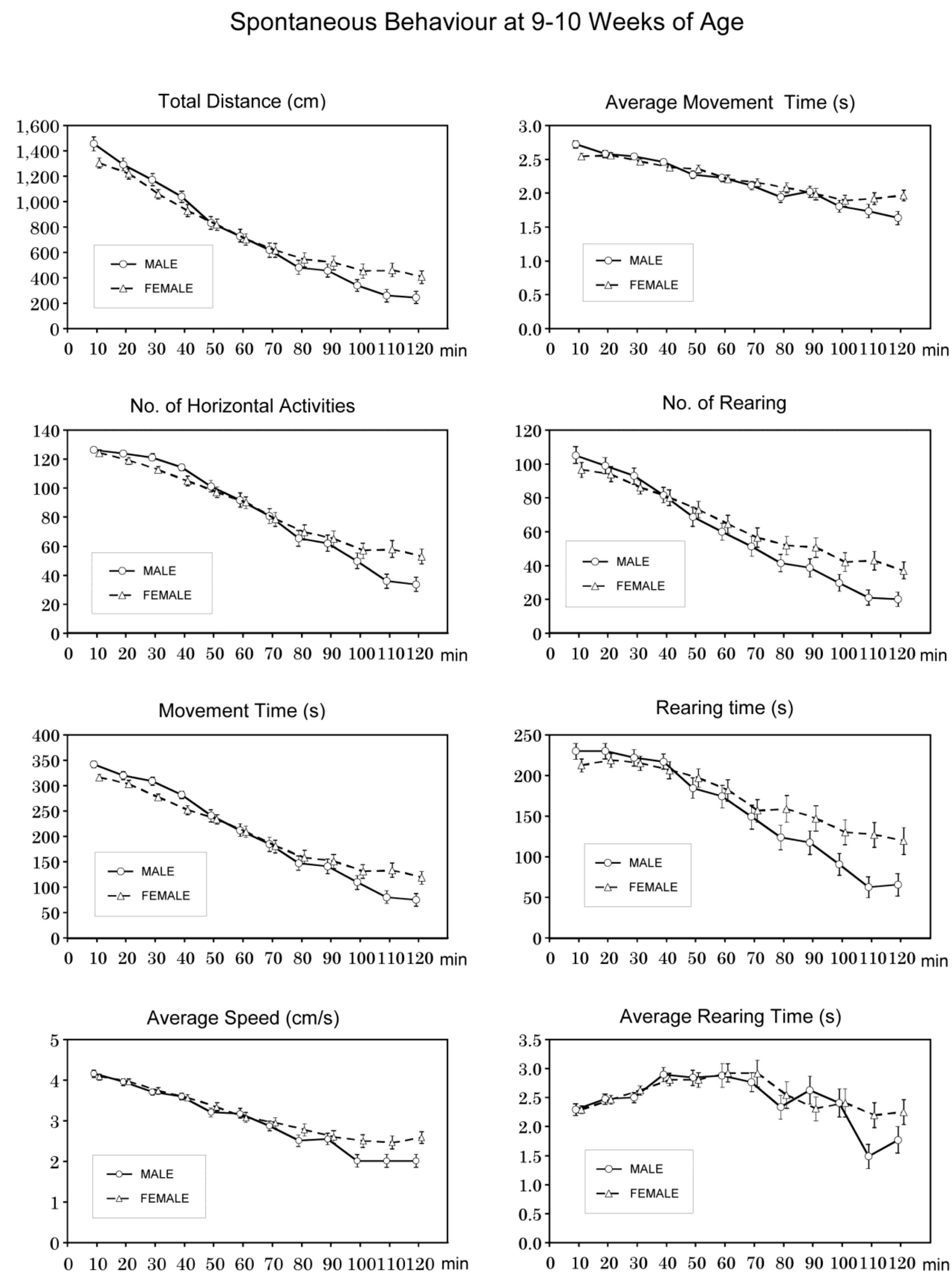

Fig. 2 Longitudinal pattern of sex differences in spontaneous behaviour at 9–10 weeks of age in F_1-generation mice. Each value represents the mean ± SE.

DISCUSSION

In this study, female mice showed lower activity levels in terms of rearing (including rearing time and average rearing time) than male mice in exploratory behaviour at 8 weeks of age. No sex difference was observed in terms of ambulation of exploratory behaviour in adult mice. Sex differences in exploratory behaviour of adult mice showed quantitative changes only (without different longitudinal pattern). In spontaneous behaviour of adult mice, most variables in ambulation and rearing excluding average rearing time showed qualitative changes only (with different longitudinal pattern). Since the results are based on old data collected over 6 years, the genetic drift over generations might influence the results. Nevertheless, it seems that genetic drift had little influence on the results because the mice were purchased from the same major supplier for each study.

The differences reported in the present study might be influenced by/due to chronic psychosocial stressor (individual housing) exposure of mice. Numerous studies (Baer 1971; Brain 1975) have suggested that individually housed rodents, including mice, may exhibit physiological and behavioural changes when compared with their group-housed counterparts (ARRP 2012). Nevertheless, several studies reported that no effects of individual housing on behavioural activities in mice (Arndt et al. 2009; Bartolomucci et al. 2009). Wild house mice are usually territorial, burrow in underground tunnels, and live alone or with their families (Mackintosh 1970; Ohdachi et al. 2015). Dominant males have their own territories and their territories include several breeding females, some of their offspring, and a few subordinate males (Bronson 1979). In the present study, it seems that few effects of individual housing on exploratory behaviour were found in both sexes.

Because body size of mice is characterized by sexual dimorphism (Korkman 1957; Eisen and Hanrahan 1972), these changes in exploratory and spontaneous behaviour may be caused by differences in body weight between the sexes. Wirth-Dzieciolowska et al. (2005) reported that selection for bodyweight induced differences in exploratory behaviour of mice. They found that the lighter group displayed a steady increase in behavioural activity during three sessions in an open-field test but displayed lower activity during the entire session than the other groups. Nevertheless, Tanaka (2010) reported that few variables associated with exploratory behaviour, except for rearing time in immature females, were influenced by the bodyweight of mice under natural conditions. Therefore, it seems that these changes in exploratory and spontaneous behaviour are caused by sex differences.

In the previous report (Tanaka 2015b), sex differences were observed in terms of ambulation and rearing of exploratory behaviour measured by the apparatus with a doughnut-shaped cage. The rate of hyperactive individuals (8.8%) of male mice was similar to the present study (6.2%). That of female mice (15.2%) was more than the present study (7.5%). In the present study, exploratory and spontaneous behaviour was measured by the apparatus with a rectangular cage. Tanaka (2015a) indicated that exploratory behaviour is influenced by differences in measuring apparatuses. These results indicate that the walls of the rectangular cages interfere with mice movement under general conditions. Illenberger et al. (2018) indicated that testing environment shape (round vs. square chambers) influences baseline and sex differences in the behaviour of rats. It, therefore, appears that the different effects on exploratory and spontaneous behaviour compared to the previous study are due to different shapes of measured cages.

Female rats were generally more active than males; however, the pattern of their activities did not differ from that of males in the open field (Valle 1970). Male Wistar rats displayed more defecation and less ambulatory behaviour than females in the open field (Masur 1972). Archer (1974) reported that male Sprague–Dawley rats showed a lower latency time and more stationary sniffing than female rats. In mice, Archer (1977) found that males showed a lower latency time (C57BL and BALB/c) and more stationary sniffing (C57BL) than females. Archer (1975) suggested that male rats typically showed more defecation behaviour than female rats. However, in mice, neither sex typically shows more defecation behaviour than the other (Archer 1975). In general, males display less ambulatory activity than females in both rats and mice. However, many studies have also reported no significant differences between the sexes.

Gray (1971) suggested that the uncertainty relating to sex differences in exploratory behaviour in mice may be caused by the predominant use of inbred strains in studies of these species. However, according to Beatty (1979), whether differences in the degree of inbreeding can explain this discrepancy remains unclear. Hsieh et al. (2017) indicated that outbred CD1 mice are as appropriate as inbred C57BL/6J mice in social behaviour performance. Tuttle et al. (2018) reported that phenotypic variations, including behaviour, indicate similar levels between inbred and outbred mice.

Lightfoot (2008) reported female rodent daily activity levels that were from 20% to more than 50% higher than those of males. Bronstein et al. (1975) observed that female Sprague–Dawley rats traversed a significantly greater distance during open-field testing than male rats, regardless of whether the animals had been handled or not. Gray (1979) suggested that similar to outbred rat strains, outbred mice strains exhibited the typical rat pattern of higher defecation rates and lower activity among males. Nevertheless, the results of the present study show the reverse in terms of rearing in the exploratory behaviour of CD1 (ICR) mice.

Broida and Svare (1984) reported that intact females were more active than their male counterparts and that although gonadectomy in adulthood reduces behavioural levels in both the sexes, it does not eliminate sex differences in spontaneous behaviour in Rockland–Swiss albino mice. Guttman et al. (1975) found that motor activity in the barrier apparatus, as measured by jumping, reached a peak during oestrus and decreased between metoestrus and dioestrus in female mice. Palanza et al. (2001) reported that proestrus mice were less sensitive to the decrease in exploratory propensity induced by individual housing than oestrus and dioestrus mice. It seems, therefore, that gonadal hormones and the oestrous cycle influence activity levels in female mice. In general, the oestrous cycle is thought to render females more variable than males. Nevertheless, Prendergast et al. (2014) indicated that randomly cycling female mice were no more variable than males on any trait.

In this study, sex differences in variables related to the rearing of exploratory behaviour showed quantitative changes. Spontaneous behaviour of female mice decreased slowly over time compared to males. Exploratory and spontaneous behaviour was measured in the same animals in this study. In male mice, the activity levels of exploratory behaviour correlated with spontaneous behaviour levels, but females showed lower correlations than males. Therefore, the weak correlations between exploratory and spontaneous behaviour might be due to the differences in the stage of the oestrous cycle when behavioural testing, even though female mice were not examined for the oestrous cycle in the present study. However, Prendergast et al. (2014) propose that the oestrous cycle need not be monitored when utilizing female mice. It, therefore, appears that these differences in relationships between exploratory and spontaneous behaviour are due to sex differences.

From the results of this study, it appears that sex differences are indicated in the rearing time and the average rearing time in exploratory behaviour of adult CD1 mice, and no difference in sex in other variables. On the other hand, in spontaneous behaviour, no sex difference is found in each variable in the 120-minute total, but the longitudinal patterns differ in males and females except for the average rearing time. These results suggest that the relationship between exploratory behaviour, indicative of response to a novel environment, and spontaneous behaviour, indicative of response under less external stimuli, differs in males and females.

CONFLICT OF INTEREST

The author declares no conflicts of interest.

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