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Research report

Behavioral and cognitive profile of mice with high and low exploratory phenotypes

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Abstract

Temperament is the heritable and relatively stable pattern of basic emotions, such as fear and anger. We explored behavioral features in mice to select distinct phenotypes with extremes of temperament. In a new environment (open-field) with a central object, two groups of 15 mice from 79 screened were separated according to high or low exploration of the object to compose the high and low exploratory groups, respectively. Their performance was mostly identical in the same task 1 week later and still distinguishable 8 months later, suggesting the presence of trait or temperamental features. These mice were further tested in other behavioral tasks. Compared to low exploratory mice, high exploratory mice were less anxious in the light/dark task and the elevated plus maze, showed increased locomotion in an open-field, improved their performance along trials in the Lashley maze (with appetitive stimulus) and had higher latency to step-down in the inhibitory avoidance task (with aversive stimulus). High exploratory mice were aggressive in the intruder test, whereas low exploratory mice were non-aggressive or submissive. These results show that individual differences in temperament influence a range of behaviors in mice. The behavioral profile of low and high exploratory mice resembled the depressive and hyperthymic temperaments of patients with unipolar depression and bipolar disorders, respectively, which may be relevant for modeling mood disorders.

Keywords: Temperament; Open-field; Novelty-seeking; Harm avoidance; Mood disorder; Animal model; Bipolar disorder; Depression

1. Introduction

Temperament is the heritable and relatively stable bias regarding automatic impulses in response to basic associative stimuli, such as punishment and novelty, which give rise to basic emotions, such as fear and anger [1]. These temperamental characteristics are essentially the same in man and other mammals and influence exploratory behavior [1]. Harm avoidance and novelty-seeking are independent dimensions of temperament that can be expressed in various degrees [2]. Harm avoidance is associated with fearfulness, low energy, pessimism and timidity [2], whereas novelty-seeking is expressed as curiosity, impulsivity, active avoidance of conditioned signals of punishment and appetitive approach in response to novelty and reward, being related to anger.

Selection based on exploratory behavior is a useful tool to study the biological bases of temperament or personality [3]. Based on these inter-individual behavioral differences, psychogenetic selection has been employed to study the bases of temperament in rodents, such as the Roman high (RHA) and low (RLA) avoidance rats [3] and aggressive and non-aggressive mice [4]. In the Roman rat line, which have been selected according to performance on two-way active avoidance, RHA show less emotional reactivity and conditioned

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fear, higher novelty-seeking behavior, increased alcohol and sugar intake and higher levels of labyrinth exploration than RLA [5]. Similarly, aggressive (SAL) mice adopt defensive burying, higher rearing and exploration, in contrast to a passive strategy and high immobility/freezing of non-aggressive mice [4]. These results suggest that RHA and aggressive rodents show 'disinhibited' temperaments, whereas RLA and non-aggressive rodents are 'inhibited'. These rodent lines have reinforced the idea that extremes of a natural temperament variation have distinct behavioral, pharmacological, physiological and neuroendocrinological profiles [3].

In this work, we used a single screening task consisting of exploration of an object in a new environment to distinguish two groups of mice, willing to represent extremes of temperament, i.e., high and low exploratory mice, respectively. The basic assumption is that the pattern of exploratory behavior results from a combination of harm avoidance (fear) and novelty-seeking (curiosity) temperaments. The screening task was repeated to verify stability over time, which should occur for temperament/trait features [1]. Moreover, other behavioral and cognitive characteristics were evaluated to verify if additional expected features are also expressed in the same animals.

2. Materials and methods

2.1. Animals

Experiments were performed with 79 CF1 male adult mice (starting at 16 weeks old, 35–45 g), housed four per cage and kept on a 12 h light/12 h dark cycle with food and water available ad libitum, except during behavioral testing and when specified otherwise. All behavioral experiments occurred during the light phase between 11:00 am and 6:00 pm and were in accordance with our institutional animals care protocols and the principles of laboratory animal care as stated in the Guide for the Care and Use of Laboratory Animals.

2.2. Behavioral separation of high and low exploratory mice

2.2.1. Open-field with a central object

This test was used to separate two extreme mice populations regarding exploration of an object in a new environment [6]. The animal was placed in an open-field (50 cm × 50 cm × 50 cm) with an object (a white cylinder of 1.5 cm radius and 6 cm high) placed on the center of the arena to stimulate exploration. Exploratory behavior was recorded for 5 min and a software registering X and Y horizontal coordinates at four frames per second analyzed the time spent by the animal in and out of an imaginary center square of 30 cm × 30 cm. Seventy-nine mice were screened, and 15 animals were selected from each extreme of exploratory behavior (the most and the least explorers) to compose the high and low exploratory groups, respectively. These 30 animals were tested again in this same apparatus 1 week and 8 months later. Mice remained in their home cages without changing housemates until the end of behavioral testing 8 months later.

2.3. Behavioral parameters tested in low and high exploratory mice

2.3.1. Open-field without central object, followed by inclusion of an object

In the same apparatus as described above, mice were placed in the open-field without any object, where their spontaneous locomotor's reaction to the novel environment was measured for 5 min. Then, an object (a 300 mL plastic cup) was placed in the center and analysis continued for another period of 5 min for determination of time spent in the center of the field as described above.

2.3.2. Light/dark anxiety test

This anxiety test was conducted in 30 cm × 60 cm × 30 cm Plexiglas shuttle boxes with translucent covers. Each box was divided in two equal-sized compartments by a wall with a 12-cm wide open door. One compartment was painted white and brightly illuminated, and the other one was painted black with very dim light. Time spent and the number of entries in each compartment were recorded for 10 min [7].

2.3.3. Elevated plus maze test

The apparatus was made of black-painted Plexiglas, with four elevated arms (40 cm from the floor, 65 cm long and 14 cm wide) arranged at right angles (cross-like disposition). Two opposite arms were enclosed by 45-cm high walls, and the other two were open (no walls). The maze had a central 5.2 cm × 5.2 cm square platform that gave access to all arms. The illumination above the central platform was 85 lux. Each mouse was placed in the central square facing an open arm. Number of entries in each arm (when all four paws had entered the arm) and time spent in each arm were recorded for 5 min (adapted from [8]).

2.3.4. Tail suspension test

Mice were suspended by the tail using adhesive tape and an observer unaware of the group being tested recorded immobility time for 10 min (adapted from [9]). Immobility time was defined as the total duration that animal showed no movement and is considered a measure of helplessness.

2.3.5. Intruder Test

Mice were tested for aggressive behaviors in a resident–intruder paradigm [8]. The intruders were those mice with intermediate performance in the screening test (exploration of an object in a new environment) from another cage. All animals were tested only once. Besides observation of dominant and subordinate roles, latency to the first aggressive act and cumulative duration of all aggressive bouts by resident mice toward intruder mice were recorded. The resident mouse was left alone in the home cage for 2 min before placing the intruder. Mice were observed for 15 min or until the occurrence of an attack.

2.3.6. Inhibitory avoidance

The apparatus was a 50 cm × 25 cm × 25 cm plastic box with a platform (2 cm high and 4 cm × 6 cm wide) placed at the center [10]. The floor consisted of parallel 0.1 cm caliber stainless steel bars spaced 1.0 cm apart. In the training session, animals were placed on the platform and the latency to step down the four paws on the grid was recorded; when stepping down, mice received three 0.2 mA, 2 s scrambled foot shock (with a 1 s intershock interval). Test session

was performed 24 h after training and the step-down latency (to a ceiling of 180 s) was recorded. No shock was given in the test session.

2.3.7. Lashley III maze

The Lashley III maze consists of a start box, four interconnected alleys and a goal box containing a food reward. Over trials, the latency of mice to locate the goal box tends to decrease, as do their errors (i.e., wrong turns or retracing). Lashley asserted that mice's performance in this maze reflected a sequence of learned motor responses that were dependent on egocentric navigation. Animals were acclimated and trained on six successive days. On the acclimation day, each mouse was placed in the four alleys of the maze, but the openings between the alleys were blocked so that the animals could not navigate the maze. Each animal was confined to the start and subsequent two alleys for 4 min and for 6 min in the last (goal) alley, where three food pellets were present. This acclimation period promotes stable and high levels of activity on the subsequent training day. Mice were food-deprived for 16 h before each trial. On the first day, each animal was placed in the start box and allowed to traverse the maze until it reached the goal box and consumed a single food pellet. After consuming the food, the animal was returned to its home cage and the apparatus was cleaned. A ceiling time of 300 s was used, after which the mouse was placed in the goal box with the food pellet. This procedure was repeated in the subsequent four days. Both the latency and errors (i.e., a turn in an incorrect direction, including those that result in path retracing) to enter the goal box were recorded on each trial (adapted from [11]).

2.4. Order of tasks

These tasks were performed in the following order, with intervals of 1–3 weeks: screening task (open-field with central object), repetition of screening task, open-field without central object (followed by inclusion of object), light/dark anxiety test, elevated plus maze test, tail suspension task, inhibitory avoidance, Lashley III maze and intruder test. Finally, the screening task was repeated 2 months after the last task.

2.5. Statistical analysis

Student's *t*-test was used in experiments with continuous measure and symmetric distribution of data to compare both groups. A general linear model with repeated measures was used to compare performance in the Lashley maze with trials as the repeated measure. The improvement in the maze was analyzed in analysis of variance with latency, number of returns to anterior corridor and number of errors through days as within-subjects factors. Sphericity was assumed for all analyses, except for the number of errors analysis, which was corrected with the Greenhouse–Geisser epsilon. Inhibitory avoidance performance was analyzed with Wilcoxon for within and Mann–Whitney for between group differences because a ceiling time was used. In the intruder test, Fisher's exact test (2×3) was conducted for aggressive behavior using three definitions: attack, absence of attack and being attacked. Correlations between these tests were analyzed with Pearson's and Spearman's tests for parametric and non-parametric data, respectively. $P < 0.05$ was considered statistically significant.

3. Results

After screening 79 mice in the task involving reaction to novelty (time spent around a central object) in a new environment, the top and bottom 15 mice regarding time spent in the center of the open-field were selected and defined as high and low exploratory, respectively. The mean time of the whole group ($n = 79$) in the center of the open-field was $20.2 \pm 14.3\%$ (mean $\pm$ S.D.), and the higher and lower cut-off values for these 15 mice were >30% and <11%, respectively. The remaining 49 animals (between 11% and 30% time in the center of the open-field) were kept to maintain the home group of high and low exploratory mice and were later used as intruders in the aggression test. In order to confirm that these behavioral traits were reproducible, the same task was performed 1 week later (17 weeks of age). Indeed, the two selected groups remained very distinct ($t = 5.32$; $P < 0.001$) in the second trial (Fig. 1), and mice performance in the first and second trials had a correlation of 0.70 (Pearson correlation; $P < 0.001$) (Table 1). Two mice from the high exploratory group which spent less than 11% of the time in the center of the open-field in the second trial and one mouse from the low exploratory group that spent more than 30% in the second trial were excluded from further behavioral testing (final sample size of 13 and 14 in the high and low exploratory groups, respectively). When this task was repeated 8 months later, their performance was still significantly different ($t = 2.2$; $P < 0.05$) with a correlation with the first trial of 0.43 (Pearson correlation; $P < 0.05$), showing that this behavior is relatively stable over time. Fig. 1 shows the results of all 27 mice in these three trials.

Other behavioral measures putatively related to novelty were tested in these two groups. In the open-field test without a central object (reactivity to a novel environment), high exploratory mice showed a significantly higher locomotor activity compared to low exploratory mice (high exploratory mice 7075.6 ± 382.8, low exploratory

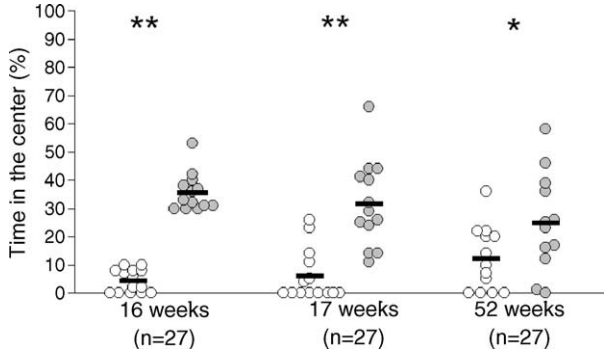

Fig. 1. Performance of low and high exploratory mice in the open-field with a central object. Three experiments were performed with the same mice at ages 16, 17 and 52 weeks. Mice were categorized in high ($n = 13$) and low exploratory groups ($n = 14$) in the first experiment (16 weeks) according to their performance. Dots represent individual mice (white, low exploratory; gray, high exploratory) and dash represents mean values. $^{*}P < 0.05$; $^{**}P < 0.001$.

Table 1
Correlations (R values) of individual ($n = 27$) performance across tasks

	1st OF	2nd OF	3rd OF	No object	Object	Locom	ELC	TLC	TST	PM_XOA	PM_TOA	InAv	LSL
1st OF		0.70**	0.43*	0.26	0.48**	0.59**	0.60**	0.71**	−0.12	0.51**	0.41*	0.36	−0.46
2nd OF	0.70**		0.26	0.15	0.67**	0.42*	0.37	0.31	−0.34	0.24	0.19	0.30	−0.31
3rd OF	0.43*	0.26		0.16	0.25	0.10	0.20	0.19	0.05	0.04	−0.10	0.09	−0.31
No object	0.26	0.15	0.16		0.32	0.32	0.16	0.21	0.22	0.19	0.10	0.17	−0.35
Object	0.48*	0.67**	0.25	0.32		0.47*	0.05	0.13	−0.22	0.31	0.31	0.09	−0.26
Locom	0.59**	0.42*	0.10	0.32	0.47*		0.47*	0.41*	−0.21	0.42*	0.42*	0.21	−0.29
ELC	0.60**	0.37	0.20	0.16	0.05	0.47*		0.86**	0.001	0.38*	0.40*	0.54**	−0.30
TLC	0.71**	0.31	0.19	0.21	0.13	0.41*	0.86**		0.11	0.49**	0.53**	0.36	−0.26
TST	−0.12	−0.34	0.05	0.22	−0.22	−0.21	0.001	0.11		−0.08	−0.15	−0.13	0.12
PM_XOA	0.51**	0.24	0.04	0.19	0.31	0.42*	0.38*	0.49**	−0.08		0.88**	0.35	−0.16
PM_TOA	0.41*	0.19	−0.10	0.10	0.31	0.42*	0.40*	0.53**	−0.15	0.88**		0.25	−0.10
InAv	0.36	0.30	0.09	0.17	0.09	0.21	0.54**	0.36	−0.13	0.35	0.25		−0.33
LSL	−0.46*	−0.31	−0.31	−0.35	−0.26	−0.29	−0.30	−0.26	0.12	−0.16	−0.10	−0.33	

OF, open-field; No object, open-field without object; Object, open-field with object after habituation; ELC, entries in the light compartment; TLC, time in the light compartment; TST, tail suspension test; PM_XOA, entries in the open arms in the plus maze; PM_TOA, time in open arms, InAv, inhibitory avoidance; LSL, Lashley maze latency in the last trial.
Pearson correlations for all variables, except for inhibitory avoidance, where Spearman Rho was calculated.
* Correlation is significant at the 0.05 level (two-tailed).
** Correlation is significant at the 0.01 level (two-tailed).

mice 5324.5 ± 511.1—means ± S.E.M.; $t = 2.74$; $P < 0.05$) (Fig. 2), and this result was statistically correlated with results of 1st open-field ($r = 0.59$; $P < 0.01$). However, the time in the center of the open-field in the habituation period without the center object was not statistically different between both groups ($t = 1.35$; $P = 0.19$). In contrast, when the central object was introduced after the 5 min habituation phase, time in the center of the open-field was again higher in the high exploratory group ($t = 2.36$; $P < 0.05$—Fig. 3). Therefore, the behavioral difference between high and low exploratory mice was at least partly related to the presence of an object to be explored. However, both mice groups showed increased object exploration if preceded by the 5 min habituation period compared to their previous trial when 17 weeks of age, but it only reached statistical significance in low exploratory mice ($P = 0.07$ for high exploratory and $P < 0.01$ for low exploratory mice).

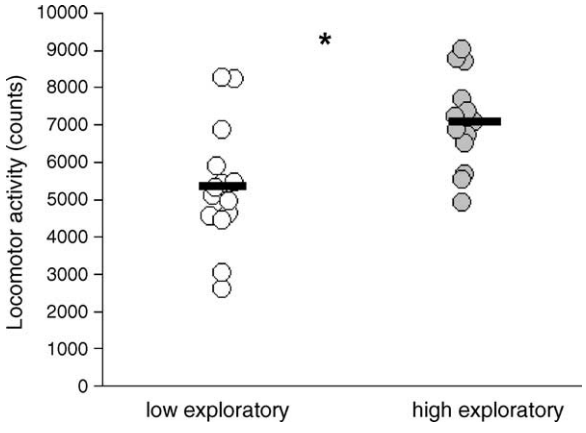

Fig. 2. Locomotor activity of low and high exploratory mice in the open-field without central object. Spontaneous locomotion was recorded for 5 min when mice were 19 weeks of age ($n = 27$). Dash represents mean values. * $P < 0.05$.

In the elevated plus maze, high exploratory mice exhibited significantly higher entries in open arms than low exploratory mice ($t = 2.69$; $P < 0.05$) but time spent in open arms failed to reach statistical significance ($t = 1.77$; $P = 0.08$) (Fig. 4). Time and number of entries in the closed arm were not statistically different between groups ($P = 0.08$ and 0.70, respectively). In the light/dark test, high exploratory animals entered more times and spent more time in the light compartment compared to low exploratory mice ($t = 3.61$ and 4.04, respectively; both $P < 0.001$) (Fig. 5).

The intruder test was performed with high and low exploratory mice against mice with intermediate performance in the screening test (time in the center of the open-field >11% and <30%). Nine out of the 13 high exploratory mice showed aggressive and dominant behavior towards the intruder. In contrast, none of the low exploratory mice attacked the intruder and two were attacked by and subordinated to the intruder. Due to the absence of attacks by the low exploratory group, latency to attack and cumulative aggressive

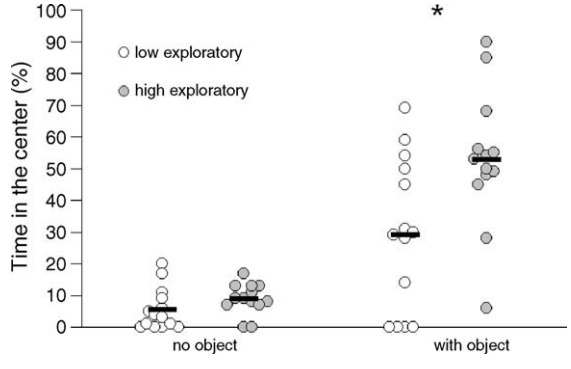

Fig. 3. Dot-plot of time spent in the center of an open-field in low and high exploratory mice before and after placing a central object. Mice (19 weeks old) explored an open-field for 5 min, followed by another 5 min after placing a central object ($n = 27$). * $P < 0.05$.

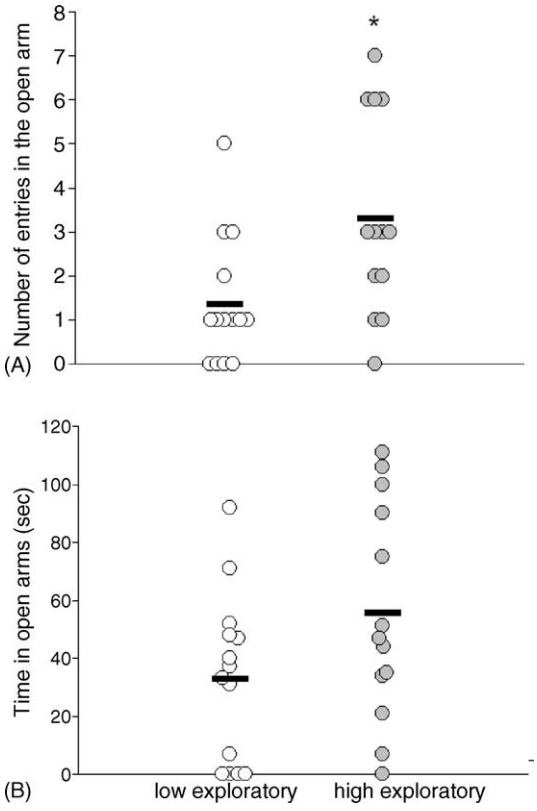

Fig. 4. Dot-plot of elevated plus maze task in low and high exploratory mice. (A) Number of entries and (B) time spent in the open arms. Mice were 21 weeks old ($n = 27$). Horizontal bars represent means. $^{*}P < 0.05$.

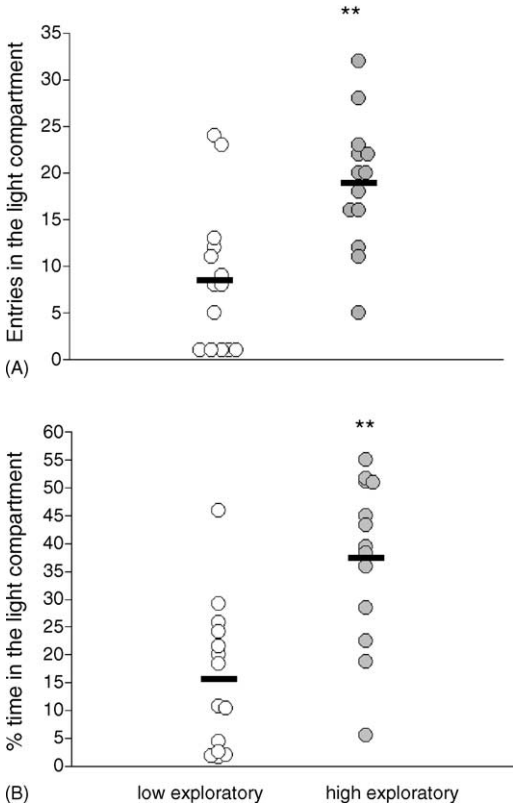

Fig. 5. Dot-plot of light/dark task in low and high exploratory mice. (A) Number of entries and (B) time spent in the light compartment. Mice were 25 weeks old ($n = 27$). Horizontal bars represent means. $^{**}P < 0.001$.

bouts could not be compared between groups. Fisher analysis shows a significant difference between groups ($P < 0.001$).

In the Lashley maze task, which evaluates performance in a maze stimulated by food, high and low exploratory mice showed a similar latency to find the reward in the first trial ($t = 0.59$; $P = 0.56$). In the four subsequent trials, low exploratory mice failed to improve performance in the maze ($F(4, 52) = 1.11$; $P = 0.36$), in contrast to high exploratory mice, which improved performance as shown by the significant lower latency to find the food reward between first and fifth trial ($F(4, 48) = 2.98$; $P < 0.05$). Furthermore, high exploratory mice were statistically different from the low exploratory in the fourth and fifth trial ($t = 2.42$ and 2.77, respectively; $P < 0.05$) (Fig. 6). Moreover, the number of wrong entries declined trial-dependently in high exploratory group (7.6 ± 1.1 to 3.2 ± 0.7; $F(4, 28.3) = 7.47$, $P < 0.01$) but not in the low exploratory (6.1 ± 0.7 to 4.7 ± 0.6; $F(4, 52) = 1.1$; $P = 0.36$).

In the inhibitory avoidance task, latency to step down in the training session was similar for both groups. In the test session, both low and high exploratory mice improved performance as shown by their increase in step-down latency ($P < 0.01$) compared to the training session. However, in the test session high exploratory mice showed a higher latency to step down when compared to low exploratory mice ($Z = 2.2$; $P < 0.05$) (Fig. 7). Together, these tasks show that high exploratory mice have higher cognitive performance and/or more appetitive approach towards reward and more avoidance of conditioned punishment.

In the tail suspension test, immobility is considered a measure of helplessness, persistence and depressive state. In this task, immobility time of high exploratory (mean ± S.E.M.: 145 ± 14 s) and low exploratory (154 ± 8 s) mice were not statistically different ($t = 0.599$; $P = 0.55$).

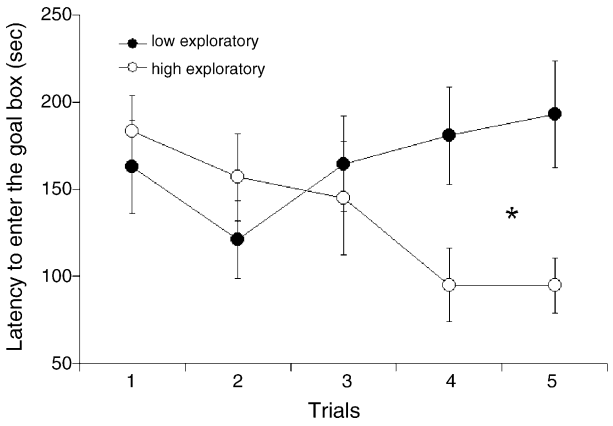

Fig. 6. Performance of low and high exploratory mice in the Lashley maze. Low and high exploratory mice were tested for five daily consecutive trials for time latency to reach the goal box. Values are shown as means ± S.E.M. Mice were 38 weeks old ($n = 27$). $^{*}P < 0.05$, ANOVA with repeated measures.

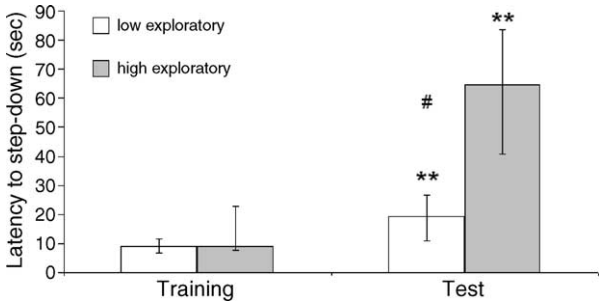

Fig. 7. Inhibitory avoidance in low and high exploratory mice. In the training day, mice received a foot-shock after stepping down from the platform and were tested 24 h later. Mice were 44 weeks old ($n = 27$). $^{*}P < 0.01$ between training and test session; $^{\#}P < 0.05$ between high and low exploratory mice.

Table 1 shows correlations between tasks (except for the intruder test), which are mostly in agreement with the direct comparisons between groups.

4. Discussion

The present results confirm that individual behavioral differences can be categorized in mice, reflecting temperamental traits that influence a range of behaviors and task performances. Also, performance in the main task used to separate extremes of temperament was reproducible and relatively stable over time, as expected for such trait features. Exploratory behavior motivated by a central object was used to enhance the contribution of the novelty-seeking component in the new environment, which is by itself anxiogenic. This selection strategy also differentiated groups in terms of locomotor response in a novel environment (without a central object), which is another parameter used as a measure of exploratory behavior and novelty-seeking [7]. The differential load of novelty-seeking characteristics between groups was confirmed in other tasks, since high exploratory mice showed more aggression (against intruders), avoidance of conditioned punishment (electric footshock) and appetitive approach to reward (food). Moreover, the contribution of harm avoidance in our screening procedure was confirmed, since tasks mostly based on fear (elevated plus maze and light/dark test) clearly differentiated both mice groups. Also, as a 5 min habituation increased object exploration in both groups (Fig. 3), initial anxiety by the novel environment was certainly involved and may have played a more pronounced role in low exploratory mice. Interestingly, no difference between high and low exploratory mice was found in the tail suspension test, which is thought to reflect levels of helplessness, but also persistence, cognitive perception of an inescapable situation and adoption of energy conserving strategies, similarly to the forced swimming test [12]. This result is in disagreement with the results of the forced swimming test in aggressive and non-aggressive mice, in which non-aggressive showed higher immobility time [13].

In contrast to other screening procedures (e.g., active avoidance task, aggressive behavior), our strategy to select temperamental extremes is relatively non-stressful (5 min exploration of an open-field with an object). Therefore, mice can be easily and rapidly selected and used thereafter without having experienced a significant event that may alter their future behavioral responses, such as suffering repetitive shocks or being defeated [14]. Since the basic emotional responses (e.g., fear, anger) involved in our screening task have been shown to have a high genetic influence [1,3], such strategy may allow the study of biological substrates of temperament without the need for psychogenetically selected lines/strains.

Matzel et al. [11] have recently shown in a group of 56 mice a positive correlation between exploration of the center of an open-field with four out of five tasks of learning and memory, including the Lashley maze and inhibitory avoidance task. In our study, using a design where high and low exploratory were pre-selected, high exploratory mice also showed a better performance in the Lashley maze and increased latency to step-down in the test session of the inhibitory avoidance task. These results can be interpreted both as higher learning ability or memory, but also as higher avoidance of conditioned punishment (as in the inhibitory avoidance task) and increased appetitive approach to reward (as in the Lashley maze), as predicted in the temperament model by Cloninger et al. [2]. Importantly, high exploratory mice were less anxious and showed higher latency to step down, which may seem counterintuitive, but is coherent with the proposal by Cloninger et al. [2]. In contrast, rats selected as anxious in the plus maze had higher retention scores in the inhibitory avoidance task than non-anxious rats [15].

Several investigations and observations show that underlying temperaments can predispose to and differentiate unipolar from bipolar mood disorders. Studies with the four-dimensional model by Cloninger et al. [2] showed that bipolar patients highly express novelty-seeking characteristics (related to anger), whereas harm avoidance (related to fear) is more evident temperamental feature of patients with unipolar depression [16–20]. Thus, a strategy based on extreme temperamental features can be useful to improve animal models for bipolar disorder and unipolar depression. In this regard, the profile of high exploratory mice (high novelty-seeking/low harm avoidance) is compatible with the hyperthymic temperament [21] or the disinhibited phenotype thought to predispose to bipolar disorder [22]. On the other hand, behavioral characteristics of low exploratory mice (low novelty-seeking/high harm avoidance) resembles the depressive temperament [21], which is related to patients with unipolar depression or the inhibited phenotype proposed to precede unipolar depression [22]. Considering that both temperament and propensity for a mood disorder have a possibly common high genetic influence [2,23,24] and that temperament and mood are closely related, the selection of extremes of temperament may be useful for the development of animal models for mood disorders. Such strategy may favor modeling the natural and likely neurobiological substrates

accounting for differences in temperament and possibly genetic predisposition to different mood disorders.

In conclusion, the selection of extremes of temperament from a simple and non-stressful task of object exploration differentiates groups of mice with particular behavioral characteristics, allowing the investigation of neurobiological substrates of temperament. Also, such inter-individual differences may be relevant to improve validity of animal models for mood disorders.

Acknowledgments

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References

[1] Cloninger CR. A new conceptual paradigm from genetics and psychobiology for the science of mental health. Aust N Z J Psychiatr 1999;33:174–86.
[2] Cloninger CR, Svrakic DM, Przybeck TR. A psychobiological model of temperament and character. Arch Gen Psychiatr 1993;50:975–90.
[3] Steimer T, Driscoll P. Inter-individual vs line/strain differences in psychogenetically selected Roman High (RHA) and Low (RLA) Avoidance rats: neuroendocrine and behavioral aspects. Neurosci Behav Rev 2005;29:99–112.
[4] Sluyter F, Korte SM, Bohus B, Van Oortmerssen GA. Behavioral stress response of genetically selected agressive and nonagressive wild house mice in the shock-probe/defensive burying test. Pharmacol Biochem Behav 1996;54:113–6.
[5] Escorihuela RM, Fernandez-Teruel A, Gil L, Aguilar R, Tobena A, Driscoll P. Inbred Roman high- and low-avoidance rats: differences in anxiety, novelty-seeking, and shuttlebox behaviors. Physiol Behav 1999;67:19–26.
[6] Dulawa SC, Grandy DK, Low MJ, Paulus MP, Geyer MA. Dopamine D4 receptor-knock-out mice exhibit reduced exploration of novel stimuli. J Neurosci 1999;19:9550–6.
[7] Kabbaj M, Devine DP, Savage VR, Akil H. Neurobiological correlates of individual differences in novelty-seeking behavior in the rat: differential expression of stress-related molecules. J Neurosci 2000;20:6983–8.
[8] Ferrari PF, Palanza P, Parmigiani S, Rodgers RJ. Interindividual variability in Swiss male mice: relationship between social factors, aggression, and anxiety. Physiol Behav 1998;63:821–7.
[9] Steru L, Chermat R, Thierry B, Simon P. The tail suspension test: a new method for screening antidepressants in mice. Psychopharmacology 1985;85:367–70.
[10] Dall'Igna OP, Da Silva AL, Dietrich MO, Hoffmann A, de Oliveira RV, Souza DO, et al. Chronic treatment with caffeine blunts the hyperlocomotor but not cognitive effects of the *N*-methyl-D-aspartate receptor antagonist MK-801 in mice. Psychopharmacology 2003;166:258–63.
[11] Matzel LD, Han YR, Grossman H, Karnik MS, Patel D, Scott N, et al. Individual differences in the expression of a "general" learning ability in mice. J Neurosci 2003;23:6423–33.
[12] West AP. Neurobehavioral studies of forced swimming: the role of learning and memory in the forced swim test. Prog Neuropsychopharmacol Biol Psychiatr 1990;14:863–77.
[13] Veenema AH, Meijer OC, de Kloet ER, Koolhaas JM, Bohus BG. Differences in basal and stress-induced HPA regulation of wild house mice selected for high and low aggression. Horm Behav 2003;43:197–204.
[14] Miczek KA, Covington 3rd HE, Nikulina Jr EM, Hammer RP. Aggression and defeat: persistent effects on cocaine self-administration and gene expression in peptidergic and aminergic mesocorticolimbic circuits. Neurosci Biobehav Rev 2004;27:787–802.
[15] Ribeiro RL, Andreatini R, Wolfman C, Viola H, Medina JH, Da Cunha C. The "anxiety state" and its relation with rat models of memory and habituation. Neurobiol Learn Mem 1999;72:78–94.
[16] Brown SL, Svrakic DM, Przybeck TR, Cloninger CR. The relationship of personality to mood and anxiety states: a dimensional approach. J Psychiatr Res 1992;26:197–211.
[17] Young LT, Bagby RM, Cooke RG, Parker JD, Levitt AJ, Joffe RT. A comparison of Tridimensional Personality Questionnaire dimensions in bipolar disorder and unipolar depression. Psychiatr Res 1995;58:139–43.
[18] Janowsky DS, Morter S, Hong L, Howe L. Myers Briggs Type Indicator and Tridimensional Personality Questionnaire differences between bipolar patients and unipolar depressed patients. Bipolar Disord 1999;1:98–108.
[19] Richter J, Eisemann M, Richter G. Temperament and character during the course of unipolar depression among in patients. Eur Arch Psychiatr Clin Neurosci 2000;250:40–7.
[20] Tillman R, Geller B, Craney JL, Bolhofner K, Williams M, Zimerman B, et al. Temperament and character factors in a prepubertal and early adolescent bipolar disorder phenotype compared to attention deficit hyperactive and normal controls. J Child Adolesc Psychopharmacol 2003;13:531–43.
[21] Maremmani I, Akiskal HS, Signoretta S, Liguori A, Perugi G, Cloninger R. The relationship of Kraepelian affective temperaments (as measured by TEMPS-I) to the tridimensional personality questionnaire (TPQ). J Affect Disord 2005;85:17–27.
[22] Hirshfeld-Becker DR, Biederman J, Calltharp S, Rosenbaum ED, Faraone SV, Rosenbaum JF. Behavioral inhibition and disinhibition as hypothesized precursors to psychopathology: implications for pediatric bipolar disorder. Biol Psychiatr 2003;53:985–99.
[23] Smoller JW, Finn CT. Family, twin, and adoption studies of bipolar disorder. Am J Med Genet 2003;123C:48–58.
[24] Akiskal KK, Akiskal HS. The theoretical underpinnings of affective temperaments: implications for evolutionary foundations of bipolar disorder and human nature. J Affect Disord 2005;85:231–9.