Archival Report

Biological Psychiatry

Waving Through the Window: A Model of Volitional Social Interaction in Female Mice

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ABSTRACT

BACKGROUND: Mouse models of social behavior fail to account for volitional aspects of social interaction, and current neurobiological investigation of social behavior is performed almost exclusively using C57BL/6J mice, the background strain of most transgenic mice. Here, we introduce a mouse model of operant social self-administration and choice, using a custom-made apparatus.

METHODS: First, we trained adolescent and adult female C57BL/6J and CD1 mice to self-administer palatable food pellets and then to lever press under increasing fixed-ratio response requirements for access to an age-matched female social partner. Next, we tested their motivation to seek social interaction using a progressive ratio reinforcement schedule, relapse to social seeking after social isolation, and choice between palatable food versus social interaction. We also tested social conditioned place preference in adult female CD1 and C57BL/6J mice.

RESULTS: Adolescent and adult female mice of both strains showed similar rates of food self-administration. In contrast, CD1 mice demonstrated significantly stronger social self-administration than C57BL/6J mice under both reinforcement schedules. CD1 but not C57BL/6J mice demonstrated robust social seeking after social isolation. In the choice task, CD1 mice preferred social interaction, whereas C57BL/6J mice preferred food. CD1 but not C57BL/6J mice demonstrated robust social conditioned place preference. The strain differences were age independent.

CONCLUSIONS: Our data show that CD1 mice are a better strain for studying female social reward learning. Our mouse operant social model provides a tool for research on neurobiological substrates of female social reward and disruption of social reward in psychiatric disorders using mouse-specific genetic tools.

https://doi.org/10.1016/j.biopsych.2021.10.023

Social interaction is a critical aspect of animal behavior. Social interaction can serve as a strong natural reward and promote survival through formation of social groups (1). Maladaptive social interactions feature prominently in neuropsychiatric disorders, including autism, schizophrenia, and drug addiction (2–4). Positive social interactions and social support can have a protective effect against neuropsychiatric disorders, including drug addiction (3), posttraumatic stress disorder and anxiety disorders (5,6), and schizophrenia (7). Therefore, it is important to understand neurobiological bases of rewarding social interaction using rodent behavioral models (3,8–10). Mice offer diverse genetic tools for identification and manipulation of specific cell types and circuits of social behavior (11–18). However, there is debate about whether mice are an appropriate model for social behavior given their lower social motivation compared with rats (19–21).

Mouse studies on social behavior have relied on measures such as time spent in contact with a social partner or preference for a social-paired context [but see (22)]. These measures fail to assess volitional (subject-controlled) rewarding social interaction because the social interaction is experimenter imposed. Additionally, most mechanistic studies of social behavior have used either C57BL/6 mice or mice bred on a C57BL/6 genetic background. It has been suggested that C57BL/6 mice are a socially motivated mouse strain (23–25). However, we and others reported that in C57BL/6 mice, social conditioned place preference (CPP) is highly variable, only weakly expressed under specific experimental conditions, and typically not observed under conditions where CPP for addictive drugs and food is reliably observed (25–27). A recent study demonstrated operant social self-administration in adult male or female C57BL/6 mice trained to nose poke for social interaction with a novel adolescent partner (22). However, interpretation of these data and their translational relevance in the context of operant social reward are unknown because an alternative account of these results is that the rewarding stimulus is dopamine-dependent novelty exposure (28) rather than social interaction.

In addition to strain and species, both developmental stage and sex are important factors to consider in social behavior studies. Across species, the adolescent stage is characterized by strong social motivation and brain maturation, including reward-related circuits (19,21,29–34). Rats engage in social play most fervently during the juvenile stage and into adolescence (20,21). Play behavior is weaker in mice; however, mice engage in behavior typical of the adolescent period in humans,

including increased novelty seeking and risk taking (35). Models of social behavior in mice are typically conducted in juvenile to young adult mice and seem particularly sensitive to parametric considerations (23,24,30). Sex differences across development are an additional critical factor in guiding social interactions and social reward (25,30,36). Thus, age, species, strain, environmental experience, and sex are factors to consider when using social behavior models in rodents (11,23,27,30,37–39).

Here, we introduce an operant model of social learning and choice in female mice based on a model recently developed in rats (40–44). We systematically compared female adolescent and adult C57BL/6 mice and outbred CD1 mice. We had three reasons for focusing exclusively on female mice. The first was the need for animal models developed in females (45,46). The second was that, as described below, male C57BL/6J mice did not show reliable operant social self-administration. The third was that male CD1 mice cannot be used in studies on rewarding operant social interaction with a same-sex peer because they will lever press for the opportunity to attack another male mouse (47–49). Unexpectedly, the results described below demonstrated that operant social self-administration, social seeking during periods of isolation, and choice of social interaction over palatable food are significantly stronger in female CD1 mice than in female C57BL/6J mice and that these effects are age independent.

METHODS AND MATERIALS

Subjects

We used 194 mice, 84 C57BL/6J (resident mice: 40 females, 6 males; partner mice: 34 females, 4 males) and 110 female CD-1 (resident mice: 58 females, partner mice: 40 females). Additional details are provided in the Supplement. We started adolescent and adult food self-administration at postnatal days 26–28 and postnatal days 70–74, respectively.

Experiment 1: Effect of Age and Strain on Operant Social Self-administration, Seeking, and Choice

We trained groups of adolescent and adult female C57 and CD1 mice to lever press for access to an age- and sex-matched social partner. We also included a control group of adult mice for each strain that were trained to lever press to obtain access to an empty chamber. The experiment included 5 phases: 1) food self-administration, 2) social self-administration under a fixed-ratio (FR) 1–to–FR6 reinforcement schedule, 3) social self-administration under a progressive-ratio (PR) reinforcement schedule, 4) social seeking tests under extinction conditions after 1 or 15 isolation days, and 5) discrete choice between social interaction (FR1–FR24 schedule) versus food (FR1 schedule). The details of each phase are provided in the Supplement.

Experiment 2: Effect of Housing Condition on Social Self-administration in CD1 Mice

We housed adult female CD1 mice in groups of 4 or in isolation for 60 days. We then housed them in isolation for 7 additional days before social self-administration (FR1–FR6 reinforcement schedule) training. We then either group housed the mice or kept them isolated to test the effect of acute social devaluation (group housing) on social self-administration under the FR6 schedule.

Experiment 3: Effect of Strain on Social CPP

Experiment 3 included 4 phases: pretest, CPP training, CPP test 1, and CPP test 2. During the 15-minute pretest, we allowed the mice to freely explore all three chambers of the CPP apparatus (26). We used counterbalanced side assignment such that initial baseline preference was approximately 50% between each of the two chambers (unbiased CPP procedure). During CPP training, we restricted the mice to one side of the chamber for 30 minutes either with a social partner (paired side) or in isolation (unpaired side). We conditioned mice for 7 days, with one 30-minute session in the morning and another 30-minute session in the afternoon separated by 3 hours or more. We conducted a 15-minute CPP test session 2 days after the final conditioning session (CPP test 1), during which time the mice were again allowed to freely explore the apparatus. We retested the mice 7 days later (CPP test 2). We measured social CPP by subtracting time spent in the unpaired side from time spent in the paired side. We also performed behavioral analysis in a single 30-minute conditioning session during which mice directly interacted. The details of this analysis are provided in the Supplement.

Statistical Analysis

A detailed description of the statistical procedures is provided in the Supplement.

RESULTS

Effect of Age and Strain on Operant Social Self-administration, Social Seeking, and Social Choice

Overview. In experiment 1, we used our custom-built, automatic social self-administration chambers (Figure S1) to examine social self-administration in C57BL/6J and CD1 adolescent and adult female mice. Our original intention was to develop the operant social self-administration in male and female C57BL/6J mice because this is the background strain for most transgenic mouse lines. However, in a pilot study we failed to demonstrate reliable social self-administration in these mice (Figure S2). Thus, we developed the operant social model using the outbred CD1 strain. Male CD1 mice engage in aggressive social interactions with other male mice, which they find rewarding (47), whereas female CD1 mice typically do not (but see [50]). Thus, we compared operant social behavior exclusively in female CD1 and C57BL/6 mice. We trained adolescent and adult female mice of both strains to lever press for access to an age- and sex-matched social partner and compared them with control groups for each strain where adult mice were trained to lever press to obtain access to an empty chamber. We conducted the experiment in 5 consecutive phases: 1) food self-administration (8 days, 1 hour/day, FR1 schedule) (Figure S3), 2) social self-administration (23 days, 1 hour/day, FR1-6 schedule), 3) social PR testing (3 days, up to 3 hours/day), 4) social seeking after 1 or 15 isolation days (30-minute test under extinction conditions), and 5) food versus social choice testing (6 days, 10 trials/day, FR1 schedule for

food throughout testing, FR1–FR24 schedule for social interaction).

Food Self-administration. There were no strain differences for food rewards earned during self-administration under the FR1 schedule, although there were differences in lever pressing between strains (Figure 1; see Table S1 for statistical details). The analysis of the mean number of pellets during the last 4 days of food self-administration, which included the between-subjects factors of strain (C57BL/6J, CD1) and age (adolescent, adult), showed no significant effects. The analysis of lever presses, which included the between-subjects factor of strain and age and the within-subject factor of lever (inactive, active), showed a significant lever × strain interaction ($F_{1,34}$ = 4.7, p = .04) owing to age-independent higher active lever responding in CD1 females.

We also compared the same adult C57BL/6J and CD1 mice with control groups of adult C57BL/6J and CD1 mice that lever pressed to open the door and access an empty chamber (no-partner controls) during phase 2 of the experiment (Figure S3; see Table S1 for statistical reporting). Control mice earned slightly more food pellets, but there was no significant effect of strain on food rewards earned.

Social Self-administration Under Different FR Reinforcement Schedule Requirements. Lever presses for social interaction under the different FR schedule conditions were significantly higher in CD1 mice than in C57BL/6 mice; this effect was age independent (Figure 2). For the analysis, we averaged data from the final 4 days of social self-administration on the FR1 schedule, 2 days on the FR2 and FR4 schedules, and 4 days on the FR6 schedule. The analysis of social rewards earned, which included the between-subjects factors of strain and age, and the within-subjects factors of FR schedule (1, 2, 4, 6), showed a significant FR × strain ($F_{3,126}$ = 6.3, p < .001). The analysis of lever presses, which included the between-subjects factors of strain and age and the within-subjects factors of FR schedule and lever, showed significant strain × FR schedule × lever interaction ($F_{3,126}$ = 39.8, p < .001). These interactions reflect the higher sensitivity of CD1 mice to increased FR requirements (Figure 2).

We also compared the same adult C57BL/6J and CD1 mice with no-partner control groups of adult C57BL/6 and CD1 mice (Figure S4; see Table S1 for statistical reporting). The analysis of this data set showed significantly higher responding for social interaction and higher sensitivity to the FR requirements in CD1

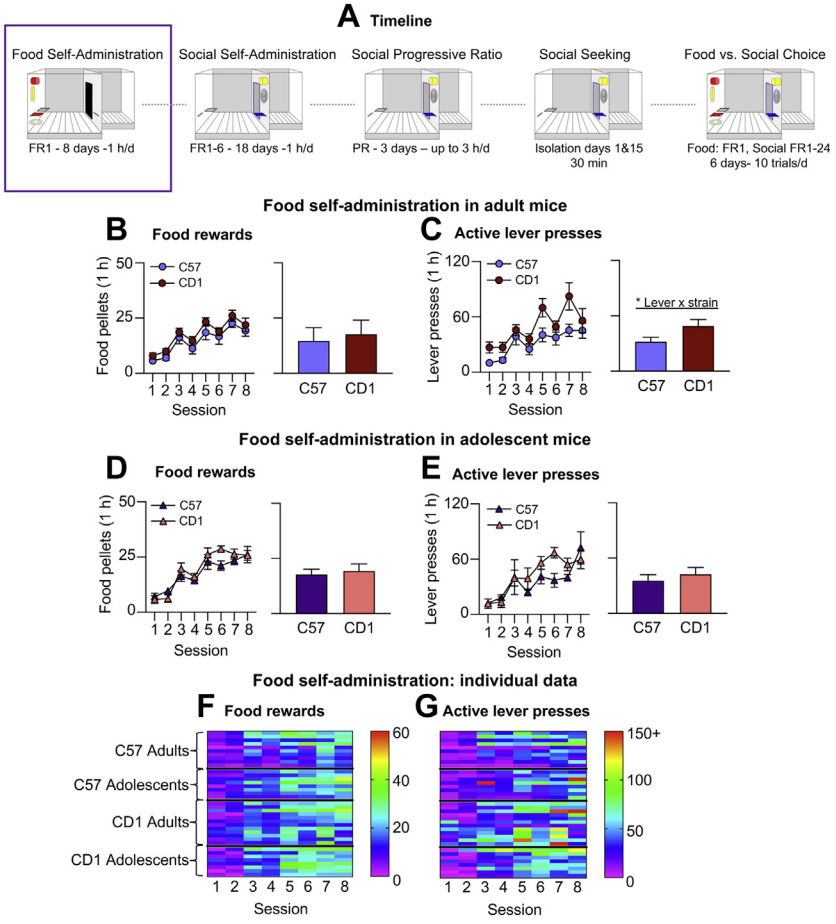

Figure 1. Adult and adolescent C57BL/6J and CD1 mice train similarly to self-administer palatable food pellets. **(A)** Timeline of the experiments. Purple box highlights the phase of training that is described in the figure. **(B–E)** Food self-administration training in adult (**B, C**) and adolescent (**D, E**) female mice: **(B, D)** food pellets earned, **(C, E)** lever presses. Bar graphs to the right in panels **(B–E)** represent average data from the final 4 sessions of training. **(F, G)** Individual data heat maps (CD1 adults: n = 12, CD1 adolescents: n = 8, C57BL/6J adults: n = 10, C57BL/6J adolescents: n = 8; all females). Data are mean ± SEM. *Denotes significant lever × strain interaction (p < .05). FR, fixed-ratio.

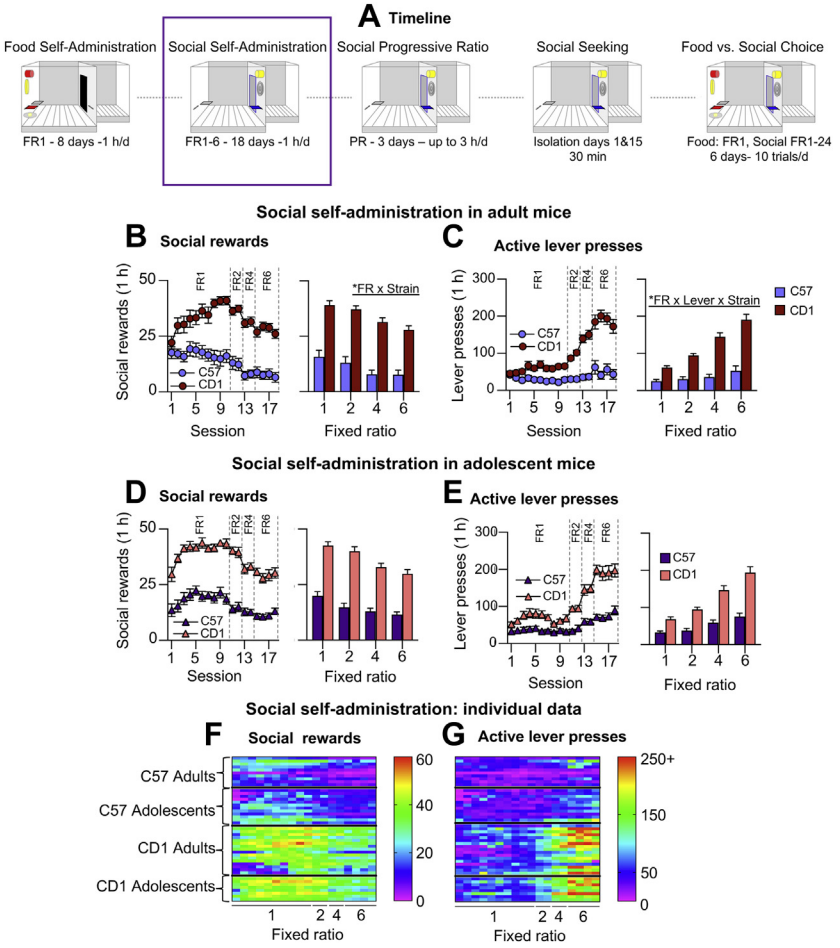

Figure 2. CD1 mice lever press more for access to a social partner on an increasing FR reinforcement schedule requirement than C57BL/6J mice independent of age. **(A)** Timeline of the experiments. Purple box highlights the phase of training that is described in the figure. **(B–E)** Social self-administration training in adult **(B, C)** and adolescent **(D, E)** female mice: **(B, D)** social rewards earned, **(C, E)** lever presses. Bar graphs to the right in panels **(B–E)** represent average data from the 2 training sessions at FR2 or FR4 or the final 4 training sessions at FR1 or FR6. **(F, G)** Individual data heat maps (CD1 adults: n = 16, CD1 adolescents: n = 8, C57BL/6J adults: n = 10, C57BL/6J adolescents: n = 12; all females). Data are mean ± SEM. *Denotes significant FR × strain interaction **(B, D)** or FR × lever × strain interaction **(C, E)** (both $p < .001$). FR, fixed-ratio; PR, progressive-ratio.

mice than in C57BL/6J mice. The CD1 mice also showed higher nonreinforced lever presses in the absence of the social reward but showed significantly higher operant responding when the door opening resulted in social interaction, an effect that was stronger at the higher FR requirements (Figure S4).

Social Self-administration Under a Progressive Ratio Schedule. Lever presses for social interaction under the PR schedule were significantly higher in CD1 mice than in C57BL/6J mice; this effect was age independent (Figure 3). The analysis of the number of social rewards earned, which included the between-subjects factors of age (adolescent-trained, adult-trained) and strain and the within-subjects factor of session (1, 2, 3), showed a significant effect of strain ($F_{1,42}$ = 28.2, $p > .001$), but no other significant main or interaction effects. The analysis of lever presses is provided in Table S1.

We also compared the same adult C57BL/6J and CD1 mice with no-partner control groups of adult C57BL/6J and CD1 mice (Figure S5; Table S1). The statistical results showed that lever presses were higher in the partner condition than in the no-partner condition in both strains and, as with the FR schedule, higher non-reinforced lever presses in the CD1 mice without social interaction.

Social Seeking During Social Isolation. Non-reinforced lever presses during the social-seeking tests were significantly higher in CD1 mice than in C57BL/6J mice; additionally, in CD1 mice (but not C57BL/6J mice) the duration of social isolation had no effect on adult social seeking, but appeared to increase (incubate) adolescent social seeking (Figure 4). The analysis, which included the between-subjects factors of age (adolescent-trained, adult-trained) and strain and the within-subjects factors of isolation day (1, 15) and lever showed significant strain × isolation day ($F_{1,34}$ = 6.9, p = .01), age × isolation day ($F_{1,34}$ = 10.7, p = .002), and age × isolation day × lever ($F_{1,34}$ = 8.4, p = .006) interactions.

We also compared the same adult C57BL/6J and CD1 mice with no-partner control groups of adult C57BL/6J and CD1 mice (Figure S6; Table S1). The data showed that in CD1 mice, lever presses in the presence of the social partner were significantly higher than in the absence of the partner on both test days. In contrast, for C57BL/6J mice, responding for the social partner was higher after 1 isolation day, but not 15 isolation days.

Choice Between Social Interaction and Food. Under the FR1 schedule for both food and social interaction, CD1 mice

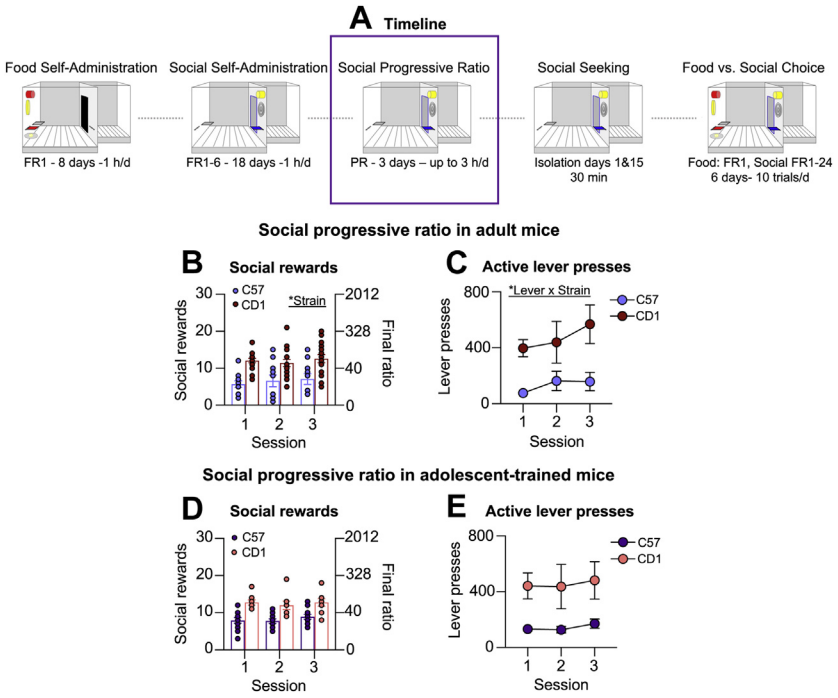

Figure 3. CD1 mice earn more social rewards on a PR reinforcement schedule than C57BL/6J mice regardless of age of social self-administration training. **(A)** Timeline of the experiments. Purple box highlights the phase of training that is described in the figure. **(B–E)** Social PR responding in adult **(B, C)** and adolescent **(D, E)** female mice: **(B, C)** social rewards earned during each session (sessions ended after either 30 minutes of no reinforcement or 3 hours), **(C, E)** lever presses during each session (CD1 adults: n = 16, CD1 adolescent-trained: n = 8, C57BL/6J adults: n = 10, C57BL/6J adolescent-trained: n = 12; all females). Data are mean ± SEM. *Denotes significant main effect of strain **(B, D)** ($p <$ .001) or lever × strain interaction **(C, E)** (p = .001). FR, fixed-ratio; PR, progressive-ratio.

preferred social interaction, whereas C57BL/6J mice preferred food; this effect was age independent (Figure 5). We then increased the FR requirements for social interaction progressively from FR1 to FR24 while keeping the FR1 schedule for food. In both strains, preference for social interaction decreased with increased response requirements for this reward. The analysis of the preference score, which included the between-subjects factors of age (adolescent-trained, adult-trained) and strain and the within-subjects factor of FR schedule, showed a significant FR schedule × strain interaction ($F_{4,132} = 3.7$, $p = .007$).

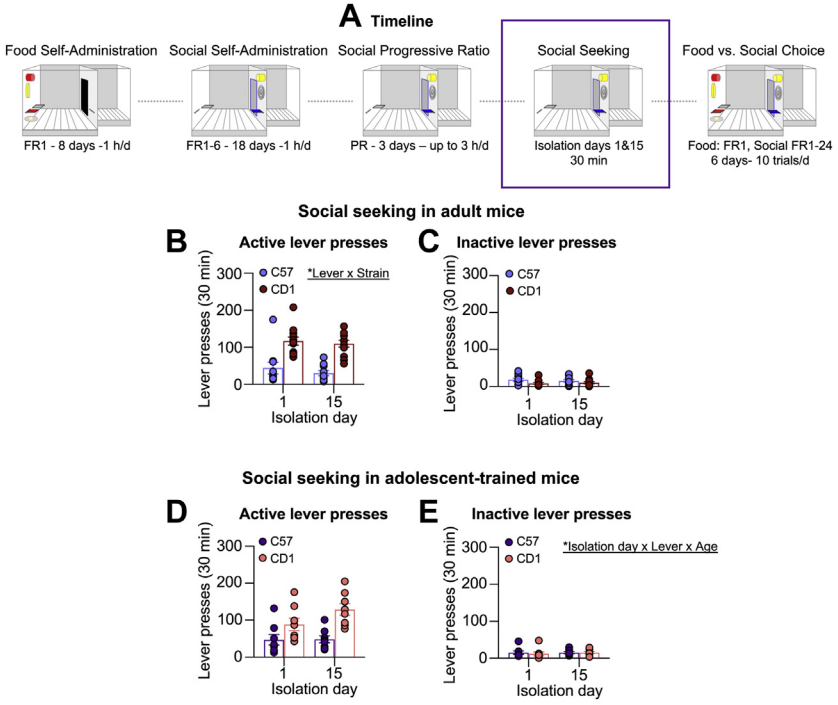

Figure 4. CD1 mice lever press more on the lever previously reinforced with social interaction during social isolation than C57BL/6J mice. **(A)** Timeline of the experiments. Purple box highlights the phase of training that is described in the figure. **(B–E)** Social seeking in adult **(B, C)** and adolescent-trained **(D, E)** female mice: **(B, D)** active lever presses during testing, **(C, E)** inactive lever presses during testing (CD1 adults: n = 16, CD1 adolescent-trained: n = 8, C57BL/6J adults: n = 10, C57BL/6J adolescents: n = 12; all females). Data are mean ± SEM. *Denotes significant effect of lever × strain interaction **(B, D)** ($p <$ .001) and isolation day × lever × age interaction **(C, E)** (p = .006). FR, fixed-ratio; PR, progressive-ratio.

We also compared the same adult C57BL/6J and CD1 mice with no-partner control groups of adult C57BL/6J and CD1 mice (Figure S7; Table S1). CD1 mice preferred social interaction over food when lever presses were rewarded with their social partner but preferred food when lever presses were not reinforced with the partner. In contrast, in C57BL/6J mice, the presence or absence of the social partner had no effect on their preference for food.

Taken together, experiment 1 results showed that adolescent and adult female CD1 mice showed high social self-administration under both FR and PR reinforcement schedules, higher non-reinforced social seeking during isolation, and stronger preference for social reward than female adolescent or adult C57BL/6J mice.

Effect of Housing Conditions on Operant Social Self-administration in CD1 Mice

In experiment 2, we first housed adolescent female CD1 mice in groups of 4 or in isolation for 60 days before social self-administration training in adulthood. We included a no-partner control group of isolated mice (Figure 6). The analysis of social rewards earned included the between-subjects factor of housing conditions (isolated, grouped, control) and within-subjects factor of FR schedule. Analysis of lever presses included an additional within-subjects factor of lever. For the analyses, we averaged data from the final 4 days of social self-administration on the FR1 schedule and 2 days on the FR2, FR4, and FR6 schedules. Both isolated and group-housed mice earned more social rewards ($F_{2,21}$ = 9.0, p = .002) and lever pressed more to access a social partner than control mice ($F_{2,21}$ = 4.8, p = .02). However, there were no differences in operant social self-administration between isolated and group-housed mice (p values > .05). We then group housed a subset of the mice from both groups and compared them with a group that remained isolated while continuing operant social self-administration on the FR6 schedule (Figure 6). The analysis included the between-subjects factor of housing conditions (isolated, regrouped) and within-subjects factor of session. Regrouped mice lever pressed fewer times for social partner access ($F_{1,14}$ = 11.5, p = .004). We observed a trend toward fewer social rewards earned in regrouped mice, but this effect was not statistically significant ($F_{1,14}$ = 3.3, p = .09).

Effect of Strain on Social CPP in Adult Mice

In experiment 3, we used a social CPP procedure to determine if adult female C57BL/6J and CD1 mice form a preference for a context paired with social interaction. CD1 but not C57BL/6J mice showed strong and persistent CPP for up to 7 days after CPP training (Figure 7). We analyzed time spent in the social-paired context relative to the isolation-paired context during

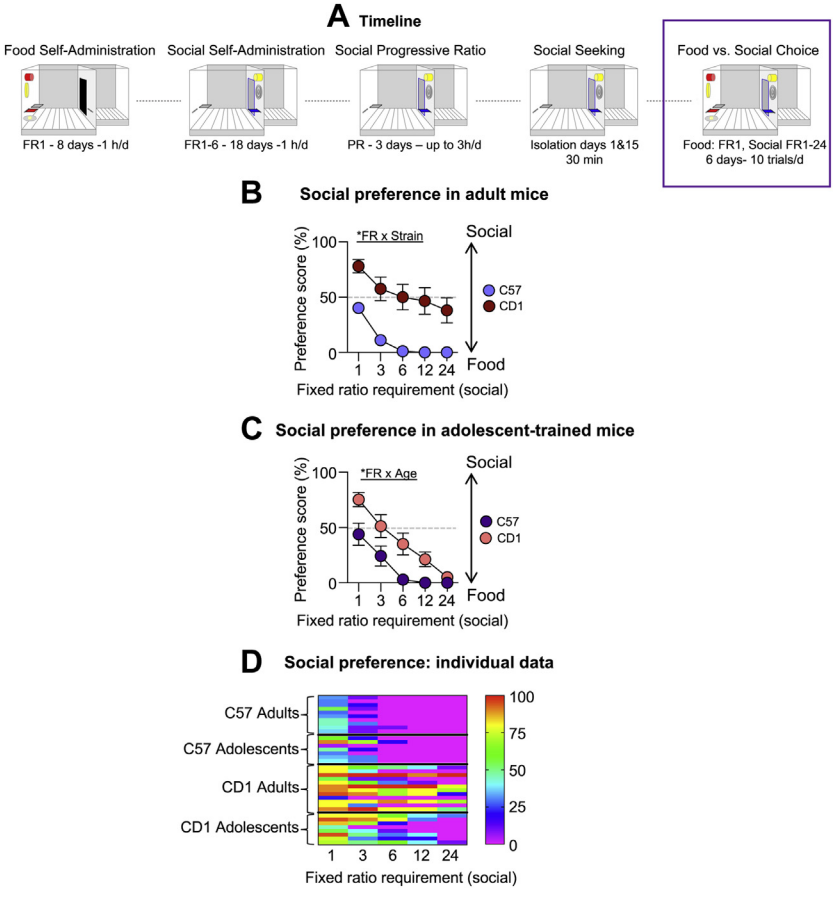

Figure 5. CD1 mice prefer social interaction over access to palatable food under low (FR1) but not higher (FR3–FR24) effort level conditions; C57BL/6J mice prefer food over access to social interaction regardless of the effort level required. **(A)** Timeline of the experiments. Purple box highlights the phase of training that is described in the figure. **(B, C)** Preference score % (# social trials/(# social trials + # food trials) × 100) in adult **(B)** and adolescent **(C)** female mice. **(D)** Individual data heat maps (CD1 adults: n = 16, CD1 adolescent-trained: n = 8, C57BL/6J adults: n = 10, C57BL/6J adolescent-trained: n = 12; all females). Data are mean ± SEM. *Denotes significant FR × strain interaction (p = .007) **(B)** or FR × age interaction (p = .032) **(C)** (p = .007). FR, fixed-ratio; PR, progressive-ratio.

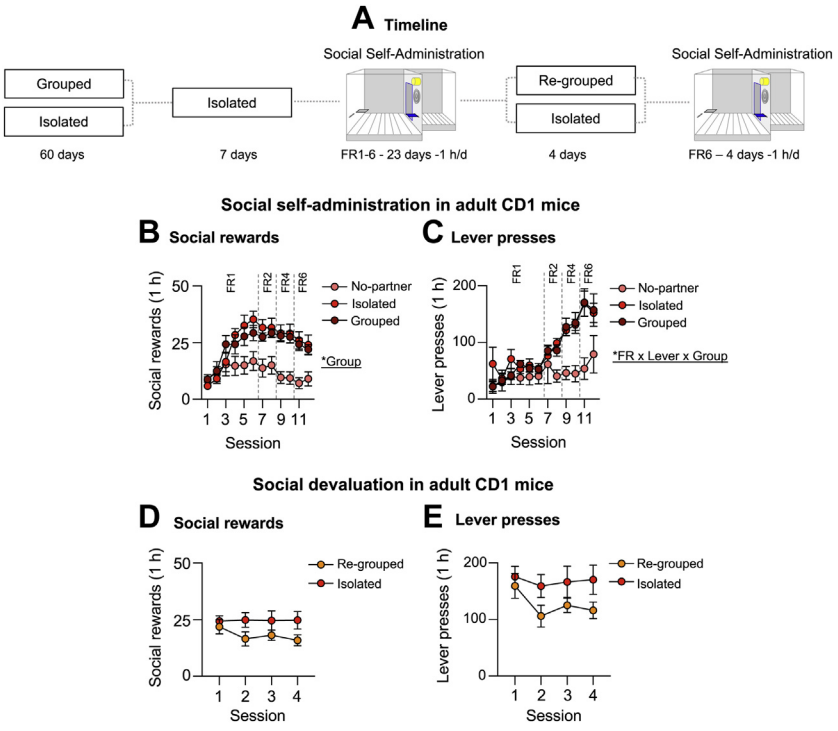

Figure 6. Effect of housing condition on social self-administration in adult CD1 mice. **(A)** Timeline of the experiments. **(B, C)** Social self-administration training in group housed or isolated mice (control: n = 8, isolated: n = 8, grouped: n = 8). **(D, E)** Social self-administration (FR6 schedule) in regrouped or continuously isolated mice. **(B–E)** Social rewards earned **(B, D)** and lever presses **(C, E)** (isolated: n = 8, regrouped: n = 8). *Denotes significant main effect of group **(B)** (p = .002) or FR × group interaction **(C)** (p = .007) or main effect of group **(D)** (p = .004). FR, fixed-ratio.

a 15-minute test session that took place 2 days after the final conditioning session (CPP test 1) and then retested the mice 7 days later (CPP test 2). The analysis, which included the between-subjects factor of strain and the within-subjects factor of test day (2, 7), showed a significant interaction between test day and strain ($F_{2,28}$ = 5.2, p = .012).

We also analyzed direct unconditioned social interaction in both mouse strains during one of the 30-minute conditioning sessions (Figure 6). Female CD1 mice spent more time in contact with their social partners (t_{14} = 7.1, $p < .0001$) and more time sniffing (t_{14} = 9.6, $p < .0001$) and grooming (t_{14} = 3.5, $p < .0001$) their partners than female C57BL/6J mice. We also assessed aggressive behavior. Both strains occasionally engaged in biting behavior; the duration of this behavior was minimal (approximately 2–4 seconds during the 30-minute session) and similar between strains ($p > .05$). Neither strain attacked their partners or engaged in fighting behavior during the conditioning session.

The results of experiment 3 confirm those of experiment 1 and show that social interaction is more rewarding to female CD1 mice than to female C57BL/6J mice.

DISCUSSION

We introduce an operant model of social self-administration in female mice. We found that outbred female CD1 mice showed reliable social self-administration under different reinforcement schedules, showed strong social-seeking behavior during isolation, and preferred social interaction over food under low effort conditions when given a choice between the two rewards. In contrast, inbred female C57BL/6J mice showed weak social self-administration and weak social-seeking behavior during isolation and strongly preferred food over social interaction. These strain differences were similar in mice trained for social self-administration during adolescence and adulthood. There were no strain differences in food self-administration, indicating that the strain differences in social self-administration were not due to differences in operant learning. Additional evidence for a stronger response to rewarding social interaction in CD1 female mice is that they spent more time engaging in nonaggressive social interaction when given direct access to a social partner and showed persistent social CPP, which was not observed in C57BL/6J female mice. Additionally, although C57BL/6J mice lever pressed for access to a social partner, under some conditions (social seeking after 15 isolation days or during choice), the operant response of C57BL/6 mice was similar to control mice whose lever press previously resulted in access to an empty chamber. These results, together with the negative CPP results, suggest that lever pressing of C57BL/6J female mice in some operant tasks is driven by aspects of the task (e.g., guillotine door's sound, interaction with the metal screen divider) unrelated to social interaction.

Strain Differences in Social Self-administration, Social Seeking, and Choice

Several studies reported strain differences reflecting unconditioned (interaction time with another mouse) or conditioned (CPP) social reward (23–25,51,52). A general conclusion from these studies is that social interaction is more rewarding in C57BL/6J mice than in DBA/2J, BALB/CJ, or A/J mice. Based on these results, the present data on weak operant social self-

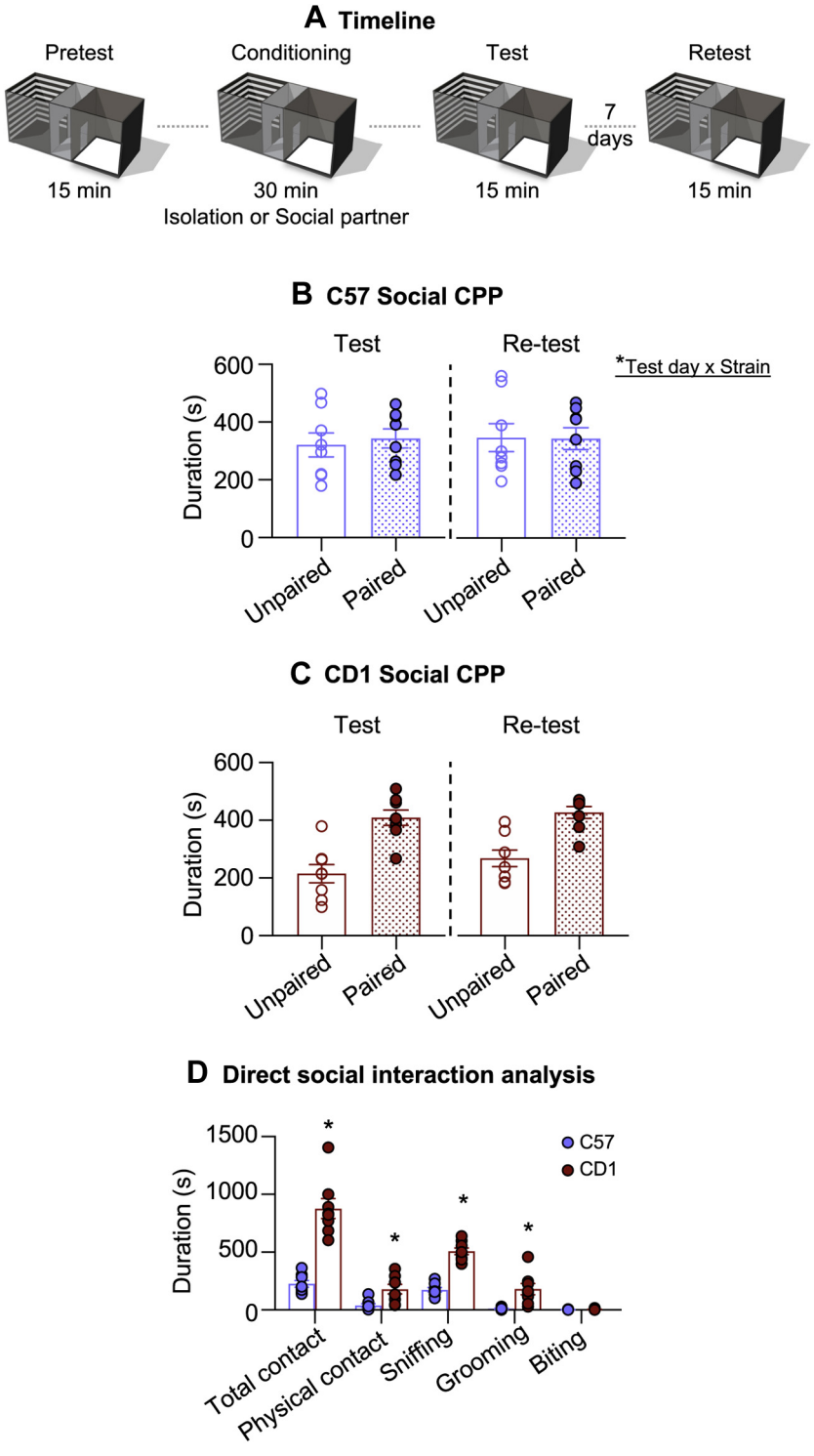

Figure 7. CD1 mice show robust social CPP, whereas C57BL/6J mice do not. **(A)** Timeline of the experiments. **(B, C)** Social CPP in C57BL/6J **(B)** and CD1 **(C)** adult mice during 15-minute test and retest sessions. **(D)** Direct social interaction assessment during 30-minute session (CD1 mice: $n = 8$, C57BL/6J mice: $n = 8$; all females). Data are mean ± SEM. *Denotes significant test day × strain interaction **(B, C)** ($p = .01$), **(D)** ($p < .001$). CPP, conditioned place preference.

administration and lack of social CPP in C57BL/6J mice were unexpected. However, our results are consistent with our recent findings of weak and inconsistent/unreliable social CPP in male and female C57BL/6J mice that is highly dependent on variations in experimental conditions (e.g., bedding type) that do not impact drug CPP (26). Our present and previous results

also agree with those of Kummer *et al.* (27), who reported that male C57BL/6J mice prefer a cocaine-paired context over a social-paired context when given a choice between the two rewards. Our results support the notion that outbred mouse strains may produce more reliable and consistent data than inbred strains, contrary to popular dogma (53).

Our operant and CPP results with female C57BL/6J mice do not agree with results from a recent study by Hu *et al.* (22), who reported social self-administration in male and female C57BL/6J mice. However, within the framework of operant social self-administration these results should be interpreted with caution. Unlike our study, in which the social reward was access to a familiar social peer of the same age and sex, the social reward in the study by Hu *et al.* (22) was access to a novel juvenile mouse of either sex. Thus, while the results of Hu *et al.* may have limited translational relevance for situations where social interaction occurs between adults and unfamiliar adolescents, their relevance to more common peer-related social interactions among adolescents and adults is questionable.

Overall, our study indicates that CD1 female mice are more appropriate for studies on mechanisms of rewarding social interaction than commonly used female (or male) C57BL/6J mice. Our study also illustrates that unlike in rats, where different common strains reliably perform operant social self-administration (41), the mouse strain is a critical factor in studies on operant social self-administration, as is the case for other types of social behavior (23–25,51,52). Our results with the C57BL/6J female mice from established models of drug and non-drug rewards—operant self-administration and CPP—also indicate that results about neural mechanisms of social reward using this strain should be interpreted with caution.

Lack of Age Differences in Social Self-administration, Social Seeking, and Choice

Adolescence is a critical period for social interaction across species characterized by hormonal and neurodevelopmental changes, including maturation of limbic and cortical areas. It is also a period of increased risk taking and novelty seeking (29,34,54). Adolescent rats engage in rewarding social play behavior (8,20) and display social CPP (38,55). Thus, similar to most humans, rats are social animals that find social interaction particularly rewarding during adolescence (8,54). Whether or not social reward is stronger in adolescent than in adult mice has been debated because of their limited repertoire of social behaviors (11,20). Mice experience an adolescent developmental stage similar to that of rats (31,35,56–58). However, there are fewer systematic examinations of social reward in adolescent versus adult mice, and data are mixed because mouse social behavior is highly sensitive to housing conditions, strain, sex, and partner novelty (22,23,26,30,52). Additionally, developmental studies of social behavior in mice have primarily focused on time points within the juvenile to early adolescent period, without examining social behavior into adulthood. Terranova *et al.* (30) showed that social interaction between female CD1 mice peaks between postnatal days 23 and 32, which is roughly equivalent to early adolescence, although the last time point examined was postnatal day 47, which is still within the late adolescent period (29).

We did not find evidence for age differences in operant social self-administration. However, given the length of our operant training, we could not assess all measures within the adolescent period, as our self-administration training alone was 23 days and thus ended during early adulthood. Nevertheless, even at earlier time points when our adolescent mice were well within the adolescent period, they did not show within-strain differences in social self-administration compared with adults. Overall, our data suggest that social reward stays consistent from adolescence to adulthood in female C57BL/6J and CD1 mice.

Conclusions

Recently, more focus has been given to the lack of biomedical research performed in female animals (59). The bias toward exclusively studying male animals has been especially prominent in neuroscience and biomedical research (45). Reasons for excluding female animals include the erroneous dogma that female behavior is always or frequently more variable than male behavior owing to estrous cycle–dependent behavioral changes (45,46). Here, we introduced a model of social behavior exclusively in female mice of a particular strain (CD1), which is different from the common practice of developing an animal model in male mice of a particular strain and then determining in future studies if the model generalizes to females of the same strain and other strains. We propose that our model is ideally suited to study circuit mechanisms of complex volitional social interaction in adolescent and adult CD1 female mice. These mechanistic studies could provide insight into neuropsychiatric disorders with a component of social dysfunction, such as depression, autism, schizophrenia, and drug addiction. Beyond mechanistic questions in CD1 female studies, we hope that the new model will inspire future studies to address two important questions. The first is the generality of the model to other males and females of mouse strains beyond CD1 and C57BL/6J. The second is whether breeding outbred female CD1 mice with transgenic C57BL/6J male mice will maintain the social phenotype in the hybrid F1 female offspring in a manner akin to the maintenance of the aggressive phenotype of the hybrid F1 males from this breeding scheme (47,48,60).

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the Intramural Research Program of the National Institute on Drug Abuse (to BTH and YS).

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

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Received Jun 8, 2021; revised Oct 12, 2021; accepted Oct 29, 2021.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.biopsych.2021.10.023.

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