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Social valence dictates sex differences in identity recognition

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Social valence is the directional emotional significance affiliated with social experiences. Maladaptive social information processing has been linked to mood disorder susceptibility, which is more prevalent in women. To determine whether there are sex differences in social valence processing, we employed behavioral tasks that associated conspecific identity recognition with either positive or negative valence, as well as tasks in which valence information originated from social targets. Male mice demonstrated identity recognition regardless of social valence. While male and female mice performed similarly in the positive social valence task, female mice did not show identity recognition following the negative social valence task. In vivo calcium imaging of the dorsal CA1 further revealed sex differences in negative social valence processing with reduced hippocampal representation of social information in female mice. Finally, enhancing dorsal CA1 neuronal activity by ampakine rescued identity recognition in female mice. These results suggest that sex differences in social valence processing may contribute to the heightened vulnerability to social stress-related mood disorders in women.

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INTRODUCTION

Social relationship dynamics influence mental health and mood disorder vulnerability [1, 2]. Social interactions carry emotional meaning, where negative experiences lead to behaviors that aim to prevent conflict, and nurturing interactions are generally rewarding. The emotional affect attached to social interactions is termed social valence. Differential processing of negative valence-associated social stimuli (e.g., greater neural response to sad faces) was observed in depression [3], which is more prevalent in women [4–6]. Nonetheless, sex differences in social valence processing remain poorly studied.

The hippocampus supports social cognition [7], with dorsal CA2 [8], dorsal CA1 (dCA1) [9–12], and ventral CA1 [13] subregions required for social memory. Emerging findings support key roles of dCA1 in social valence processing. Rodent studies revealed that dCA1 activity represented the spatial location [14, 15] and valence assignment of social targets [9, 12]. dCA1 neurons activated by social defeat, a form of negative social valence, were also more active in mice susceptible to this stressor [16] (but also see [17]). Given that there are sex differences in dCA1 activity during the processing of aversive contextual information [18, 19], we propose dCA1 could contribute to sex differences in social valence processing.

Using newly developed behavioral tasks that associate the identity of social targets with social valences [20], we examined identity recognition in both male and female C57BL/6 mice. In addition, we used UCLA miniscope to measure dCA1 activity during identity recognition. We found that sex differences in social valence processing could be reflected in dCA1 activity.

MATERIALS AND METHODS

Animals

Male and female adult C57BL/6 mice (8–12 weeks old), CD1 retired breeders (3–6 months-old), and Swiss Webster resident pairs (3–6 months-old) were obtained from *Charles River*. C57BL/6 mice used as social targets were obtained from *Jackson Laboratory* to ensure they would be from different litters as the subject mice. Sex-matched conspecifics were used to eliminate preferences towards the opposite sex, unless otherwise specified. Experiments were approved by the Facility Animal Care Committee at the Douglas Research Centre and followed guidelines from the Canadian Council on Animal Care (protocol no.: DOUG-5935).

Positive social valence and positive object valence tasks

Our behavioral procedures for social valence tasks (Fig. 1) were previously described [20]. Subjects were food restricted for 6–8 h prior to a daily habituation session (10 min) to chocolate food pellets (20 mg, 1 pellet per min, *BioServ*) over 3 days in a modified cage with a reward port. Training was conducted over two consecutive days where subjects were exposed to a reward and a neutral trial. The inter-trial interval was 2 h, and trial order was counterbalanced. During the positive social valence trial, subjects freely explored a CD1 mouse in a perforated enclosure adjacent to the reward port for 10 min. Upon each bout of interaction with the positive social valence mouse, subjects received one food pellet. In the neutral trial, a different CD1 mouse was placed in the same location, but no food reward was given. We also conducted positive object valence training (Fig. 2) in another cohort by replacing conspecifics with inanimate objects (dissimilar in appearance and touch but similar in size). All behavioral experiments were performed under ambient red light, with static white noise around 60 dB. A total of 27 male and 20 female mice were trained for these tasks.

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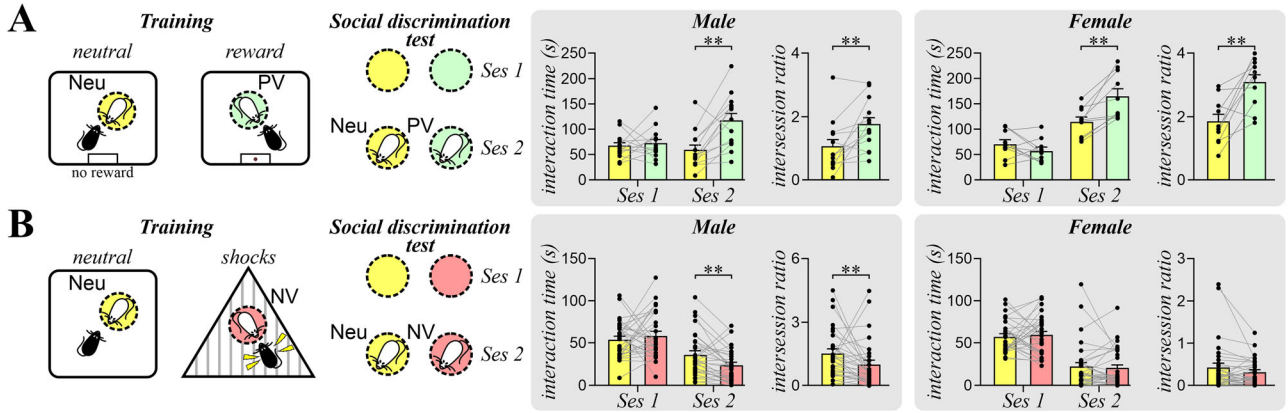


Fig. 1 Sex difference in identity recognition in the negative, but not the positive, social valence task. A Behavioral schematic of the positive social valence task. Neutral trials with a neutral mouse (Neu, yellow) and reward trials with a positive valence-associated mouse (PV, green). Histograms show the interaction time during session 1 (Ses 1, empty cups) and session 2 (Ses 2, with conspecific mice) of the social discrimination test and the intersession ratio (Ses 2/Ses 1 interaction time) for each conspecific. Male: n = 13. Female: n = 10. **B** Behavioral schematic of the negative social valence task. Neutral trials with a neutral mouse (yellow) and shock trials with a negative valence-associated mouse (NV, red). Histograms show the interaction time and intersession ratio during the social discrimination test for each conspecific. Male: n = 31. Female: n = 32. Data are presented as mean ± SEM. **p < 0.01, Wilcoxon test.

Negative social valence and negative object valence tasks

Two hours prior to the first training session, mice were habituated to two contexts for 5 min. Negative social valence trials (Fig. 1) took place in a custom-made triangular shock box with black walls and a metal grid floor, while neutral trials were conducted in a rectangular cage with transparent walls and a paper floor. Subjects explored each context which contained an empty perforated enclosure at the center. Training was conducted over 3 consecutive days where subjects were exposed to a negative valence and a neutral trial. Each trial was 5 min long. The trial order was counterbalanced. In the negative social valence trial, footshocks (0.3 mA, 1 s) were delivered at 4 and 4.5 min, to allow sufficient interaction time with the negative valence-associated mouse (NV-mouse) prior to shock delivery. In the neutral trial, no footshock was given.

We also enhanced the association between the negative experience and conspecific identity or objects (Fig. 2) by delivering footshocks following each interaction bout. The habituation procedure remains the same. Training procedures in different experiments include i) one 5 min trial per day for 1 day; i) one 5 min trial per day for 3 days; ii) three consecutive 3 min trials per day for 1 day (used in negative object valence). The interval between NV and Neu trials was always 2 h.

Finally, before negative social valence training, a set of mice were pre-exposed to both the enclosure-constrained Neu and NV CD1 mice in the Neu and NV context, respectively, for 5 min daily for 3 days. After pre-exposure, mice were trained for conflict-based negative social valence tasks.

Conflict-based negative social valance task

The negative social valence trial (Figs. 3–6) took place in a rectangular cage containing a freely-moving NV-mouse (CD1 for males, Swiss Webster (SW) for females). Aggressive SW female mice were identified using a rival aggression protocol [21], which requires housing a female SW mouse with a castrated male SW mouse. The neutral trial was conducted in an open field with a perforated enclosure at the center, which contained a different mouse of the same strain as the NV-mouse. During training, subjects explored each context during 3 trials for 3 min, with a 3 min intertrial interval. In female subject experiments, the negative context was the homecage of the SW pair, which contained olfactory cues from the resident male and female conspecifics that may facilitate the subsequent identification of the NV-mouse. To make the olfactory cues in both interactions comparable, bedding from the homecage that the neutral female shared with their male partner was placed in the neutral context. Intervals between NV and Neu trials were 2 h.

Trials with the NV-mouse were ended early if the subject jumped out of the cage to escape or showed a submissive posture. Subjects (n = 5) were removed when they experienced less than 15 total attacks and at least 1 non-escape trial with no attacks.

A total 210 male and 234 female mice were trained by various versions of negative social valence tasks.

Social discrimination tests (SDT)

SDTs were used to quantify investigation time of different valence-associated conspecifics and inanimate objects. A three chambered arena (8 min sessions) was used for all positive and negative valence experiments using footshocks. An open field (5 min sessions) was used for all conflict-based negative social valence experiments. In the first session, the testing arena contained 2 empty wire cups. In the second session, the cups contained familiar mice or objects from previous training sessions, unless otherwise stated.

Three chamber social novelty preference test

Mice, whose prefer interacting with novel conspecifics [22], were placed in the center chamber of a three chambered arena and allowed to explore the apparatus. The test consisted of three 8 min sessions: 1) the adjacent chambers contained empty cups; 2) one of the adjacent chambers held a cup containing a novel conspecific; 3) one adjacent chamber held a cup containing the now familiar conspecific from the previous session, while the cup in the opposite chamber held a novel conspecific. Conspecific location was counterbalanced for all sessions and social targets were sex-matched C57BL/6 or CD1 mice.

A total of 32 male and 32 female mice were trained by the social novelty preference test.

Estrous monitoring

Monitoring was conducted in the morning over 7 days, beginning 3 days prior to behavioral training and ending before the SDT. Vaginal lavage was performed by flushing 0.9% NaCl into the vaginal canal with a transfer pipette. Samples were examined under a tissue culture microscope (*Nikon*) to assess estrous cycle stage [23]. Results were independently verified by two experimenters and grouped into sexually receptive (proestrus/estrus) and non-receptive (metestrus/diestrus) stages.

Surgeries

For all stereotaxic procedures, C57BL/6 mice were anesthetized with isoflurane and received subcutaneous injections of carprofen (20 mg/ml) during and 3 days post-surgery. Following the termination of experiments, mice were perfused with phosphate buffered saline (PBS) with heparin (0.2%) and 4% paraformaldehyde (*Sigma-Aldrich*). Brains were extracted and sectioned for cannula or gradient refractive index (GRIN) lens placement verification (Supplementary fig. 1).

Cannula implantation. Bilateral cannula implantation for drug infusion was targeted to dCA1 (AP: −1.70; ML: ±1.50; DV: −1.50) one week before behavioral training. Intrahippocampal infusions *of APV (*1 mM, 0.5 µl, *HelloBio*, Fig. 4), CX516 (0.8 mM, 0.5 µl, *MedChemExpress*, Fig. 6) or vehicle (PBS, 0.5 µl) were delivered 30 min prior to each training trial.

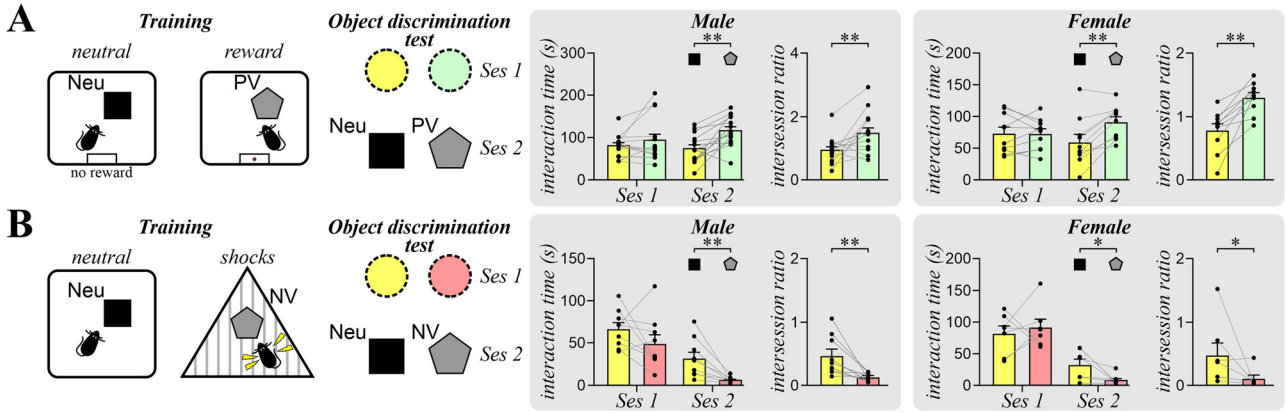


Fig. 2 Object recognition in both sexes in the positive and negative object valence tasks. A Behavioral schematic of the positive object valence task. Neutral trials with a neutral object (Neu, black square) and reward trials with a positive valence-associated object (PV, gray pentagon). Histograms show the interaction time during session 1 (Ses 1, empty cups) and session 2 (Ses 2, objects) of the object discrimination test and the intersession ratio (Ses 2/Ses 1 interaction time) for each object (Neu: yellow; PV: green). Male: n = 14. Female: n = 10. **B** Behavioral schematic of the negative object valence task. Neutral trials with a neutral object (black square) and shock trials with a negative valence-associated object (NV, gray pentagon). Histograms show the interaction time and intersession ratio during the object discrimination test for each object (NV: red). Male: n = 9. Female: n = 7. Data are presented as mean ± SEM. *p < 0.05, **p < 0.01, Wilcoxon test.

GRIN lens and baseplate implantation. As previously described [24], C57BL/6 mice were unilaterally (right side) injected with a viral construct expressing GCaMP6f (AAV2/9-SYN-GCaMP6f; 350 nL, *CNP Viral Vector Core*). Two coordinates targeting dCA1 were tested with comparable results (set 1: AP: −1.60; ML: +1.70; DV −1.40 and set 2: AP: −1.90; ML: +1.40; DV: −1.10). One week post-injection, the cortical tissue above the injection site was aspirated and a GRIN lens (0.25 pitch, 1.8 mm diameter, 4 mm length, *Edmund Optics*) was secured with dental cement. A baseplate was cemented three weeks later for UCLA Miniscope (v3; *miniscope.org*) docking.

Behavioral analysis

For calcium imaging experiments, behavioral analysis was performed from videos annotated by *DeepLabCut* [25]. For other experiments, interaction time was manually analyzed and included time when subjects were sniffing or oriented towards the cup. Periods where animals were oriented away, grooming, or climbing the enclosure to evade foot shocks were not considered social interactions.

An intersession ratio (interaction time with a conspecific or inanimate object / interaction time with an empty cup at that same location) was calculated to control for innate differences in exploratory drive and side preference.

In vivo calcium imaging analysis

Using the UCLA miniscope (v3), calcium imaging and behavioral videos were recorded at 30 frames/second (Miniscope-DAQ-QT-Software; Aharoni-Lab *github*). Concatenated calcium imaging video files were motion corrected and aligned [26]. Videos were downsampled to 10 frames/second to extract calcium transients from each cell segment by Constrained Non-negative Matrix Factorization for microEndoscopic data (CNMFe) [27]. Segments with >60% overlapping spatial footprints were discarded. The rising phases of calcium transients (the variable 'S' from CNMFe, which represent the onset of calcium events) were binarized and downsampled to 5 Hz using customized MATLAB codes to obtain the frequency of calcium activity. All MATLAB codes are available at https://github.com/tpwonglab/sexe-diff-social-memory.

Defining social ensembles. Social ensembles were defined as described [28]. Cosine similarity index (CSI) was used to identify dCA1 neurons with increased activity during social interactions: CSI of neuron $n = 2B \cdot C_n / (|B|^2 \cdot |C_n|^2)$, where C is the calcium signal vector and B is the behavioral vector (binary logical values of social interaction frames). Calcium signal vector of social ensembles was calculated from the mean frequency of calcium activity from neurons active in 40% of all social interaction bouts during session 2 of the SDT. We randomly arranged 8 equally divided portions of the behavioral vector and generated 10,000 shuffled behavioral vectors. CSIs from original data were higher than 95% of CSIs calculated from shuffled behavioral vectors. Activity of nonsocial ensembles was calculated using behavioral vectors from interactions with a specific empty cup.

For calcium activity in social and nonsocial ensembles, we averaged the frequency of calcium activity from neurons active in >40% of interaction bouts with social and nonsocial targets, respectively. Ensemble size was estimated by dividing the number of neurons in these ensembles by the total number of recorded neurons in each mouse.

Linear support vector machine classifier. Linear support vector machine classifier from MATLAB (*fitclinear*) was used to decode spatial and social information in the SDT. High dimensional calcium activity was used to train and test the classifier. We tested the accuracy of dCA1 activity to decode spatial (e.g., empty cup NV vs. empty cup Neu) and social information (e.g., empty cup Neu vs. mouse-containing cup Neu). We balanced the number of samples for each of the classifiers (randomly down sampling in the larger class). Decoding accuracy was cross-validated 50 times to obtain the averaged decoding accuracy across these repetitions and was compared to accuracy obtained from shuffled behavioral vectors.

Statistical analysis

Prism10 (GraphPad) was used. All experiments were randomized and analyzed in blind. Experimenters had no knowledge of the infused drugs in pharmacological experiments. Sample sizes were determined from our experience of performing similar experiments. Normality was determined by the Shapiro-Wilk's test. Wilcoxon tests (2-tailed) for non-parametric pairwise comparisons (e.g., intersession time within sessions, intersession ratios) were used. Student's t-tests (2-tailed) were used for parametric data. One-way or two-way repeated measures ANOVA were conducted with post-hoc Holm-Šídák's multiple comparisons test. All data were presented as mean ± SEM.

Data sharing

All raw data for statistical analysis can be found in supplementary materials. MATLAB data from calcium imaging will be shared on Zenodo (https://doi.org/10.5281/zenodo.14646581) after the publication of the paper.

RESULTS

Sex differences in social valence tasks

Although social interactions are generally rewarding for rodents [29], previous studies have linked social targets with additional positive or negative valence for studying associative learning [9, 12, 30]. We modified these tasks to study the impact of valence on social recognition as follow: in positive social valence experiments, male and female adult mice interacted with two sex-matched CD1 mice: one is associated with a reward (food pellet; positive valence-associated mouse or PV-mouse; Fig. 1A).

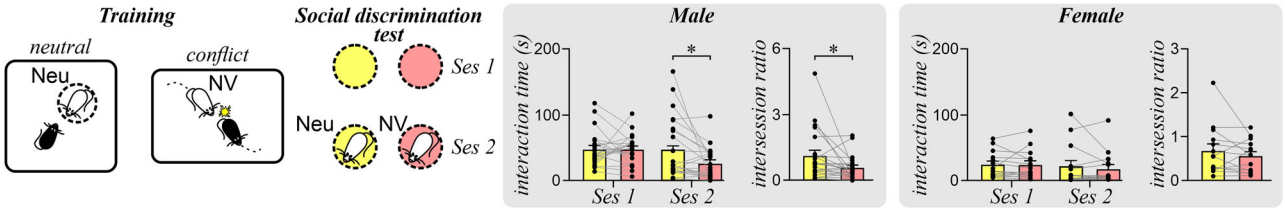


Fig. 3 Sex difference in identity recognition in the conflict-based negative social valence task. Behavioral schematic of the conflict-based negative social valence task. Neutral trials with a neutral mouse (Neu, yellow) and conflict trials with a negative valence-associated mouse (NV, red). Histograms show the interaction time during session 1 (Ses 1, empty cups) and session 2 (Ses 2, with conspecific mice) of the social discrimination test and the intersession ratio (Ses 2/Ses 1 interaction time) for each conspecific. Male: n = 22. Female: n = 14. Data are presented as mean ± SEM. *p < 0.05, Wilcoxon test.

The other mouse that was not associated with additional valence information is considered 'neutral'. The decision to interact in future encounters was not determined by social novelty, but instead by the emotional valence associated with conspecific identity (spending more time with the PV-mouse). As expected, in a subsequent discrimination test (SDT) both sexes spent more time exploring the reward-associated mouse.

In negative social valence experiments, another cohort of mice became familiar with a neutral and a shock-associated CD1 negative valence-associated mouse (NV-mouse, Fig. 1B). Although we expected subjects to avoid the NV-mouse in the SDT, only male mice but not female mice showed lower interaction time and intersession ratio with the NV-mouse compared to the neutral mouse. These findings suggest female subjects did not differentiate between the identities of these mice.

Sex differences in identity recognition in the negative social valence task were not due to diminished social memory capability. Both sexes displayed intact identity recognition in the positive social valence task (Fig. 1A) and showed a preference toward novel mice regardless of their strains in social novelty tests (Supplementary Fig. 2). Moreover, we performed the negative social valence task with same-strain C57BL/6 targets, which may be easier to recognize than mice from a different strain [31]. Male, but not female, subjects continued to show decreased interaction and intersession ratio with the NV-mouse (Supplementary Fig. 3A). Avoidance was not found in male and female control mice trained without footshocks (Supplementary Fig. 3B), eliminating potential social preferences that were not dictated by prior aversive experience.

We attempted several variations to enhance identity recognition of female mice in the negative social valence task. We tested the impact of using male social targets as female mice may show stronger social memory for opposite-sex conspecifics [32]. Although interaction times with both neutral and NV-mice were increased, we did not observe avoidance of the NV-mouse (Supplementary Fig. 4A). Next, we delivered footshocks following each bout of interaction with the NV-mouse. First, we used two contexts for neutral and negative social valence trials (Supplementary Fig. 4B). Second, subjects were introduced to a shock box containing both conspecifics and an empty cup but were only shocked upon interaction with the NV-mouse in one (Supplementary Fig. 4C) or three training sessions (Supplementary Fig. 4D). Lastly, female mice were trained twice in a shock box containing both neutral and NV-mice, however, several contextual cues were changed between sessions (i.e., cup color and shape, training room) to reduce the influence of contextual information (Supplementary Fig. 4E). In all cases, we failed to elicit a decrease in interaction or intersession ratio with the NV-mouse. Finally, since the estrous status of female mice affects social behaviors [33], we separately examined the performance of sexually receptive (estrus/proestrus) and nonreceptive (diestrus/metestrus) female mice in the negative social valence task. Nonetheless, both groups displayed no identity recognition (Supplementary Fig. 4F). Together, these findings demonstrate that negative, but not positive, social valence hinders identity recognition in female mice.

No sex differences in object valence tasks

To determine whether the sex difference in negative social valence identity recognition is due to deficits in associative learning, we conducted positive and negative object valence tasks. These tasks associate inanimate objects with appetitive rewards or footshocks. Both male and female mice demonstrated increased investigation of a positive valence-associated object (Fig. 2A) and decreased investigation of a negative valence-associated object (Fig. 2B). Preferences in investigation were influenced by object valence as neither sex demonstrated changes in exploration when both objects were neutral (Supplementary Fig. 5). The maintenance of object recognition, regardless of valence, supports the notion that associative learning of negative stimuli is intact in both sexes.

Sex differences in a conflict-based negative social valence task

Aggressive encounters between conspecifics are important for establishing social hierarchy and have been used to elicit rodent identity recognition [9]. Based on this model, we developed a conflict-based negative social valence task by training mice to become familiar with two aggressive mice: a neutral mouse confined to an enclosure and an agonistic NV-mouse who was freely-moving, which allowed for physical attack. For male mice, we used aggressive CD1 males that are commonly used for social defeat [16, 34], while aggressive SW mice were used for female experiments [21]. Subsequent avoidance of the NV-mouse in the SDT supports identity recognition. In the SDT, only male but not female mice exhibited social avoidance (Fig. 3).

Several experiments were conducted and showed that male mice discriminated between conspecifics through a learned understanding of both individuals in the conflict-based task. We trained subjects with the neutral and NV-mice but conducted the SDT with the neutral and a novel mouse (Supplementary Fig. 6A). Subjects preferred interacting with the novel mouse, indicating they recognized the neutral conspecific as familiar. These findings suggest that the avoidance of the NV-mouse in the previous experiment (Fig. 3) was not due to a lack of familiarity with the neutral mouse. The decreased interaction with the NV-mouse was specific to the association of the aversive experience with the social identity of the NV-mouse, since no avoidance was observed when novel mice were used in the SDT (Supplementary Fig. 6B) or when no physical attacks happened during training (Supplementary Fig. 6C).

We acknowledge that interactions with the partitioned neutral mouse may differ in somatosensory quality from the direct attacks experienced with the NV-mouse. However, freely-moving interactions with neutral, nonaggressive SW mice that did not attack failed to rescue identity recognition in female mice (Supplementary Fig. 6D). It is possible that the lack of avoidance of the NV-mouse may be in part attributed to a fewer, but not statistically significant, number of attacks from female compared to male aggressors (Supplementary Fig. 7A). However, attack number did not correlate with SDT

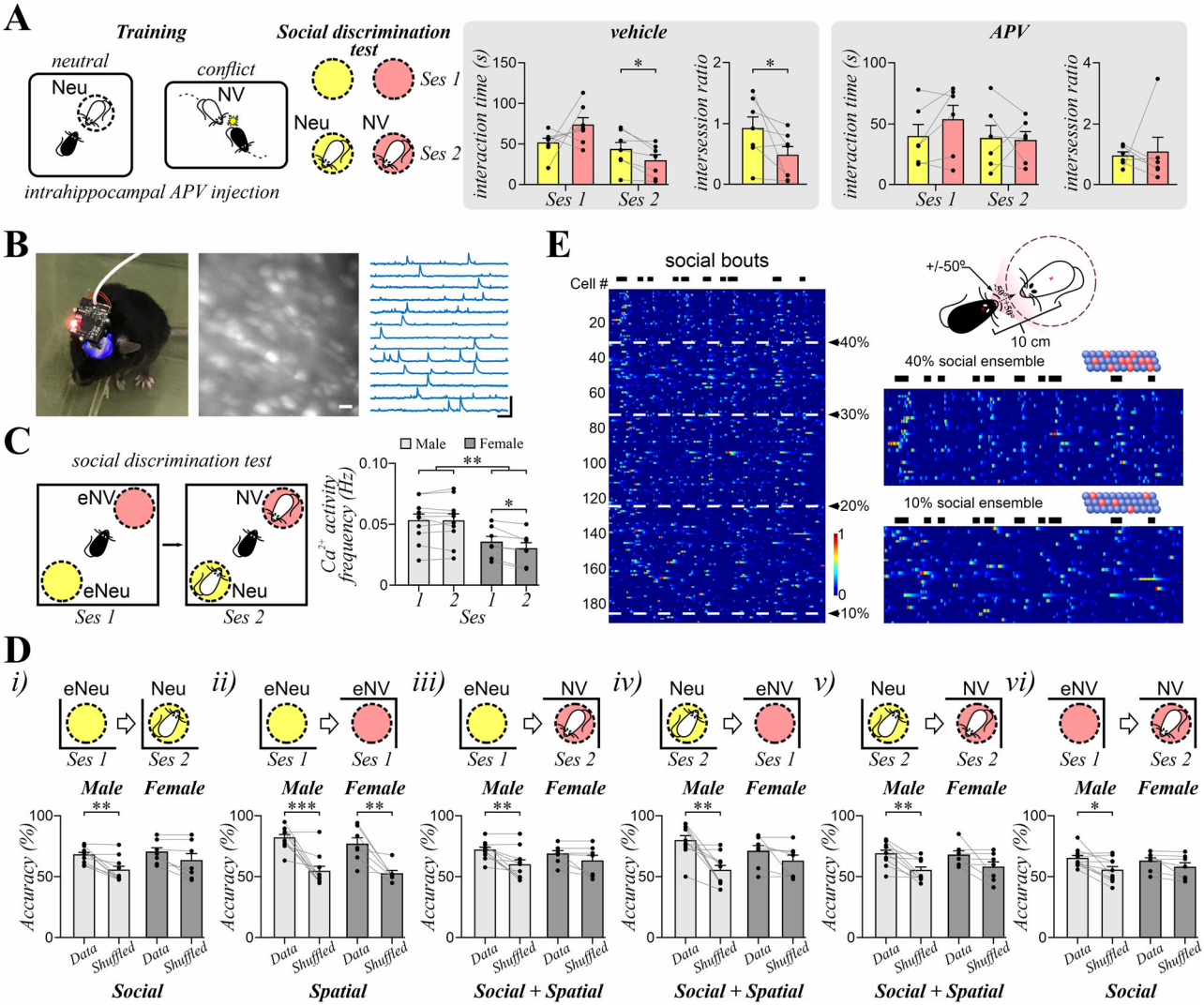


Fig. 4 Sex differences in dCA1 neuronal activity during identity recognition. A Left: Behavioral schematic of the conflict-based negative social valence task. Bilateral intrahippocampal APV (n = 7) or vehicle injections (n = 6) were administered before each trial. Neutral trials with a neutral mouse (Neu, yellow) and conflict trials with a negative valence-associated mouse (NV, red). Histograms show the interaction time during session 1 (Ses 1, empty cups) and session 2 (Ses 2, with conspecific mice) of the social discrimination test and the intersession ratio (Ses 2/Ses 1 interaction time) for each conspecific. Data presented as mean ± SEM. *p < 0.05, Wilcoxon test. **B** *Left:* A subject mouse with a miniscope for in vivo calcium imaging. *Middle:* Micrograph from in vivo calcium imaging recording showing individual GCaMP6f-expressing dCA1 neurons (scale bar = 20 µm). *Right*: Traces represent normalized GCaMP6f fluorescent signals from dCA1 neurons (scale bar: vertical: 100%, horizontal: 1 min). **C** *Left*: Behavioral schematic of the social discrimination test. Subjects explore in session 1 (Ses 1, empty cups) and session 2 (Ses 2, with conspecific mice). Empty cups in Ses1 are labeled according to the identity of the neutral (eNeu) or NV-mouse (eNV) that they will hold in Ses 2. NV and Neu social targets are from the conflict-based negative social valence task. *Right*: Overall frequency of dCA1 calcium activity in Ses 1 and Ses 2 of the social discrimination test in male (blue) and female (purple) subjects. Male: n = 10. Female: n = 7. **p < 0.01, Effect test of sex from two-way ANOVA. *p < 0.05, paired Student's t test. **D** Six scenarios that represent changes in social interaction (scenarios i and vi), cup location (scenarios ii), and social interaction x cup locations (scenarios iii, iv, v) were examined. dCA1 activity was used to train linear support vector machine classifiers to decode these scenarios. Decoding accuracy of different scenarios of the social discrimination test by dCA1 activity in male and female mice. Decoding accuracy from data was compared with those that came from null models of shuffled data. Note that while both male and female mice displayed significant spatial information decoding by dCA1 activity, significant social information decoding was found in male mice only. Male: n = 10. Female: n = 7. Data presented as mean ± SEM. *p < 0.05, **p < 0.01, ***p < 0.001, paired Student's t-test. **E** Social interaction was defined as < 10 cm and ± 50° between the head and heading direction of the subject mouse, respectively, and the center of a wire cup containing the target mouse. *Left:* The normalized calcium signal (normalized by the maximum neuron.C from CNMFe analysis) for each dCA1 neuron was sorted according to their activity during bouts of social interaction (black rectangles above raster plots). *Right:* Social ensembles of dCA1 neurons that were active during 40% (top) or 10% (bottom) of social bouts. Scale bars: 1 min.

interaction time with the NV-mouse in both males and females, indicating that differences in identity recognition cannot be explained by the number of agonistic encounters (Supplementary Fig. 7B). Together, female mice show diminished negative social valence identity recognition compared to male mice.

Sex differences in identity recognition are related to dCA1 activity

To determine whether dCA1 is required for identity recognition in the conflict-based negative social valence task, we inhibited dCA1 N-methyl-D-aspartate receptor (NMDAR) activity which supports synaptic plasticity mechanisms underlying social memory

functions [10, 35]. Blocking dCA1 NMDARs with bilateral infusions of the NMDAR antagonist APV, but not the vehicle, before the neutral and negative social valence trainings abolished identity recognition (Fig. 4A). Although central to social memory mechanisms [8], the adjacent CA2 subregion appears resistant to NMDAR-mediated plasticity [36] and plasticity mechanisms associated with social memory in the CA2 are NMDAR-independent [35]. Thus, dCA1 functioning is required for identity recognition.

Recently, dCA1 population activity was shown to be selective for individual social targets in male C57BL/6 mice [12]. Since hippocampal activity is highly sensitive to stress [37], we hypothesized that there are sex differences in social information representation in dCA1 during stressful experiences. We conducted in vivo calcium imaging in dCA1 of freely behaving mice during SDT following the conflict-based negative social valence task (Fig. 4, B and C). Comparing the mean frequency of calcium activity from all dCA1 neurons during SDT (session 1: two empty cups; session 2: neutral and NV-mice in each cup), revealed lower activity in female mice than male mice during both SDT sessions.

We next used activity from all dCA1 neurons to train linear support vector machine classifiers to decode spatial and social information (Fig. 4D). Compared to null models from shuffled data, we found significantly higher decoding accuracy of dCA1 activity in male mice for spatial and social information. While similar decoding accuracy for spatial information was found in female mice, the decoding accuracy for social identity fell to chance levels. These findings prompted us to further examine dCA1 population activity related to social interaction in the SDT.

We focused on neurons that are active during at least 40% of all social interaction bouts in session 2 of the SDT (Fig. 4E). The mean activity vector of these neurons and the social interaction bout vector displayed a significant cosine similarity index (CSI; [38]) when compared to shuffled social interaction bout vector or other behavioral vectors (e.g., speed, head direction (Supplementary Fig. 8A)). We named them social ensembles and isolated social ensembles for the neutral mouse (ensb Neu) and the NV-mouse (ensb NV). The activity of a social ensemble was specific to its associated mouse target. As shown in Fig. 5A, the activity of ensb NV was elevated during interactions with the NV-mouse and showed lower activity during interactions with the neutral mouse or with the empty cups in session 1 of the SDT (Fig. 5B). Activity of ensb Neu was similarly selective for interactions with the neutral mouse in session 2 of the SDT. Since the cup location between SDT sessions was unchanged, elevations in ensemble activity in session 2 only were presumably due to conspecific presence and not repeated visits of the same spatial location.

Next, we compared social ensemble activity between male and female mice. In male mice, the activity of ensb NV and ensb Neu were highest during interactions with the NV-mouse and neutral mouse, respectively. However, in female mice, ensb NV activity during interactions with the NV-mouse was similar to those during interaction with empty cups in session 1. These findings suggest a comparable representation of social and non-social interactions by ensb NV in female mice. Since social ensembles are sparsely distributed, we compared their size and found a significant decrease in both ensb NV and ensb Neu size in female compared to male subjects (Fig. 5C).

The decreased social representation and size of dCA1 social ensembles in female mice are in line with the sex differences in identity recognition. In addition, these findings echoed the reduced decoding accuracy of social interactions in female mice when compared to male mice (Fig. 4D). Nonetheless, these properties may result from an overall lower activity of dCA1 neurons (Fig. 4C). To determine whether the reduced dCA1 ensemble properties in female mice can also be found during interactions with objects, we identified dCA1 nonsocial ensembles specific for the empty cups NV or Neu in session 1 of the SDT. Unlike social ensembles, nonsocial dCA1 ensembles of both male and female mice exhibit significantly higher activity during visits to the corresponding empty cup than other cups (Fig. 5D, E). In addition, although we observed a group effect of sex between nonsocial ensemble size, multiple pairwise comparisons revealed no difference in the ensemble size of eNV and eNeu between male and female mice (Fig. 5F). Finally, when we compared the CSI of social and nonsocial ensemble vectors with the corresponding social target or object vectors between male and female mice, we found a significant decrease in CSI of social ensembles in female mice only (Supplementary Fig. 8B). Compared to male mice, dCA1 social ensembles in female mice exhibited decreased representation of social information and size but no changes in nonsocial ensemble properties.

Although female mice did not show identity recognition in negative valence tasks, the decrease in interaction time with both the NV and Neu mice suggests a generalized fear to both social targets (see Figs. 1B and 3). Indeed, previous findings have reported higher fear generalization in female than male mice [19, 39]. Fear generalization could be due to a poor association between the context and aversive experience, so that generalization can be ameliorated by a stronger encoding of context via context pre-exposure. We predicted pre-exposing female mice to both social targets before negative valence training could rescue individual recognition. After interacting with both NV and Neu CD1 targets over 3 days, we trained female mice with the shock-based negative valence task and found female mice were able to differentiate between the NV and Neu mice in the SDT (Fig. 6A). Finally, since female mice displayed a lower frequency of dCA1 calcium activity than male mice (Fig. 4C), we proposed that identity recognition of female mice in the negative social valence task could be rescued by enhancing dCA1 activity using CX516, a form of ampakine facilitating endogenous AMPA receptor function and neuronal firing [40]. As expected, female mice receiving dCA1 injection of CX516, but not vehicle, were able to discriminate between the Neu and NV-mice after conflict-based negative valence training (Fig. 5B). Together, these findings further support the notion that a change in social information processing, likely due to lower dCA1 activity, is responsible for the sex differences in negative social valence processing.

DISCUSSION

We demonstrated that while male and female mice can identify individuals, female mice exhibited difficulty in identifying a conspecific associated with negative social valence. Significantly, this observed sex difference cannot be attributed to impaired social memory capacity in female mice, as evidenced by sustained positive social valence identity recognition (Fig. 1) and social novelty preference (Supplementary Fig. 2). This also did not stem from deficits in associative learning, as in addition to positive social valence, female mice exhibited valence-associated learning of object identity in the positive and negative object valence tasks (Fig. 2). Despite attempts at enhancing recognition by optimizing task designs (Supplementary Fig. 3,4), little improvement in identity recognition in negative social valence tasks was observed in female mice. Moreover, hormonal influence from differences in estrous cycle stage did not account for these effects (Supplementary Fig. 4). Our miniscope data also showed female mice display lower dCA1 representation of social information than male mice (Fig. 5). Finally, identity recognition of female mice in the negative social valence task was rescued by enhancing dCA1 activity using CX516 (Fig. 6). Therefore, our findings support a dCA1 mechanism specific to the impact of negative social valence on identity recognition in female mice.

dCA1 is thought to encode spatial information pertaining to other social targets in the environment [14, 15], representing a critical aspect of social cognition. Emerging data also support important roles of dCA1 in identity recognition. While inhibiting

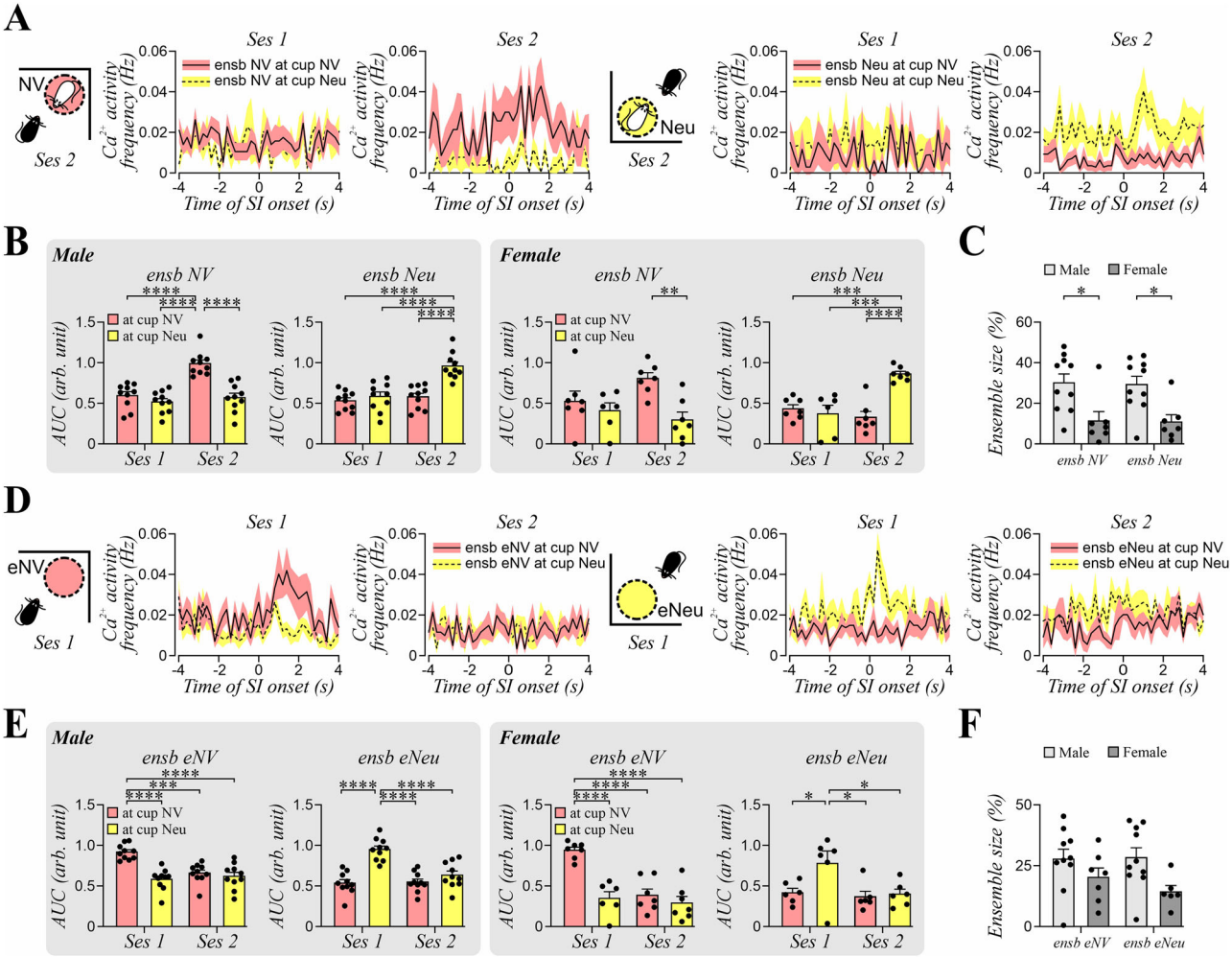
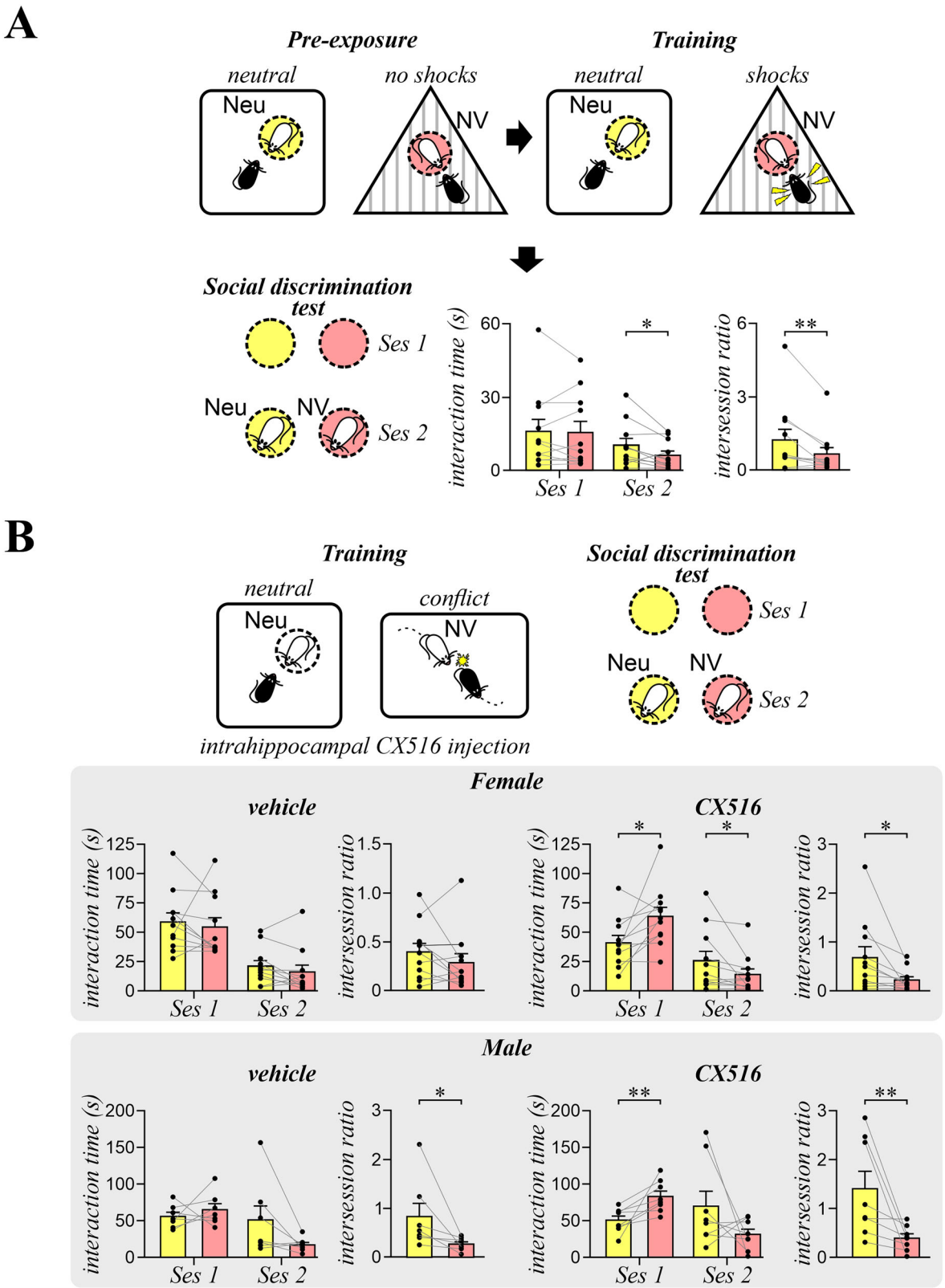


Fig. 5 Sex differences in dCA1 social ensemble properties. A Line plots of mean activity (frequency of calcium activity, ± SEM) of dCA1 ensembles recorded from male mice for the NV-mouse (ensb NV, *left*) and Neu mouse (ensb Neu, *right*) during interaction with cup NV and Neu in different sessions of the social discrimination test. **B** Histograms of the area under curves (AUC) of averaged ensb NV and ensb Neu activity during interactions with different cups in Ses 1 and Ses 2 in male (*Left*) or female subjects (*Right*). Male: n = 10. Female: n = 7. Data presented as mean ± SEM. **p < 0.01, *** p < 0.001, **** p < 0.0001, Holm-Šídák's multiple comparisons tests after one-way ANOVA. **C** Ensemble size for ensb NV or ensb Neu in male and female subjects. Male: n = 10. Female: n = 7. Data presented as mean ± SEM. *p < 0.05, Holm-Šídák's multiple comparisons tests after two-way ANOVA. **D** Line plots of mean activity (frequency of calcium activity, ± SEM) of dCA1 ensembles for empty cup eNV (ensb eNV, *left*) and empty cup eNeu (ensb eNeu, *right*) during interaction with cup NV and Neu in different sessions of social discrimination test. **E** Histograms of the area under curves (AUC) of averaged ensb eNV and ensb eNeu activity during interactions with different cups in Ses 1 and Ses 2 in male (*Left*) or female subjects (*Right*). Male: n = 10. Female: n = 7. Data presented as mean ± SEM. *p < 0.05, **p < 0.01, *** p < 0.001, **** p < 0.0001, Holm-Šídák's multiple comparisons tests after one-way ANOVA. **F** Ensemble size for empty cups eNV or eNeu in male and female mice. Male: n = 10. Female: n = 7. Data are presented as mean ± SEM.

dCA1 impaired negative valence-associated identity recognition [9], dCA1 activity accurately represented social identity in a positive valence task in male mice [12]. Using a conflict-based negative social valence task in the current study, we further showed a lower dCA1 representation of social interactions in female mice compared to male mice (Fig. 5). This may be due to a lower dCA1 firing rate, as negative social valence identity recognition in female mice was rescued by enhancing dCA1 activity with CX516 (Fig. 6). Similarly, using cFos to label dCA1 neurons revealed more active cells and better contextual fear memory in male than female mice at retrieval [18]. Although no sex differences in synaptic and firing properties from recorded dCA1 pyramidal neurons was found in a brain slice study [41], these studies are unlike the current study that examined dCA1 activity in freely-moving mice. Higher dCA1 activity in male mice than female mice could be important for the processing of contextual information [42], such as the identity of the two familiar conspecifics in the current study. Future miniscope studies could examine the effect of CX516 on the social information decoding by dCA1 neurons in female mice. Whether the intact identity recognition of female mice in the positive social valence task is related to higher dCA1 activity during this task or the recruitment of extrahippocampal regions in reward-related tasks [43] should be investigated in future.

The avoidance of both the neutral and NV social targets by female mice in the SDT may be due to an impact of social stress on reducing social interaction, such as the impact of social defeat on California [44] and C57BL/6 mice [45]. However, defeated mice do not display avoidance to mice of nonaggressive strains [28, 46], suggesting a contribution of social memory for the aggressive strain to avoidance expression. Alternatively, our data suggests a generalization of negative memories to the neutral mouse. Fear generalization is a shared cognitive symptom of depression, post-traumatic stress disorder, and anxiety which are more prevalent in



women [47–50]. One of the factors underlying fear generalization is a poor association between negative valence and social identity. Previous studies of contextual fear conditioning revealed fear generalization in female mice was reduced by the pre-exposure to the context that was later associated with shocks [19, 39]. Similarly, pre-exposing female mice to social targets before the stressful experience also improved the discrimination between NV and neutral mice in the SDT (Fig. 5). Notably, changes in dCA1 and basolateral amygdala activity between male and female mice were proposed to underlie the higher contextual fear generalization in

Fig. 6 Identity recognition of female mice was restored by the preexposure of social targets or the dCA1 injection of CX516 (ampakine). **A** *Left:* Behavioral schematic of the conflict-based negative social valence task with preexposure of social targets. Neutral trials with a neutral mouse (Neu, yellow) and conflict trials with a negative valence-associated mouse (NV, red). Histograms show the interaction time during session 1 (Ses 1, empty cups) and session 2 (Ses 2, with conspecific mice) of the social discrimination test and the intersession ratio (Ses 2/Ses 1 interaction time) for each conspecific. n = 11. Data presented as mean ± SEM. *p < 0.05, **p < 0.01, Wilcoxon test. **B** *Top:* Behavioral schematic of the conflict-based negative social valence task. Bilateral intrahippocampal vehicle (female: n = 11; male = 7) or CX516 (ampakine; female: n = 11, male: n = 8) injections were administered before each training trial. Histograms show the interaction time during different sessions of the social discrimination test and the intersession ratio for each conspecific. Data presented as mean ± SEM. *p < 0.05, **p < 0.01, Wilcoxon test.

female mice [19], which are in parallel to our data implicating dCA1 involvement.

The stressful nature of the negative social valence task may underlie its effects on identity recognition in female mice. Stress-related elevations in hippocampal corticosterone, associated with fear generalization [51, 52], are higher in female than male mice [53]. Sex differences in negative valence identity recognition may also have ethological importance. Previous findings using the same conflict-based encounter in female mice suggested that resulting hypervigilance, demonstrated as an exaggeration in defensive behaviors towards neutral mice, may underlie the inability to discriminate threatening from non-threatening social targets [21].

Although our study suggests an important role of social ensembles in dCA1 in regulating social valence processing, several limitations should be addressed in future studies. Although calcium transients represented by GCaMP signals are widely used as proxies for neuronal firing [54–57], these signals lack the temporal resolution to capture precise changes in hippocampal neuronal firing during social interaction. Future studies using in vivo electrophysiology techniques are needed to verify sex differences in dCA1 representation of social targets and confirm our findings. Beyond manipulating dCA1 activity using ampakine or APV, the causal role of dCA1 social ensembles in social valence processing could be examined by expressing opsins or DREADDs in these ensembles using approaches such as TetTag or robust activity marking systems [16, 58]. The hippocampus is known to differentially process social and nonsocial information [12, 59, 60]. Our findings suggest a novel role for negative valence in the processing of social, but not nonsocial, stimuli in female mice. Why the processing of nonsocial stimuli in female mice is insensitive to negative valence remains another research direction to be explored in future studies.

Our findings have implications on negative social valence processing in humans. While women typically outperform men in facial recognition tasks [61, 62], they exhibit more errors than male participants when negative valence is introduced [63]. Women spend more time processing negative faces [64] and show greater limbic [65, 66] and cortisol responses [5] compared to men. This supports our hypothesis that negative social valence imparts greater consequences in women. There remains limited knowledge regarding the involvement of hippocampal processing in valence-associated social interactions, but some clinical support exists. Hippocampal connectivity with limbic regions is modulated by acute social stressors [67] and activity increases in the learned decision to approach or avoid valence-associated stimuli [68]. The hippocampus also emerges as a region of interest in studies examining brain regions differentially affected by negative valence between the sexes [69, 70]. Collectively, our findings offer insights into the impact of social valence on hippocampal function between the sexes, with potential implications for understanding mood disorder susceptibility and social cognition.

DATA AVAILABILITY

All MATLAB codes are available at https://github.com/tpwonglab/sexe-diff-social-memory. Raw data of all figures can be found in main text and supplementary materials. MATLAB data from calcium imaging will be shared on Zenodo after the publication of the paper.

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AUTHOR CONTRIBUTIONS

Conceptualization: AL, QWX, MPB, TPW. Methodology: AL, QWX, ASW, JQL, MY, BWW. Investigation: AL, QWX. Funding acquisition: TPW. Project administration: TPW. Supervision: TPW. Writing—original draft: AL, TPW. Writing—review & editing: AL, TPW.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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