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Effects of chronic social defeat on social interaction and partner preference in mandarin voles

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Abstract

Different types of stress produce different effects on social relationships between partners. Chronic social defeat has been found to alter the emotional and social behaviours, whether it affects partner preference remains unclear. Using monogamous mandarin voles (*Microtus mandarinus*), the present study found that 14 days of social defeat to male vole could increase social avoidance in sociality test, and reduced attacking, intimate, sniffing and exploratory behaviours, but increased avoidance defensive, immobile behaviours in social interaction test. In addition, this treatment significantly reduced side-by-side contact with partner throughout cohabitation period, and reduced the attacking behaviour to strangers after 11 days' cohabitation. Furthermore, in mandarin vole with chronic social defeat, partner preference was abolished on 5 and 7 days' cohabitation indicating that pair bonding stability was impaired by chronic social defeat. Moreover, although mandarin voles spent longer time rescuing partner than stranger in both groups, chronic social defeat did not affect rescuing significantly. Impairment of pair bonding may be due to abnormalities in social interaction induced by chronic social defeat. This finding provides some insights into mechanisms underlying effects of prolong social stress on social relationships between partners.

Keywords

chronic social defeat stress, partner preference, social interaction, rescuing.

1. Introduction

Different types of stress produce different effects on pair bonding. Stress such as interpersonal event or threatening life event often increases negative marital interaction and reduces marital satisfaction via induction of

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depression (Hammen, 1991; Edwards et al., 1998). Depressed persons display more interpersonal conflict and marital distress (Hammen, 1991; Davila et al., 1997). Risk for emotional distress can be enhanced by economic pressure and result in increased risk for marital conflict and marital distress that caused increase of devoice rate (Conger et al., 1999). However, another study found that the stressful event increased both marriage and devoice rate (Cohan & Cole, 2002). Given inconsistency of consequence of different types of stress on relationships between partners in human, mechanism underlying effects of stress on pair bonding needs further investigation.

Social defeat, as a potent stressor, is defined as losing a confrontation between conspecifics (Hollis & Kabbaj, 2014). This kind of stress is pervasive in species that live in groups, such as many rodents (Fan et al., 2017; Solomon, 2017), nonhuman primates (Arce et al., 2010) and humans (Bjorkqvist, 2001; Valmaggia et al., 2015). School bullying in children, as a social defeat, implicates in occurrence of anxiety and depressive symptoms (Yen et al., 2013; Rose et al., 2014). In rodents, exposure to the chronic social defeat stress increases the risk for many behavioural disorders including depression and anxiety-like behaviours, and social impairments (Garcia-Pardo et al., 2015; Fan et al., 2017). However, whether chronic social defeat affect formation and maintenance of pair bonding remains unclear.

In partner preference test of our previous study, the partner or stranger was tethered via a ring around their necks. The subject was found to spend some time biting the ring and tried to rescue the partner or stranger during the test. This rescuing behaviour may be one kind of empathy behaviours. In our previous study, we found that chronic social defeat impaired empathy such as consolation in mandarin voles (Li et al., 2020). Thus, we predicted that chronic social defeat could affect rescuing behaviour in partner preference tests.

Investigating effects of chronic social defeat on pair bonding and rescuing needs animal model that forms pair bonding and shows high levels of social interaction. Several monogamous rodent species such as prairie vole (*Microtus ochrogaster*: Lim & Young, 2004), California mice (*Peromyscus californicus*), mandarin vole (*Microtus mandarinus*: Yuan et al., 2019) have been used to study effects of stress on behaviours relevant to pair bond. In male prairie voles, the stress of swimming or exogenous injections of corticosterone facilitates pair bonding of males, but inhibits the formation of partner preferences in females displaying sex-specific effects (DeVries et al.,

1996). Acute exogenous corticosterone injections facilitate social preference in male prairie voles (Blondel & Phelps, 2016). However, single prolong stress, which consisted of restraint, forced swimming, and ether anaesthesia, impaired pair bonding with the result that male prairie voles exposed to this stress indiscriminately huddled with the novel and partner females following a six days cohabitation (Arai et al., 2016). Thus, the effects of stress on pair bonding may be sex-specific and dependent on types of stress. In California mice, three days of social defeat did not affect, but even facilitated formation of pair bonding (Kowalczyk et al., 2018). However, in mandarin voles 14 days of social defeats reduced social preferences (Wang et al., 2018a) and increased anxiety and depression-like behaviours (Wang et al., 2019b). We predicted that different days of social defeat may produce different effects on pair bonding formation and long-term social defeat may impair pair bonding and alter rescuing.

Using monogamous mandarin vole, the present study investigated whether 14 days of social defeat could impair pair bonding formation and rescuing. This study can provide some insights into mechanisms underlying effects of prolong social stress on social relationships between partners in humans.

2. Materials and methods

2.1. Animals

Adult male mandarin voles used in this experiment were laboratory-reared F3 generation derived from a wild population from Henan province of China. Voles were housed with a male cage-mate with unlimited access to carrots, maintained on a 12-h light/dark cycle (lights on 07:00) and at a temperature range of 21 ± 1°C. All experimental procedures were approved by the Animal Care and Use Committee of Shaanxi Normal University and were in accordance with the Guide for the Care and Use of Laboratory Animals of China. Adequate measures were taken to minimize the number of voles used and to minimize pain and discomfort.

2.2. Chronic social defeat stress paradigms

The resident-intruder paradigm was used to produce stress of repeated social defeat. In this paradigm, intruders are physically attacked and defeated by aggressive residents (Krishnan et al., 2007; Golden et al., 2011; Wang et al., 2018a). Male mandarin voles (80–120 days, 30 g) with attack latency

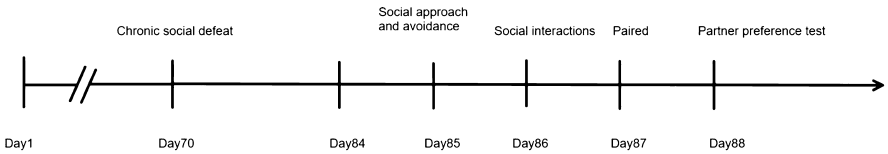

Figure 1. The timeline of the experiments.

shorter than 30 s in three consecutive screening tests were used as aggressive residents. Adult male mandarin voles (70 days, 23–27 g) were assigned to defeated group and control group. Each experimental group included animals from different litters, and animals in each litter were divided into the defeated group and control group to avoid effects of genetic diversity. In brief, voles of the defeated group were subjected to aggression from different aggressive residents each day for 10 min (the intruder exhibited a submissive defeat posture $\geqslant$5 times) for 14 consecutive days of social defeat. After 10 min confrontation, the defeated and aggressive voles were separated by a perforated Plexiglas panel (they could see, hear and smell each other, but could not make physical contact) for 24 h except confrontation. The social defeat occurred at the 9:00 a.m. each day. During the progress of social defeat, it is important to ensure that animals were not injured to avoid further impact on the subsequent behavioural tests. Control voles which have similar age, sex and weight compared with defeated voles, were also exposed to another male individual with less aggression during 10 min of social defeat. On the second day after the last defeat, behavioural tests were performed as timeline shown in Figure 1.

2.3. Behavioural test

2.3.1. Social approach and avoidance test

The test is often used to measure the level of sociality in animals. One day after chronic social defeat stress, the social approach and avoidance behaviour of the defeated (DEF: $N = 20$) and control group (CON: $N = 38$) were observed.

The test was performed in a black painted Plexiglas box (50 $\times$ 50 $\times$ 25 cm) under dimly lit conditions. The box was divided into the "interaction zone" (30 $\times$ 20 cm) and 'surrounding zone'. A wire-mesh cage (10 $\times$ 10 cm) was placed near one side wall of the interaction zone. The test consisted of two phases and each lasted 10 min. Before every test, each defeated or

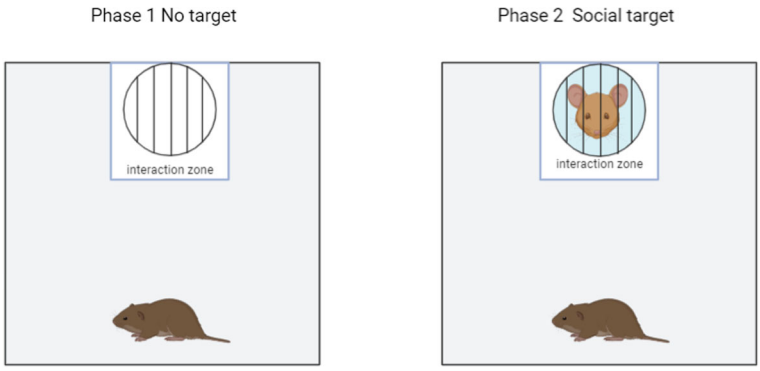

Figure 2. The social approach and avoidance test model.

control vole was placed individually in the box for 5 min for adaptation to the new situation.

In the first phase, the wire-mesh cage was empty (object stimulus: no target) and each vole was placed in the far-end of the box and permitted to move freely for 10 min. In the second phase, the wire-mesh cage containing an unacquainted adult male vole (social stimulus: social target) was placed in the same location in the box. Thus, the voles inside and outside of the wire-mesh cage could see, hear and smell each other, but could not make physical contact for 10 min. During both phases, time spent in the "interaction zone" was recorded with the digital video tracking system and quantified afterwards using J Watcher software (http://www.jwatcher.ucla.edu/) by a trained observer blind to the experimental treatments. Between sessions, the box was cleaned with 30% ethanol and dried with napkins (Figure 2).

All tests were conducted at the same time of the day for each individual vole. The social interaction ratio (Sir) was calculated as: $\mathrm{Sir} = \sum \mathrm{TIZsocial}/(\sum \mathrm{TIZsocial} + \sum \mathrm{TIZobject})$. Where TIZsocial was the time spent in the interaction zone when the wire-mesh cage contained an unacquainted female vole and TIZobject was the time spent in the interaction zone when the wire-mesh cage was empty (Henriques-Alves & Queiroz, 2015).

2.3.2. Social interaction test

Two days after chronic defeat stress, social behaviours of the defeated ($N = 26$) and control group ($N = 20$) were observed during the social interaction test. The social interaction apparatus consists of an opaque acrylic box ($30 \times 40 \times 50$ cm) without a lid under dimly lit conditions. Each defeated or control vole was placed individually in the box for 10 min for adaptation

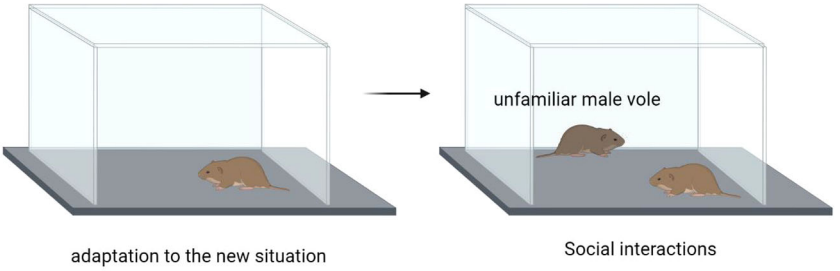

Figure 3. The social interaction test model.

to the new situation before the test. Then, an unfamiliar male vole with the similar weight and age was carefully placed in the box (Figure 3).

The behaviours were recorded with video camera for 10 min and the following behaviours were scored and analyzed using J Watcher software by a trained observer blind to the experimental treatments: exploration, immobile, self-grooming, sniffing, intimacy (including social grooming and climbing), aggression and defensive behaviour (including escaping and surrender). After end of each test, the box was cleaned with 30% ethanol and dried with napkins. All tests were performed at the same time of day for each individual vole.

2.3.3. Partner preference test

At approximately PND 87 and 3 days after chronic social defeat, the males (ten females and ten males in DEF group; seven females and seven males in CON group) were paired with virgin female in a clean cage with free access to food and water between 8:00 and 10:00 am. After 24 h of cohabitation, all test animals then underwent a 30 min partner preference test (Jia et al., 2008). The test apparatus consists of a socially 'neutral' chamber flanked by two stimulus chambers. The 'partner' animal was tethered in one stimulus chamber, while a 'stranger' animal of the same sex, age, size and social-sexual valence (not pregnant, but cohabited with other colony animal of the opposite sex for 24 h) was tethered in another stimulus chamber (Figure 4).

At the beginning, the experimental animal was placed in the test apparatus and habituated for 10 min. After that, they were moved to the neutral chamber, and the partner and stranger were tethered within their own chambers. Then the behaviour was recorded for 30 min (Agrati et al., 2008; Burke et al., 2011). All animals were returned to their cohabitation cages following the test, and were allowed to cohabit for an additional 24 h (a total 48

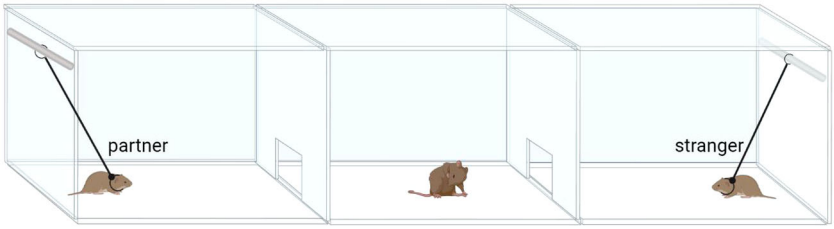

Figure 4. The partner preference test model.

cohabitation hours) and tested again in the same manner; the 'partner' was remained the same, but the 'stranger' was new. This test was repeated six times (1, 3, 5, 7, 9 and 11 days after cohabitation with their partner).

Total duration of physical contact (side-to-side contact and grooming each other) by the experimental animal was analyzed, partner preference was examined as the difference in time spent in physical contact with partner vs. stranger. In prairie vole, familiarity decreases aggressive behaviour (Firestone et al., 1991), and selective aggression is a key sign of pair bond formation (Winslow et al., 1993), so we also analyzed the aggressive behaviour (partner or stranger) in the repeated experiments to partly determine the formation of pair bond. All of the behaviours were recorded by a digital video camera and scored later by an experimentally blind observer using Noldus Observe 5.0 (Noldus, Wageningen, The Netherlands). All behavioural tests were also performed in dim light (approximately 100 lx in the centre of the apparatus) between 8:00–10:00 am.

2.3.4. Rescuing behaviour test

During partner preference test, the partner or stranger was tethered via a ring around their necks (Figure 4). The subject animals spent some time biting the ring and tried to rescue the partner or stranger during test. Duration in biting the ring was also scored as a index of rescuing using method described above.

2.4. Statistical analyses

All data were analysed using SPSS version 20.0 (SPSS Institute, Chicago, IL, USA) and checked for normality using a one-sample Kolmogorov–Smirnov tests. The results were expressed as mean ± SEM. Two-way ANOVA was used to analyse the data of social avoidance test.

Multivariate analysis of variance (MANOVA) test was used to compare difference in behaviours during social interaction test. Repeated measure

ANOVA was used to compare difference in body contact, attacking and rescuing behaviour in partner preference test in different days of pairing and a paired sample t-test was used for analysis of data in contact, attacking, rescuing partner and strangers in specific day. A p-value lower than 0.05 and a p-value lower than 0.01 was considered statistically significant and extremely significant respectively.

3. Results

3.1. The social avoidance test

Two-way ANOVA revealed significant treatment × target interaction on exploring time ($F_{1,94} = 24.252,\ p < 0.01$). While treatment (CON/DEF) produced significant main effect ($F_{1,57} = 45.291,\ p < 0.01$), presence of target (Target/No target) did not ($F_{1,57} = 2.207,\ p = 0.140$).

Results showed that adult male mandarin voles in the control group spent significantly more time in the interaction zone in the second stage (Target) than that in the first stage (No Target) ($p < 0.01$). Adult male mandarin voles in the chronic social defeat stress group spent significantly less time in the interaction area in the second stage (Target) than that in the first stage (No Target) ($p = 0.036$) (Figure 5A).

An independent-samples t-test revealed that social interaction ratio of the control group (CNO) is significantly higher than that in chronic social defeat group (DEF) ($t_{56} = 6.72,\ p < 0.001$).

3.2. Social interaction test

In social interaction test, nine behavioural variables were scored and analysed. MANOVA revealed that chronic social defeat significantly reduced attacking ($F_{1,36} = 6.057,\ p = 0.018$), intimate behaviour ($F_{1,36} = 9.733,\ p = 0.003$), sniffing ($F_{1,36} = 6.151,\ p = 0.017$), and exploratory behaviour ($F_{1,36} = 5.575,\ p = 0.023$); but significantly increased avoidance behaviour ($F_{1,36} = 4.218,\ p = 0.046$), defensive behaviour ($F_{1,36} = 9.509,\ p = 0.004$), and immobile behaviour ($F_{1,36} = 4.830,\ p = 0.033$) compared with the control group. Self-grooming and walking were not influenced by chronic social defeat (Figure 5C).

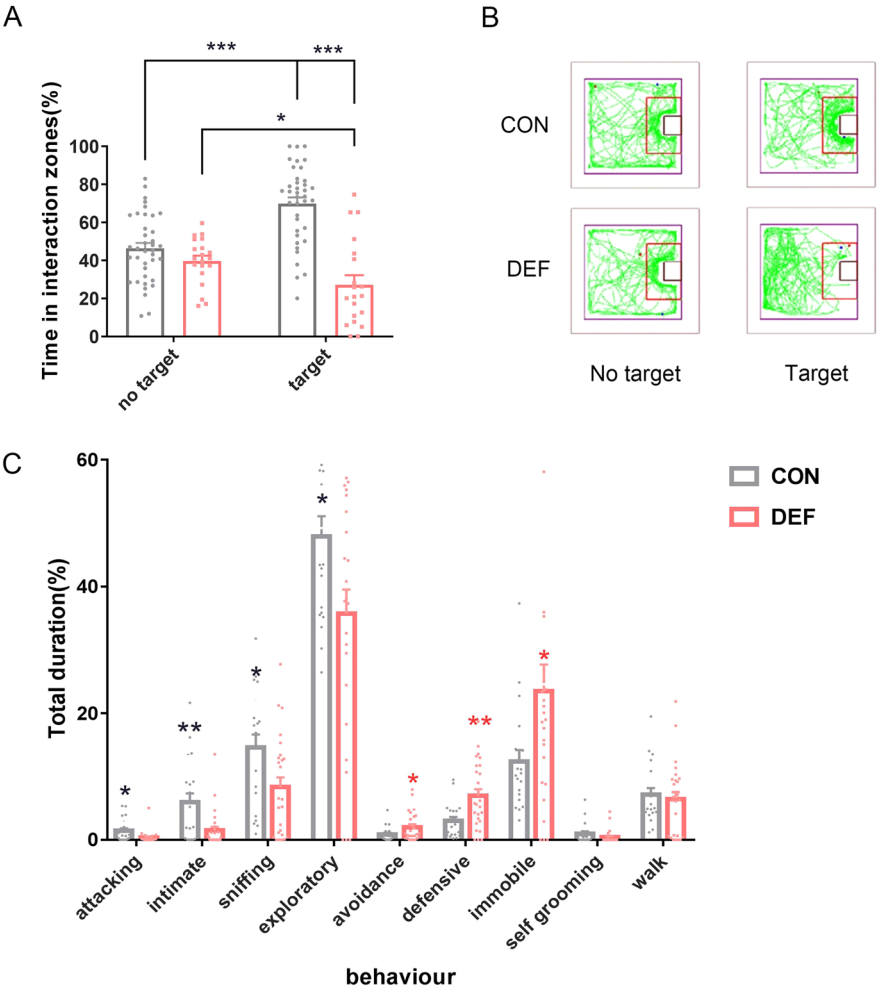

Figure 5. Effects of chronic social defeat on behaviours in social avoidance test and social interaction test. (A) The social avoidance test (mean ± standard error): percentage of total time spent in the interaction area in control (CON) and defeat (DEF) groups. (B) Representative activity trail of mandarin voles during the social avoidance test. (C) Percentage of time spent in specific behaviour in total time of social interaction test in control (CON) and defeat (DEF) groups. **Difference with $p < 0.01$; *difference with $p < 0.05$.

3.3. Partner preference test

3.3.1. The time side-by-side with partner and stranger

A paired *t*-test found that adult male mandarin voles in the control group (CON) spent significantly or very significantly more time in side-by-side

contact with the partner than with the stranger at 1 ($t_6 = 3.188$, $p = 0.019$), 3 ($t_6 = 3.084$, $p = 0.022$), 5 ($t_6 = 3.071$, $p = 0.022$), 7 ($t_6 = 8.695$, $p < 0.001$), 9 ($t_6 = 21.433$, $p < 0.001$) and 11 ($t_6 = 11.202$, $p < 0.001$) days of cohabitation (Figure 6A).

The chronic social defeat stress group (DEF) also spent significantly more time in side-by-side contact with the partner versus the stranger at 1 ($t_9 = 2.315$, $p = 0.046$), 3 ($t_9 = 3.004$, $p = 0.015$), 9 ($t_9 = 3.285$, $p = 0.009$) and 11 ($t_9 = 3.226$, $p = 0.010$) days of cohabitation. However, there was no significant difference at 5 days ($t_9 = -0.674$, $p = 0.517$) and 7 days ($t_9 = 1.234$, $p = 0.249$) of cohabitation displaying unstable partner preference in DEF group (Figure 6A).

3.4. Time side-by-side with partner

Repeated measure ANOVA revealed that chronic social defeat group (DEF) spent significantly less time in contacting with partner compared with control group (CON) ($F_{1,6} = 48.212$, $p < 0.0001$).

An independent t-test found that adult male mandarin voles in the control group (CON) spent significantly more time in side-by-side contact with the partner than the chronic social defeat stress group (DEF) at 1 day ($t_{15} = 9.742$, $p = 0.007$), 5 days ($t_{15} = 34.966$, $p < 0.0001$), 7 days ($t_{15} = 9.044$, $p = 0.009$), 9 days ($t_{15} = 6.295$, $p = 0.024$) and 11 days ($t_{15} = 6.589$, $p = 0.021$) of cohabitation (Figure 6B).

3.5. Time attacking partner and stranger

A paired t-test found that adult male mandarin voles in chronic social defeat stress group (DEF) spent significantly less time in attacking the stranger than control group (CON) at 11 days of cohabitation ($t_{15} = 2.173$, $p = 0.046$) (Figure 6C). In the control group (CON), the male mandarin voles spent significantly more time in attacking the stranger than partner at 11 days of cohabitation ($t_6 = -2.462$, $p = 0.049$).

3.6. Time rescuing partner and stranger

The rescuing behaviour may be a manifestation of empathy, thus rescuing time for partner almost in every day was longer than stranger. In the control group (CON), a paired t-test found that adult male mandarin voles rescued the partner significantly more than the stranger at 1 ($t_{15} = 3.452$, $p = 0.014$), 9 ($t_{15} = 2.622$, $p = 0.040$) and 11 ($t_{15} = 2.205$, $p = 0.046$) days of cohabitation (Figure 6D).

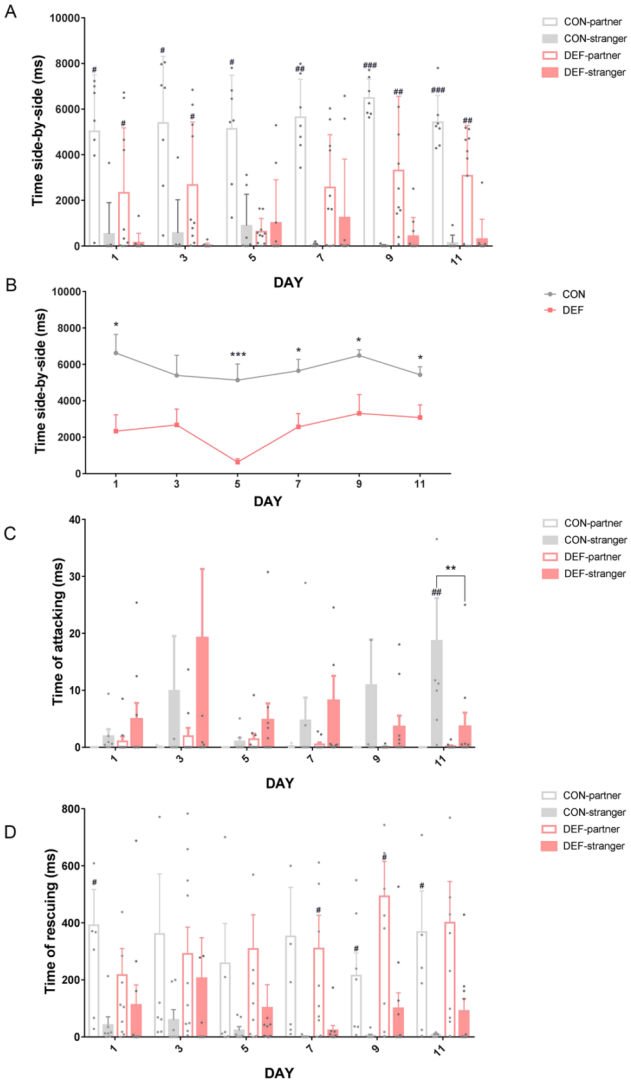

Figure 6. Effects of chronic social defeat on partner preference and rescuing behaviour. (A) The side-by-side time with partner and stranger in different days of cohabitation (mean ± standard error). (B) The total amount of time adult male mandarin voles spent side-by-side with their partner in the control (CON) and defeat (DEF) groups (mean ± standard error). (C) The duration of attacking partner and stranger in different days of cohabitation (mean ± standard error). (D) The time spent in rescuing partner and stranger in different days of cohabitation. $^{\#}$Difference in duration of behaviours on partner and stranger; *difference in times of behaviours between the control group and the defeat group. $^{***, \#\#\#}p < 0.001$; $^{**, \#\#}p < 0.01$; $^{*, \#}p < 0.05$.

After chronic social defeat stress, adult male mandarin voles also rescued the partner significantly more than the stranger at 7 ($t_{15} = 2.366$, $p = 0.042$), 9 ($t_{15} = 2.709$, $p = 0.024$) days of cohabitation.

Thus, chronic social defeat stress group (DEF) and control group (CON) did not showed difference in rescuing that means chronic social defeat does not affect the rescuing to the partner.

4. Discussion

The present study found that chronic social defeat impaired stability of pair bonding. This result is consistent with results in the present study that chronic social defeat reduced side-by-side contacts with partner, reduced attacking toward a stranger. Reduced side-by-side contacts with partner and attacking behaviour to strangers may form a tendency to build up new pair bonding with strange individual and accelerate the instability of their original partnership. This result is in line with one previous study that prolong stress impaired pair bonding in male prairie voles (Arai et al., 2016). However, this result is in contrary to previous findings that three days of social defeat did not affect, but even facilitate formation of pair bonding (Kowalczyk et al., 2018) and acute exogenous corticosterone injections facilitated social preference in male prairie voles (Blondel & Phelps, 2016). In addition, CRF treatments produced similar effects while its receptor antagonist prevented partner preference formation (Lim et al., 2007). However, stress or corticosterone treatment prevents formation of partner preference in female prairie voles displaying opposite effects on males (Lim et al., 2007). It is possible that effects of stress on partner preference may be species and sex specific or dependent on duration and types of stress.

In addition, the result that chronic social defeat significantly reduced side-by-side contacts with partner is supported by data from social avoidance test and social interaction test. In the present study, chronic social defeat increased social avoidance and reduced intimacy, sniffing and increased defensive behaviours. In accordance with present results, previous studies have demonstrated that chronic social defeat increases social avoidance in mice (Berton et al., 2006), rats (Ivanyi et al., 1991; Berton et al., 2006; Vidal et al., 2011) and California mice (*Peromyscus californicus*) (Trainor et al., 2011). In addition, chronic social defeat reduced social interaction in social interaction test in the present study. However, chronic social defeat reduced

attacking toward the stranger in the present study. This result is in agreement with finding in the social interaction test that chronic social defeat reduced attacking to a stranger with same sex. The increased attacking and decreased side-by-side contacts with partner may cause the lost of partner preference in male experiencing chronic social defeat.

On the other hand, sexual behaviours could be suppressed by social defeat in male mice (Kahn, 1961) and tree shrews (van Kampen & Merget, 2002). In addition, three weeks social defeat led deficits in production of sperm in male C57BL/6J mice (Wang et al., 2017), and subordinate males release less major urinary proteins (Silvers et al., 2017) which may reduce sexual attraction in females (Roberts et al., 2010). These abnormalities induced by chronic social defeats may influence successful copulation which subsequently affects stability of pair bonding.

Another interesting finding is that both chronic social defeated or control group spent significantly longer time rescuing partner than stranger. Given that rescuing is one type of empathetic behaviour, it is consistent with previous study that the observers show significantly more empathetic behaviour toward familiars than strangers (Martin et al., 2015). While rescuing behaviour is considered as a specific performance of empathy, it is not strange that mandarin vole rescued partner more than stranger. Most studies suggest that chronic social defeat reduces social interaction, increases plasma levels of glucocorticoid, leads to a lack of pleasure (Shimamoto, 2018). The possible explanation may be that chronic social defeat reduced time in side-by-side and especially reduced aggressive behaviour to stranger on 11 days after pairing displaying an impaired pair bonding in chronic social defeated group. However, chronic social defeat did not affect levels of rescuing. We cannot give a reasonable explanation for this result.

Alteration in stability of pair bonding and social interaction induced by chronic social defeat may be caused by changes in brain activities. Previous study found that chronic social defeat reduced levels of oxytocin (OT) and OT receptors (OTR) in the shell region of the nucleus accumbens (NACC) (Wang et al., 2018b) and decreased dopamine receptor expression in the prefrontal cortex and amygdala (Huang et al., 2016; Felippe et al., 2021). Many studies support that oxytocin and dopamine systems play important roles in formation and maintenance of pair bonding (Walum & Young, 2018). In addition, formation and maintenance of pair bonding are associated with social recognition. The normal social recognition could be disrupted by

CSDS in adult female voles and this disruption is associated with increased neural activity in the DG, CA1 and CA3 of the hippocampus and reduced levels of serotonin (5-HT) and serotonin 1A receptors (5-HT1AR) in the CA3 (Wang et al., 2019a). Thus, stability of pair bonding is changed by CSDS possibly via alteration in brain activities. However, this underlying mechanism needs further research.

In summary, present study found that chronic social defeat increased social avoidance and reduced social interaction. In partner preferences test, it reduced side-by-side contacts with partner, reduced attacking toward a stranger, but did not reduce rescuing time to partner. This finding provides some insights into mechanisms underlying effects of prolong social stress on social relationships between partners.

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