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Can Male Mice Develop Preference Towards Gentle Stroking by an Experimenter?

C. Cho, [a†] C. Chan [b†] and L. J. Martin [a,b*]

[a] Cell and Systems Biology, University of Toronto Mississauga, Mississauga, ON L5L1C6, Canada

[b] Dept. of Psychology, University of Toronto Mississauga, Mississauga, ON L5L1C6, Canada

Abstract—Gentle stroking, a type of affective touch that holds hedonic and rewarding value, is critical to our daily inter-individual communication. This positive socio-emotional aspect of touch is conveyed through a subclass of C afferents known as C-Tactile fibers in humans with an analogous system in rodents proposed. Here, we describe a novel tactile conditioned place preference paradigm using mice and demonstrate that gentle stroking by an experimenter is rewarding. In order to investigate the relationship between tactile preference and innate sociability, mice were subjected to the classic three-chambered test of social approach, where mice displayed significant preference towards the experimenter's hand. These findings suggest that gentle stroking evoked by an experimenter can play an important role in reward and preference and establish an affiliative relationship between mice and humans. Future research can potentially use this model to examine fiber type involvement and elucidate the significance of these findings for activation of the reward system.

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Key words: affective touch, gentle stroking, mouse model, conditioned place preference.

INTRODUCTION

Touch is an essential component of the somatosensory system. It is the first method of communication through which humans learn and it helps us navigate our physical world by discriminating tactile perturbations that are received through physical contact. Discriminative and sensorimotor information such as pressure, vibration, and texture are encoded peripherally by myelinated large diameter Aß fibers, while nociceptive-specific information is encoded by small diameter myelinated $A\delta$ fibers to support rapid response [1]. The functions of touch, however, reach beyond their discriminative role and are often used to communicate positive and negative emotions [2–4]. In part, this is supported physiologically by the fact that Aß and $A\delta$ fibers work in tandem with unmyelinated C fibers, which transmit information slower and respond to affective or motivational stimuli such as pain (mechanical, thermal and chemical), itch as well as gentle stroking [5].

The hedonic and motivational aspect of touch facilitates inter-individual communication that has the potential to influence social bonding [6]. This type of touch, often referred to as "affective touch" [3], is determined by the physical nature of the tactile stimuli. Specifically, sensory modalities such as temperature [7,8], texture [9], pressure and velocity [2] produce either pleasant or unpleasant experiences depending on social and environmental context as well as one's affective state. Inter-individual gentle stroking/caress is often a positive form of communication that conveys social messages such as comfort, reward, sympathy, protection and reassurance [10–12]. In humans, research has uncovered that gentle stroking which induces a pleasant sensation, activates one subclass of low-threshold mechanoreceptive C afferents (C-LTMRs), known as C-tactile (CT) fibers that are found exclusively in hairy skin [2]. CT fibers respond specifically to innocuous stimuli such as a soft brush [13] at a light stroking force of 0.3–2.5 mN with a slow rate of 1–10 cm per second [2,13,14] while being tuned to a neutral (body) temperature [8].

The significance of gentle stroking is apparent in primates and non-primate counterparts. The seminal finding by Harlow and Zimmerman [15] was one of the first to demonstrate the importance of gentle touch in primates within the context of maternal care where infant macaque monkeys separated from their mothers preferred comforting touch over food. Furthermore, primates

*Correspondence to: L.J. Martin, Department of Psychology, University of Toronto Mississauga, 3359 Mississauga Rd., Mississauga, ON L5L 1C6, Canada.
E-mail address: lj.martin@utoronto.ca (L. J. Martin).
† Denotes equal contributions.
Abbreviations: CPP, conditioned place preference; CT, C-tactile; TH, tyrosine hydroxylase.

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spend a significant amount of time reciprocally grooming, or 'allogrooming', which represents a social bonding and rewarding opportunity between conspecifics [11]. In rodents, gentle stroking is often conveyed in the form of licking and grooming and serves as an important component of social interaction [16]. Interestingly, mother-to-pup licking and grooming are typically targeted to specific body sites including head, ears and dorsal back where C fibers are densely represented [17–19]. In rats, studies found that social reward appears heavily dependent on tactile interactions between conspecifics [20,21]. Furthermore, gentle stroking of the dorsal back in rats induced 50-kHz ultrasonic vocalizations, indicative of positive emotions and developed an affiliative relationship towards the hand that performed the gentle stroking [22,23]. Recently, Mas-related G-protein coupled receptor member B4 (MrgprB4) afferents in rodents have been described as analogous to human CT fibers [19]. MrgprB4 afferents respond to massage-like stroking of hairy skin and selective stimulation of these afferents were found to be rewarding, but their relationship to human CT fibers remains to be elucidated.

Empirically, many questions remain with regards to neural mechanisms underlying gentle stroking despite a growing foundational literature for humans and animals. One barrier to translational work on rodents is the lack of a standardized behavioral method for studying gentle stroking. Towards this endeavor, we describe here a novel conditioned place preference paradigm to evaluate the rewarding value of gentle stroking of hairy skin on mice. We hypothesized that mice would develop a preference towards gentle stroking. Given the socio-affective basis of gentle stroking, we further hypothesized that mice that receive gently stroking would develop affiliative relationship towards the experimenter's hand. In order to address this, we employed the three-chambered test of social approach.

EXPERIMENTAL PROCEDURES

Animals

Male C57BL/6 mice (4–5 weeks of age; $n = 11$) acquired from Charles River Laboratories (Saint Constant, QC., Canada) were tested. Juvenile mice were used as they display extensive social interactions pertinent to the current study [24–26]. Mice were housed in groups of 3–5 per cage. All cages were enriched with a compressed cotton nesting square, crinkled paper bedding and a red plastic dome. All mice were maintained in a temperature-controlled (20 ± 1 °C) environment with a 12-hour light/12-hour dark cycle (lights on at 8am) and had access to food (Harlan Teklad 8604) and water *ad libitum*. All possible efforts were made to minimize the number of animals used and their discomfort during the experimental procedures. All experiments were approved by the University of Toronto Animal Care Committee and conducted in accordance with the Canadian Council on Animal Care (CCAC) guidelines and the Ontario Animals for Research Act.

Behavioral assays

As we did not have *a priori* expectation of effect sizes, power analyses were not used to calculate sample sizes. Instead, we adhered to standard practices in the field relating to the conditioned place preference where a range of 8–12 mice are used per group [27–29]. All animals were habituated to the experimenters by handling for 5 days before experimental procedures. For handling, each mouse was placed in the palm and was gently stroked on the dorsal side (from the nape of the neck to the base of the tail) by a gloved finger every 15 s at a velocity of 1–5 cm/s in accordance with the optimal stroking condition for activating CT afferents [30]. The force applied was 240–260 mN/cm^2 in accordance with previous research that examined pleasant tactile stimuli in rats [22]. In order to ensure a mild force was applied consistently, the experimenters were trained on a high-precision scale. Gloves were replaced after each mouse to ensure neutral olfactory cues across mice. All behavioral assays were performed during the light cycle.

Tactile conditioned place preference

Each animal's preference for gentle stroking was measured using a conditioned place preference (CPP) apparatus (see Fig. 1A for a timeline). The CPP apparatus was constructed from Plexiglas and consisted of three-compartments. The two side compartments (18 × 18 cm) served as contextually distinct conditioning zones (Fig. 1B). One of the two side compartments had black walls and a metal bar floor while the other had white walls and a metal grid floor. The middle compartment was narrower (18 × 10.5 cm) and composed entirely of green Plexiglas with small openings with sliding doors to allow passage. On the pre-conditioning day, each mouse was tested for their innate place preference by placing each mouse into the center compartment and allowing them to freely explore all three compartments for 30 min. The time spent by the mouse in each of the two opposing compartments was calculated using Noldus Ethovision XT7 software (Noldus Information Technology, The Netherlands). The compartment in which the animal spent less time was used as the stroke-paired chamber, while the opposite chamber became the neutral-stimulus chamber. The conditioning occurred over 8 sessions spread across 8-days (1 session/day). A neutral-stimulus was used as a control to test whether tactile stimulation itself, and not gentle stroking sensation, was driving the CPP response. For the neutral stimulus, mice were gently pressed with the force of 240–260 mN/cm^2 on the dorsal side with a gloved Fun-Tak mounting putty that was shaped to mimic the texture and surface area of the stroking finger. For tactile conditioning, mice were restricted to one chamber per day for 30 min, which was either paired with gentle stroking or no-stimulus. Mice were either gently stroked (1–5 cm/s with the force of 240–260 mN/cm^2) or pressed (neutral stimuli) for the duration of conditioning at 5 min intervals (5 min of continuous stimulation followed by 5 min of rest). Gentle stroking and no-stimulus were counterbalanced between

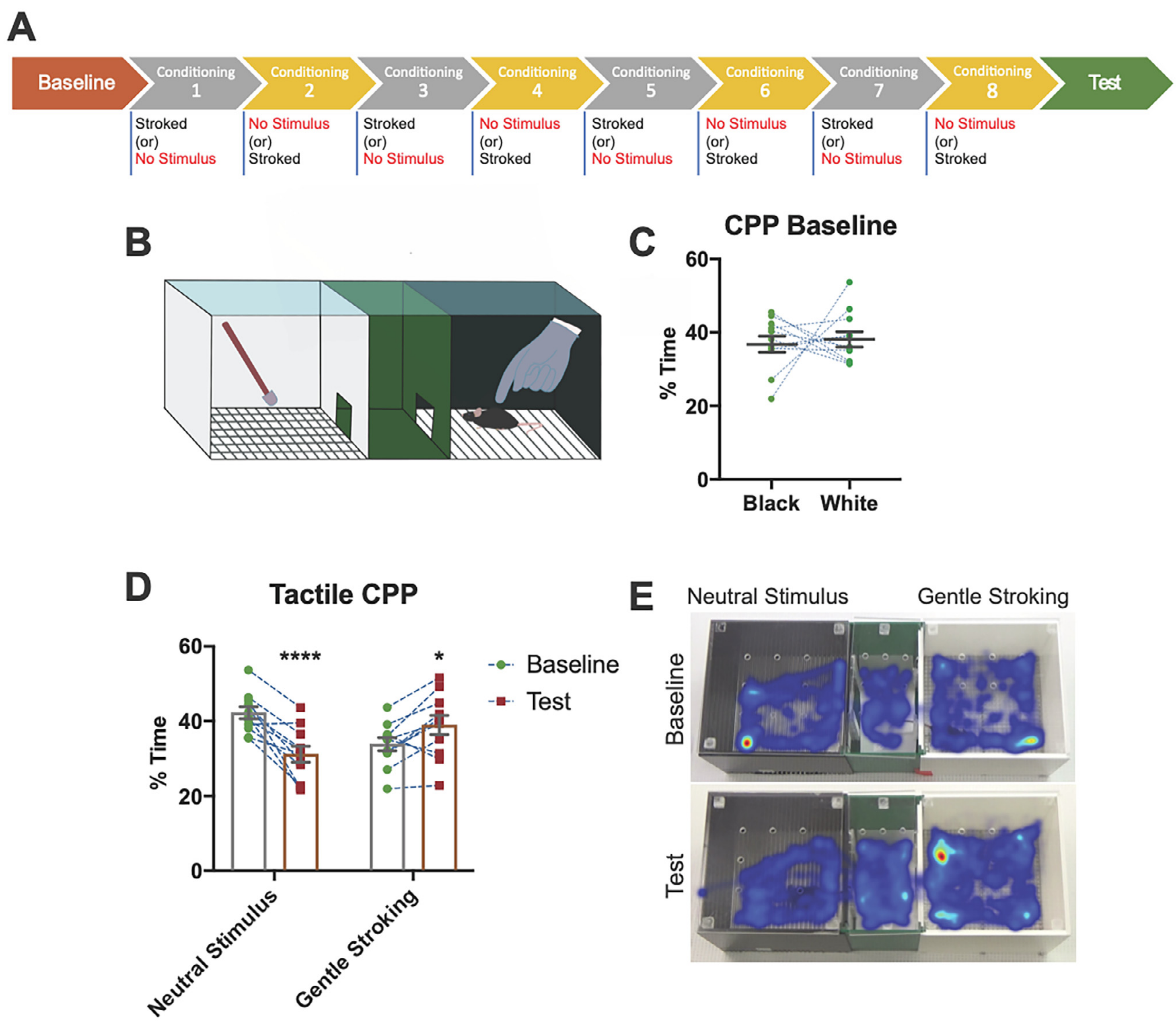

Fig. 1. Tactile conditioned place preference results in male mice ($n = 11$). **(A)** A schematic diagram of the behavioral timeline. Each mouse was exposed to 8 conditioning sessions (1 session/day) where on each day a mouse was exposed to either gentle stroking or a neutral stimulus. **(B)** An illustration of the three-chamber apparatus. Depending on their initial preference, each mouse was paired with gentle stroking in the chamber they spent less time in and a neutral stimulus in the opposite chamber. **(C)** Percent time the mice spent in white wall and black wall compartments on baseline. **(D)** Tactile preference results after conditioning. Significant increase in preference towards gentle stroking was observed. **(E)** An example heat map representation of a mouse's trajectory during CPP. In this example, black wall (left) compartment was paired with neutral stimulus and the white wall (right) with gentle stroking. $^{*}p < 0.05$, $^{****}p < 0.0001$.

mice, such that half of the mice received gentle stroking on the first session or day. Overall, the animals underwent four sessions in each compartment. Following conditioning, a post-conditioning test was conducted as described for the pre-conditioning day. The time spent in each compartment was represented as the percentage time.

Three-chambered test of social approach

Each animal's tendency for social approach was measured using an equally partitioned three-chambered Plexiglas apparatus (20 cm × 22 cm) with transparent dividing walls and small openings with sliding doors to allow passage [31] (Fig. 2A). Each mouse was first tested for their innate place preference by placing each mouse into the center chamber and allowing them to freely explore all three chambers for 10 min. The time spent in each of the two opposing chambers was calculated using Noldus Ethovision XT7 software. Immediately following this, the experimenter's gloved hand was placed in the chamber in which the mouse spent less time in. A 500 ml water bottle was filled with opaque blue-colored water similar to the color of the glove and placed in the opposite chamber. The mouse was then allowed to freely explore all three chambers that included the experimenter's hand or the water bottle for 10 min and their movements were analyzed using Noldus Ethovision XT7 software. The time spent in each compartment was represented as the percentage time.

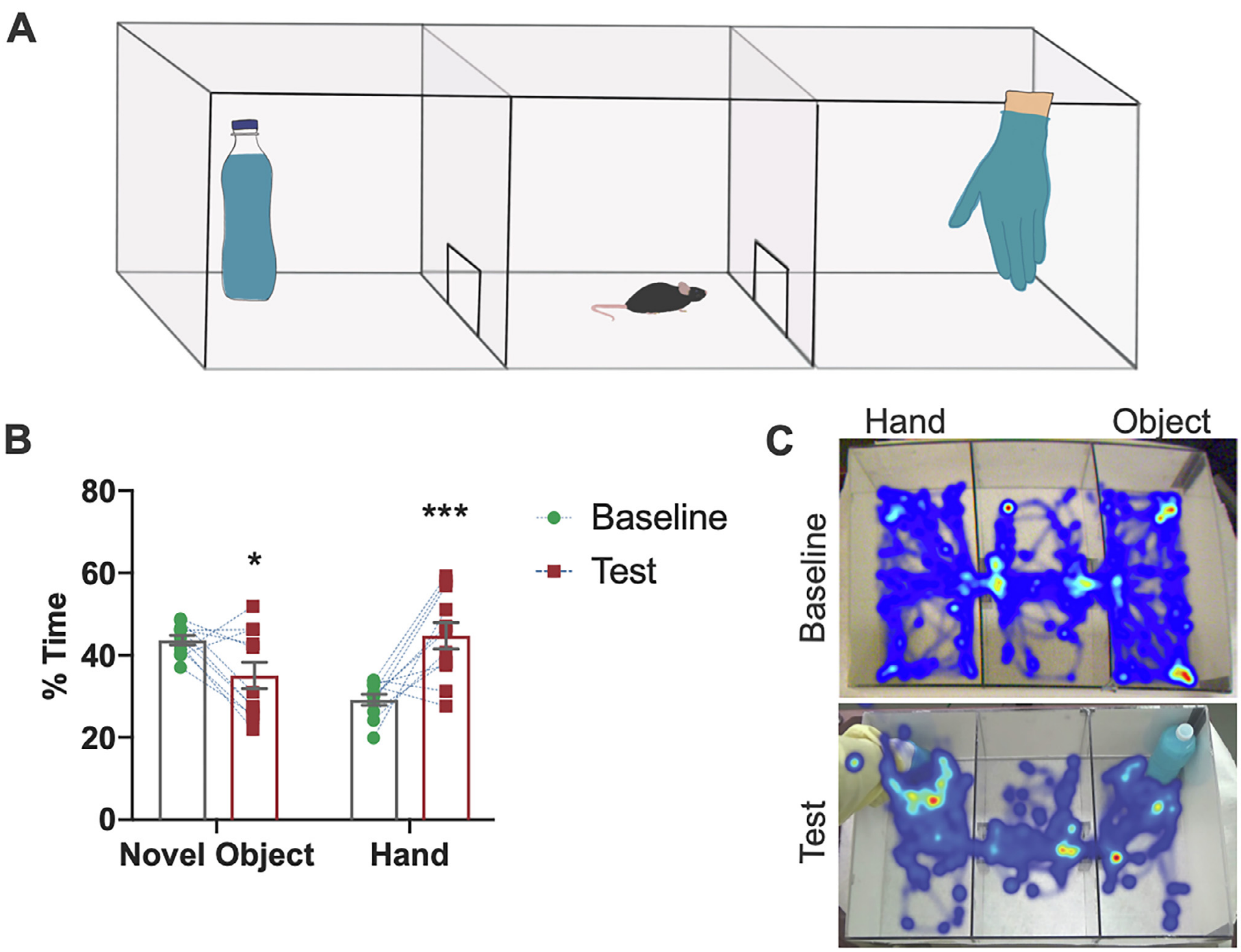

Fig. 2. Three-chambered test for sociality ($n = 11$). **(A)** An illustration of the three-chamber used for the study. Based on their initial preference, the experimenter's hand was placed in the chamber they spent less time in while a water bottle filled with opaque blue water was placed in the opposite chamber. **(B)** The three-chambered test showed a significant increase in preference towards the experimenter's hand. **(C)** An example heat map representation of a mouse's trajectory during the three-chambered test. In this example, the left compartment was paired with the experimenter's hand while the opposite chamber was paired with the novel object. $^{*}p < 0.05$, $^{***}p < 0.0005$.

Statistics

The baseline data for the tactile CPP was calculated using Student's *t*-test (paired, 2-tailed). The tactile CPP and the three-chambered test of social approach data were analyzed using a two-way repeated measures ANOVA followed by Bonferroni-corrected post-hoc comparisons. Pearson correlation was used for examining the relationship between the tactile conditioned place preference and three-chambered test of social approach. A criterion $\alpha = 0.05$ level was used. The data were presented as means ± SEM.

RESULTS

Gentle stroking is rewarding in male mice

All mice were exposed to the gentle stroking and neutral-stimulus compartment four times in total over the course of 8 days (1 conditioning session/day) (Fig. 1A). For tactile conditioning, the mice were either gently stroked or pressed with equal pressure for 30 min (Fig. 1B). Mice did not display obvious signs of distress (increase in fecal droppings) or defensive responses (i.e. flight, shelter seeking and biting). Baseline preference towards the CPP compartments were measured before conditioning (Fig. 1C). 6 out of 11 mice spent greater time in the white wall compartment while 5 mice spent greater time in the black wall compartment. Overall, no difference was found between the proportion of time spent in the white and black wall compartments ($t_{10} = 0.3342$, $p = 0.7451$). Following tactile conditioning, two-way RM ANOVA revealed a significant main effect of interaction between compartment (neutral stimulus vs. gentle stroking) and time (before vs. after conditioning) [$F_{1,20} = 36.26$, $p < 0.0001$]. Also, a significant main effect of time [$F_{1,20} = 4.843$, $p = 0.04$] but not compartment was found. Mice spent significantly increased time in the compartment paired with gentle stroking (+5.16 ± 1.91% from baseline, $p = 0.0274$) while spending significantly decreased time in the compartment paired with the neutral stimulus (−11.10 ± 1.91% from baseline, $p < 0.0001$) (Fig. 1D, E).

Male mice display preference for the experimenter's hand over a novel object

In order to test whether the preference towards gentle stroking was related to the innate sociability of the mice, we implemented the three-chambered test of social approach (Fig. 2). Following the tactile CPP, mice were allowed to freely choose between the experimenter's hand and a novel object (Fig. 2A). As a result, a significant main effect of interaction between compartment (hand vs. object) and time (before and after exposure to hand or object) was found [$F_{1,20}$ = 23.37, p = 0.0001]. Neither a significant main effect of compartment nor time was observed. Mice spent significantly increased time in the compartment with the experimenter's hand (+15.57 ± 3.53% from baseline, p = 0.0005) and significantly decreased time in the compartment with the novel object (−8.56 ± 3.53% from baseline, p = 0.0497) (Fig. 2B, C).

Tactile preference is not correlated with innate sociability

Based on the above observations, we wanted to determine whether there was a relationship between tactile preference and the innate sociability of mice (Fig. 3). A Pearson's correlation revealed a moderately positive but a non-significant relationship between tactile preference and innate sociability (r_{11} = 0.51, p = 0.11).

DISCUSSION

Gentle touch carries an important socio-emotional function to humans and non-human primates as it can relieve negative emotions and impart a sense of pleasure, relief and assurance. Similarly, increasing evidence suggest an analogous system in rodents, but the neural mechanisms remain largely elusive. In order to facilitate bridging this gap in understanding, we sought to establish a novel conditioned place preference paradigm to demonstrate gentle stroking of hairy skin can be rewarding in mice. Our results indicate for the first time in mice that gentle stroking of hairy skin can be used to establish tactile preference. The presence of tactile preference found here relates to previous studies that have used high degree of manual tactile stimuli to generate conditioned place preference in rats, which includes tickling and gentle stroking [23,24,32,33].

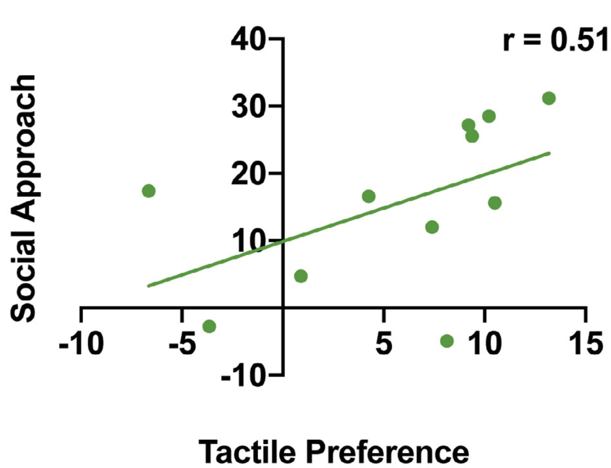

Fig. 3. Correlation plot between tactile preference and social approach (n = 11). The difference scores from the tactile preference and social approach tests were tested. A moderately positive but a non-significant relationship was found.

Contextual factors such as the identity and intentions of the toucher and social contexts greatly influence the perception of gentle stroking as pleasant. Therefore, the relationship between toucher and the recipient can dictate the hedonic experience and the behavioral response such as withdraw and approach [12]. Rodents such as mice are prey species and actively avoid human approach and contact; this would be expected to have a profound effect on their stress and anxiety [34]. In order to minimize this aversion, all mice were extensively handled by the experimenter prior to commencing the experiments. Physiologically, social touch including gentle touch decreases stress response by lowering cortisol release [35]. Licking and grooming received by the mother rat is known to affect the offspring's stress response and anxiety behavior in adulthood [16,36–39]. Furthermore, gentle stroking in rats was found to induce hypothalamic oxytocin neurons [22]. Therefore, the conditioned place preference observed here may be facilitated by a decrease in cortisol release and an increase in oxytocin level. Future studies should aim to address these questions and identify physiological changes induced by gentle stroking in our model.

Mechanistically, MrgprB4 afferents – thought to be C-LTMRs – may be activated in establishing place preference [19]. Also, gentle stroking might induce C-LTMRs to release TAFA4 – a C-LTMR specific marker and a chemokine-like protein – while inhibiting glutamate release from the afferents. In support, a functional knock-out of TAFA4 in TAFA4 knock-out mice exacerbated mechanical hypersensitivity while application of TAFA4 protein reversed the hypersensitivity [40]. In another study, vesicular glutamate transporter type 3 (VGLUT3) knock-out prevented glutamate release from C-LTMRs and reduced mechanical sensitivity following inflammation, nerve injury and trauma [41]. As TAFA4-positive C-LTMRs also co-express tyrosine hydroxylase (TH) [42], the potential role of TH-expressing C-LTMRs in affective touch cannot be discounted.

Gentle touch, in the social touch context, is essential in the formation and maintenance of relationships. This is especially true in rodents where social reward appears to be heavily dependent on tactile interactions between conspecifics [20]. Given the socio-emotional aspect of gentle stroking, we measured the association between tactile preference and sociability using the three-chambered test of social approach. The social approach test is widely used for gauging innate sociability in rodents and produces reliable results [43,44]. In this study, sociability was defined as the tendency to approach and remain in proximity to the experimenter's hand. As a result, the gently stroked mice spent significantly greater time with the experimenter's hand compared to a novel object although no significant correlation was found between tactile preference and social approach test. The lack of correlation, in part, may be due to the social variations including differences in paternal care (i.e. maternal grooming) and dominance relationships amongst cagemates. These differences may lead each mouse to react differently to gentle stroking. Overall, these data suggest an affiliative relationship at an inter-species level between mice and the experimenter. In a previous study, the same social approach test applied to male C57BL/6J mice showed significant preference for social novelty when presented with a conspecific [31,43,45]. Notably, the aforementioned study and we have both used juvenile C57BL/6 mice. Juvenile animals in the laboratory are known to display extensive social interactions [24,25], especially the C57BL/6 strain [26]. Therefore, the strong social approach behavior observed here may in part be due to the pro-social nature of the juvenile mice. Whether similar preference would be observed in adult mice remain to be investigated as the patterns of social behavior changes as mice age.

An important limitation of this study is that we did not test female mice in this study. In the context of social touch, both male and female rats were shown to acquire a conditioned preference towards a compartment paired with a playful social partner [24]. Therefore, in a similar vein, it is possible that similar tactile preference may develop in females, but further studies are needed to confirm this. Another limitation of this study is that the optimal timeline for the tactile conditioning is unclear. We allowed 24 h between each conditioning session to allow sufficient time for mice to form a robust association between the compartment and gentle stroking given that gentle stroking is a relatively a weaker unconditioned stimulus compared with drugs that are often used for conditioned place preference such as opiates, alcohol and psychostimulants [46]. However, the optimal interval between conditioning and the number of pairing sessions to induce preference remain to be found.

In conclusion, we present here a novel behavior paradigm for gentle stroking using mice. The benefits of gentle stroking cannot be underestimated based on a strong foundation of literatures regarding development and social communication [47–50]. The positive impact of gentle stroking reaches beyond normal development and has been shown to be effective in attenuating physical pain in infants [51] and the feeling of social exclusion [52]. These findings provide the rational for investigating the neural underpinnings of gentle stroking to expand our knowledge of social neuroscience and to harness its therapeutic potential. As a wealth of genetic tools are available for mice, the present model has the potential to further understand cross-species interactions and preference for gentle stroking.

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