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Short communication

Social approach–avoidance behavior of inbred mouse strains towards DBA/2 mice

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Abstract

Little is known about the genetics of social approach–avoidance behaviors. We measured social approach–avoidance of prepubescent female C57BL/6J, DBA/2J, FVB/NJ, AKR/J, A/J, and BALB/cJ mice towards prepubescent DBA/2J female mice. C57BL/6J mice showed the greatest predominance of approach, while BALB/cJ mice showed the greatest predominance of avoidance. Thus, this phenotype is affected by spontaneous genetic variation in mice and can be measured in an assay useful for future neurogenetic studies.

Theme: Neural basis of behavior
Topic: Motivation and emotion

Keywords: Social; Behavior; Affiliation; Approach; Avoidance; Inbred strain; Genetic

Disturbances of social approach/affiliation and social avoidance behaviors are disabling symptoms of autism, social phobia, schizophrenia, and certain other neuropsychiatric disorders [21,26,34,37]; however, little is known about the basic biology of these behaviors. One powerful approach for dissecting the biology of mammalian behaviors is the use of forward and reverse genetic strategies in model organisms (e.g., mice) to identify genes that affect the behaviors [3,5,7,20,32,38]. The first steps towards undertaking such studies in mice are (1) the development of assays for measuring the behavior and (2) the measurement of the behavior in a series of common inbred mouse strains.

The most commonly used assay of rodent social exploration and affiliation is the social interaction test in which one measures the amount of time that two or more rodents spend in active, nonaggressive interactions, such as sniffing, nosing, grooming, following, or playing with each other [10–12,18,22,23,39,41]. This test allows for free interaction between the two mice, which approximates an ethologically natural interaction, but which makes it difficult to distinguish the level of social approach vs. social avoidance motivation that each mouse contributes to the complex interaction. This latter difficulty is particularly problematic for genetic studies, such as QTL mapping studies, in which the social approach–avoidance of hundreds of individual F2 or N2 mice towards a standardized social stimulus must be ascertained and compared [14].

In an effort to ''standardize'' the second (stimulus) rodent, social choice tests have been developed that allow the test rodent to make a choice between social approach and social avoidance toward a stimulus rodent that is tethered or otherwise confined to a restricted area. For example, social approach and motivation for social play has been measured in juvenile rats using a T maze [15,18] or variants of a place preference apparatus [8,30]. Similar paradigms have been used to measure mating choice in mice [35,42] and voles [19,33,44].

Recently, a social choice paradigm was recommended for high-throughput genetic studies, such as ENU mutagenesis studies or QTL mapping studies of social approach–avoidance behavior [20]. Although previous investigators have compared mouse strains in aggressive [6,17,25,27,36] and mating [43] behaviors, very little work has been done in measuring nonaggressive, nonsexual social approach (affiliative) behaviors in inbred mouse strains.

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In the present study, we sought to determine baseline levels of social approach vs. social avoidance behavior in six commonly used inbred mouse strains using a social choice paradigm. These behaviors were measured in pairs of prepubescent female mice, which should minimize the possible effect of aggressive or sexual motivations in the mice and should eliminate the estrus cycle as a variable that might affect behavior.

Female mice from the inbred mouse strains C57BL/6J, FVB/NJ, DBA/2J, AKR/J, A/J, and BALB/cJ were obtained from the Jackson Laboratory (Bar Harbor, ME) at 3 weeks of age. Upon arrival at Princeton, mice were housed in groups of 4–5 per cage in temperature-controlled rooms with a 14-h-light/10-h-dark cycle (lights on at 5:00 a.m.). Mice were given 5–9 days (average of 7 days) to acclimate to the Princeton facility prior to the day of behavioral testing. They were given Purina 5015 LabChow (Ralston Purina, St. Louis, MO) and water ad libitum. All animal procedures were in strict accordance with the NIH Health Guide for the Care and Use of Laboratory Animals and were approved by the Princeton University Animal Care and Use Committee.

In each behavioral test, a 3–4-week-old female inbred mouse (the "test" mouse) was tested for its social approach vs. social avoidance towards a second ("stimulus") mouse, which was always a 3–4-week-old DBA/2J female. Thus, stimulus mice used in all tests were genetically identical. On the morning of the behavioral testing day, test mice were individually housed for 3–7 h until the time of behavioral testing later the same day (between noon and 6:00 p.m.). This period of isolation ensured that all test mice were exposed to a similar social environment (lack of social interactions) during the hours just prior to testing. Moreover, this isolation might have heightened the motivation of test mice (or at least the motivation of certain mouse strains) for social interaction. Stimulus mice remained group housed until the time of testing.

Each test mouse and each stimulus mouse was used in only one test. Behavioral testing was conducted in the colony room in a small, dimly lit (2 lx) area that was enclosed by a curtain. The behavioral testing apparatus was a black Plexiglas rectangular box (16 in. long × 6 in. wide × 9 in. tall), consisting of three interconnected chambers (Fig. 1). The two end chambers were of equal size (5.9 × 6 in.), and the middle chamber was smaller (4.2 × 6 in.) (Fig. 1C). The apparatus did not have a top or a bottom. Prior to each behavioral test, the apparatus was placed on top of a metal cart that was covered by a clean mat and clean

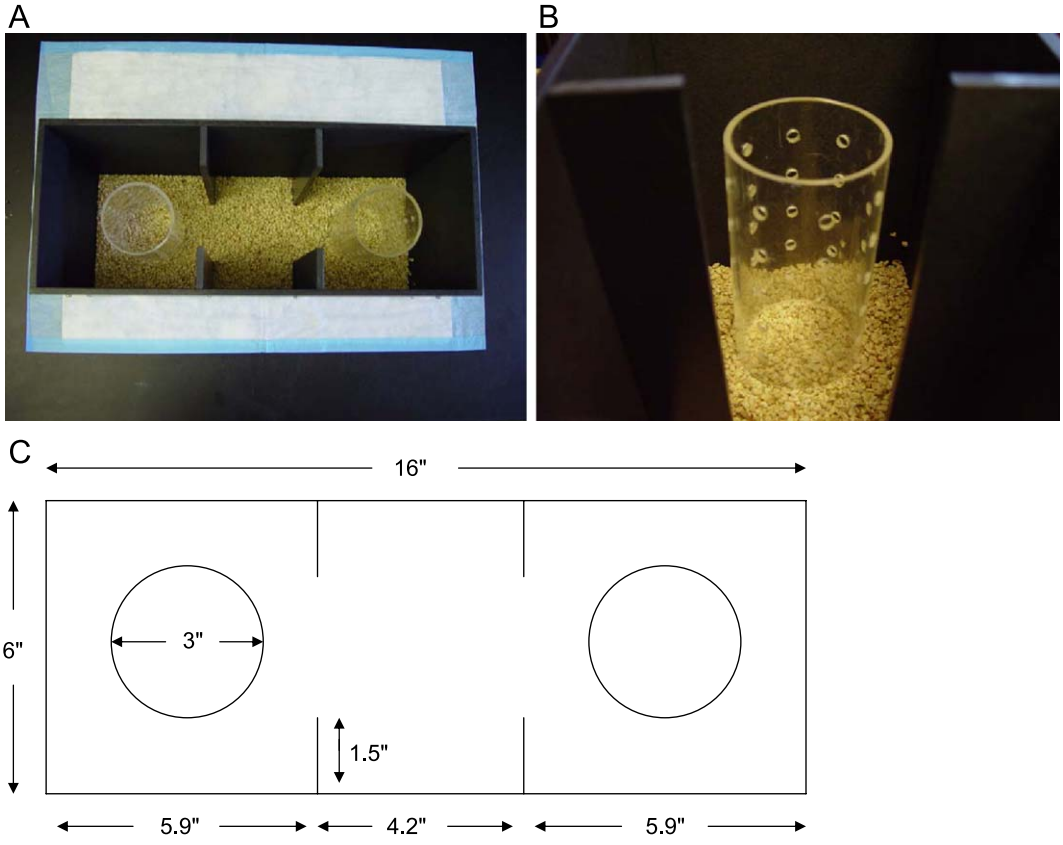

Fig. 1. Behavioral testing apparatus. (A) The social approach–avoidance testing apparatus viewed from above. There is a clear Plexiglas cylinder in each of the two end chambers, and the center chamber is empty. Prior to the start of each test, one of the end chambers was arbitrarily designated the "social side" (the side into which the stimulus mouse would be introduced), and the other end chamber was designated the "nonsocial side." (B) Multiple small holes are evenly spaced over the entire surface of the cylinders in each end chamber. (C) Dimensions of the behavioral testing apparatus.

mouse bedding (Fig. 1A). Two identical clear Plexiglas cylinders (each 3 in. in diameter, 5.8 in. tall) with removable, black Plexiglas lids were placed in the testing apparatus, one in each end chamber (Fig. 1A). The diameter of the Plexiglas cylinder was sufficiently large for a 21–28-day old DBA/2J female mouse (the stimulus mouse) to move around easily on the bottom of the cylinder. The cylinders had multiple small holes, evenly spaced over the entire surface of the cylinder, to allow for air exchange between the interior and exterior of the cylinders (Fig. 1B) and to allow for auditory, visual, and olfactory investigation between a mouse inside and a mouse outside the cylinder. The two end chambers of the apparatus were identical in every way. Prior to the start of each test, one of the end chambers was arbitrarily designated the "social side" (the side into which the stimulus mouse would be introduced), and the other end chamber was designated the "nonsocial side." Which of the two identical end chambers was designated as the "social side" was varied randomly from test to test. At the beginning of each test, the test mouse was placed in the center chamber of the apparatus and was allowed to freely explore all three chambers during a 300-s (5 min) acclimation period. The tester (A.H.) stood near the cart and used stopwatches to measure the time that the test mouse spent in each chamber during the acclimation period. The mouse was considered to be in the chamber when its head and two front paws entered the chamber. At the end of the initial 300-s period, the tops of both of the Plexiglas cylinders were removed simultaneously; the stimulus mouse was placed into the cylinder on the side that had been designated the "social side;" and then the tops were simultaneously placed back on the Plexiglas cylinders. The time that the test mouse spent in each of the three chambers was again measured over the next 300 s. At the end of each test, the mice were removed from the apparatus. The entire apparatus, including the cylinders, was then taken out of the colony room, wiped off with a paper towel moistened with a 50% ethanol solution, rinsed with copious amounts of water, and then dried. The mat and bedding that provided the floor for the apparatus was discarded, and the top of the cart was wiped off between each test to eliminate odors. A clean mat and clean bedding was placed on the cart prior to the next test.

A total of 44 C57BL/6J, 24 FVB/NJ, 37 DBA/2J, 24 AKR/J, 24 A/J, and 30 BALB/cJ mice were tested as described above. All strains were tested across multiple days. For each strain, approximately four to six mice were tested per day. In a subset of inbred mice (in 20 C57BL/6J, 20 DBA/2J, and 20 BALB/cJ test mice), the behavioral test was conducted exactly as described above, except that at the end of the usual test procedure (with the stimulus mouse in the cylinder), both cylinders were removed so that the two mice could freely interact for 120 s (2 min). During this period of free interaction, the mice were observed for any aggressive behavior, including bites, lunges, and tail rattles.

The mean time spent in each of the three chambers (social, center, and nonsocial chambers) was calculated for each mouse strain, both in the absence and then in the presence of the stimulus mouse. The time data for all three chambers cannot be included in one analysis of variance (ANOVA), because values for each of the three chambers are not independent of each other. Therefore, for analysis, an "approach–avoidance score" was calculated for each mouse by counting +1 for each second spent in the social side, 0 for each second spent in the center chamber (which represented ambivalence between approach and avoidance), and −1 for each second spent in the nonsocial side. The score was calculated both in the "absence of stimulus mouse" condition and in the "presence of stimulus mouse" condition. A positive score signified a predominance of approach toward the social side; a score of 0 signified no predominance of either approach or avoidance; and a negative score signified a predominance of avoidance. The approach–avoidance scores were analyzed using a 6 × 2 ANOVA (strain of test mouse × absence/presence of stimulus mouse) with repeated measures on absence/presence of stimulus, followed by post hoc comparisons with the Tukey procedure. The threshold for significance of the ANOVA was set at $P < 0.05$. In addition, paired *t*-tests were used to compare approach–avoidance scores for each strain in the absence vs. the presence of the stimulus mouse. Because paired *t*-tests were used for each of the six strains, a Bonferroni correction was made for multiple testing, and the threshold for significance was set at $P < 0.008$ (0.05/6 tests = 0.008).

Mean times spent in the three chambers (social, center, nonsocial) for each mouse strain, in the absence and in the presence of the stimulus mouse, are shown in Fig. 2. The analysis of variance of approach–avoidance scores revealed that various inbred strains differed in their response to a stimulus mouse (strain of test mouse × absence/presence of stimulus mouse interaction: $F_{5,176} = 9.95$, $P < 0.001$) (Fig. 3). There was a significant main effect of strain ($F_{5,176} = 6.471$, $P < 0.001$). However, due to the opposite effects of the stimulus mouse on different strains, there was no significant main effect of absence/presence of stimulus. Tukey post hoc analysis (which included all data, i.e., data from both the "absence of stimulus mouse" and the "presence of the stimulus mouse" conditions) revealed multiple significant differences between strains in social approach–avoidance scores: C57BL/6J mice showed a higher score (and thus, greater predominance of social approach behavior) than BALB/cJ ($P < 0.01$) and A/J ($P < 0.05$) mice; FVB/NJ mice showed a higher score than BALB/cJ mice ($P < 0.01$); DBA/2J mice showed a higher score than BALB/cJ mice ($P < 0.01$); and AKR/J mice showed higher score than BALB/cJ mice ($P < 0.05$) (Fig. 3). The paired *t*-tests revealed that, in the presence of a stimulus mouse, C57BL/6J and FVB/NJ mice showed a significant increase in social approach–avoidance score (an increase in approach toward the social side) ($P < 0.008$ for each strain), whereas BALB/cJ mice showed a significant decrease in social approach–avoidance score (an increase in avoidance of the social side) ($P < 0.008$), relative to baseline. The other strains showed no

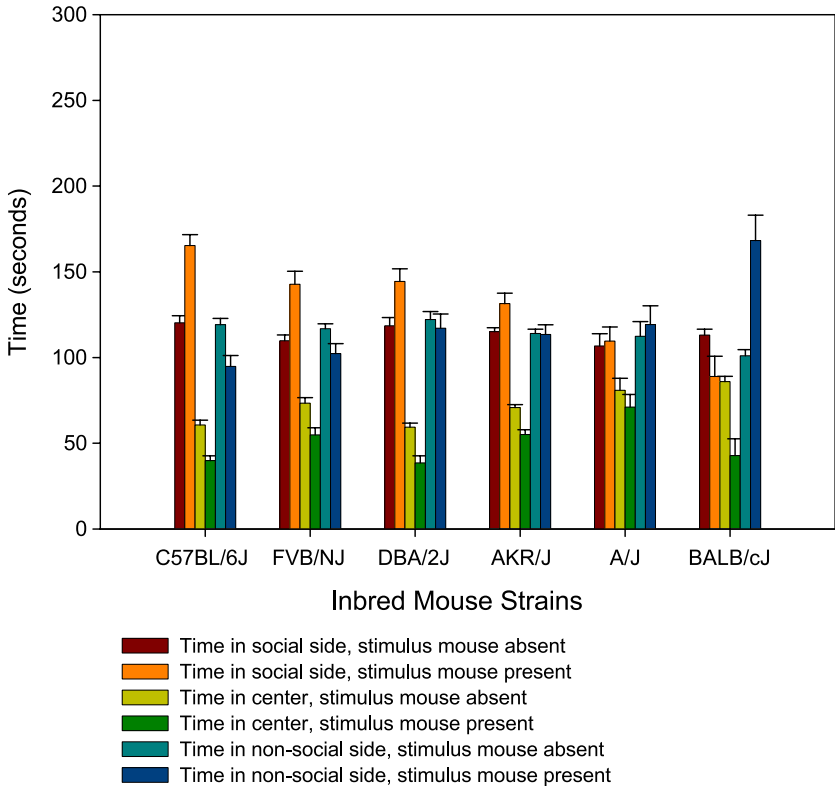

Fig. 2. Time (seconds) (mean ± S.E.) spent in each of the three chambers of the apparatus for each inbred mouse strain in the absence and the presence of a stimulus mouse.

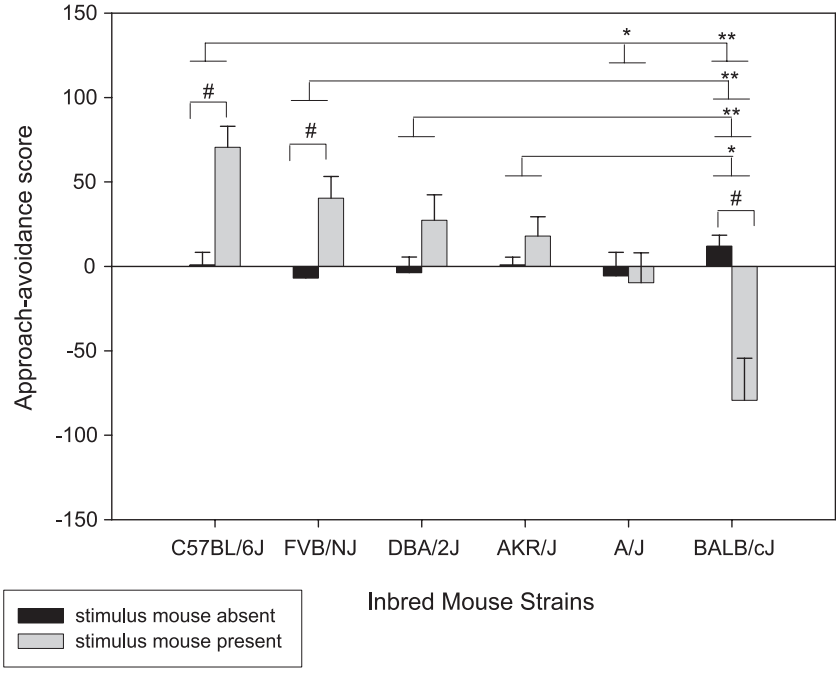

Fig. 3. Comparison of inbred strains in their social approach–avoidance towards a DBA/2 stimulus mouse. Approach–avoidance score (see main body of article for definition) is shown for all strains (mean ± S.E.) in the absence of a stimulus mouse (black bars) and in the presence of a stimulus mouse (grey bars) on the social side. Inbred strains: C57BL/6J ($n=44$), FVB/NJ ($n=24$), DBA/2J ($n=37$), AKR/J ($n=24$), A/J ($n=24$), and BALB/cJ ($n=30$). The inbred strains differed in their approach vs. avoidance of a stimulus mouse in the social side (strain of test mouse × absence/presence of stimulus mouse interaction: $F_{5,176}=9.95$, $P<0.001$). *$P<0.05$, **$P<0.01$ (Tukey post hoc analysis). In the presence of a stimulus mouse, C57BL/6J and FVB/NJ mice showed a significant increase in approach–avoidance score (increase in approach), whereas BALB/cJ mice showed a significant decrease in approach–avoidance score (increase in avoidance). $^{\#}P<0.008$ (paired t-tests).

significant change in social approach–avoidance score in the presence of the stimulus mouse (Fig. 3).

No aggressive behavior was observed between any of the C57BL/6J or DBA/2J test mice and the stimulus mice. One BALB/cJ mouse out of 20 attacked (bit) a stimulus mouse. Thus, the vast majority of mice did not display aggressive behavior in a 2-min period at the end of the test.

We have demonstrated significant differences among several inbred mouse strains in social approach–avoidance behavior of prepubescent females towards a prepubescent, female DBA/2 stimulus in a social choice test, which has been recommended for high-throughput genetic studies [20]. C57BL/6J and FVB/NJ mice showed a predominance of social approach behavior towards a stimulus mouse, whereas BALB/cJ mice showed a predominance of social avoidance from the stimulus mouse. These differences among inbred mouse strains demonstrate that genotype affects social approach–avoidance in prepubescent female mice in this assay.

In general, the social approach vs. social avoidance of one mouse towards an unfamiliar other mouse is likely to be the net result of a complex, and sometimes conflicting, set of motivations, including motivations that might lead to approach (social investigation, play, sex, or offensive aggression [19,24,30]) and motivations that might lead to avoidance (generalized anxiety or social anxiety [e.g., perception of the other mouse as a threat] [1,11]). The relative importance of these various motivations would be expected to differ, depending on the age, sex, strain (genotype), and social experience of the two mice in the interaction.

In designing our study, we were less interested in approach–avoidance based on sexual or aggressive motivations. In an effort to minimize the effect of these motivations and to eliminate the estrus cycle as a potential variable, we used pairs of prepubescent female mice, which would be expected to have no sexual and minimal aggressive motivations towards each other, and we confirmed that aggressive motivations were minimal in the prepubescent female C57BL/6J, DBA/2J, and BALB/cJ mice. The behavioral difference we found between C57BL/6J and BALB/cJ mice may have been at least partly due to differences between prepubescent females of these strains in social anxiety, i.e., anxiety in the presence of an unfamiliar female DBA/2J mouse. Previous studies have demonstrated higher levels of anxiety-related behaviors in BALB/cJ mice relative to C57BL/6J mice in some but not all behavioral paradigms [4,40].

While additional studies will be necessary to determine the relative importance of various stimuli (e.g., visual, auditory, or olfactory cues) in eliciting social approach vs. avoidance behavior, there is strong evidence from other studies that olfactory signals are important in mouse social behaviors. In particular, recognition of other mice may be mediated by olfactory perception of major urinary proteins (MUPs), which vary based on the genotype of the mice [16,29]. In our study, there did not appear to be any clear correlation between the closeness of genealogical relationship between test and stimulus (DBA/2J) mice [2], on the one hand, and tendency towards social approach vs. social avoidance, on the other.

Several other studies have compared small numbers of inbred mouse strains in social approach–avoidance behaviors. Variations in results across studies may be explained by variations in behavioral testing procedures, as well as variations in the age, sex, and social experience of mice used in the different studies. Pieper et al. [31] found that in adult mice that had been housed together, DBA/2J mice were more socially affiliative with each other than adult C57BL/6J mice in a modification of an open-field test. There were many methodological differences between the Pieper et al. study and our study, however, including differences in the behavioral testing procedure, the age of the mice, and the level of the familiarity between pairs of mice.

In contrast to our study, Avgustinovich et al. [1] found that pairs of adult male BALB/cJ mice on either side of a partitioned cage spent more time near each other than did pairs of adult male C57BL/6J mice. However, adult male BALB/cJ mice are known to show high levels of aggression towards other males [13,28], which may have prompted their social approach behavior in this study. In another study, which allowed free interaction among groups of adult male mice of the same strain, BALB/cJ mice showed significantly greater aggressive behavior than groups of C57BL/6J, but BALB/cJ males spent more time resting alone and less time in "social resting" relative to C57BL/6J mice, although these latter differences did not reach statistical significance [28].

Our results demonstrate that social approach–avoidance behavior is affected by spontaneous genetic variation in mice, and that phenotypic differences can be measured in an assay that would be useful for genetic studies. Because unknown particularities of laboratory environments can affect mouse behaviors [9], the pattern of strain differences reported here will need to be confirmed by other laboratories. Our findings are specific to interactions between prepubescent female mice, using a standard prepubescent female DBA/2J stimulus, and cannot be generalized to male mice or adult mice. Future studies are needed to measure social approach–avoidance behaviors in males, as well as in mice across various stages of development, using a period of free interaction between the mice in order to discern sexual or aggressive motivations in approach–avoidance behaviors. Moreover, future studies that use additional strains as test and stimulus mice may advance our understanding of mouse strain differences in social approach–avoidance behaviors, further paving the way for genetic studies.

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