Supplementary Materials

The Roles of Dopamine D1 Receptor on Social Hierarchy of Rodents and Non-human Primates

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Supplementary Methods

Subject

Mice and non-human primates were used in this study. All experiments were conducted in accordance with the *Guidelines for Proper Conduct of Animal Experiments by the Science Council of Japan* and were approved by the Kyoto University Primate Research Institute animal ethics committee.

A total of 116 adult male CD1 mice (8~12 weeks) were purchased from Charles-River Japan, and used for the experiments. Four mice per cage were grouped and housed together in a cage (30 x 20 x 15 cm) in the temperature controlled room under the normal 12 hours light/dark cycle for at least 2 weeks before starting experiments and remained housed together until all experiments were completed. Some of the factors that have been previously shown to be involved in social hierarchy were excluded from this study by using animals without kinship and that were approximately of equal weight and age.

To extend the rodent findings into non-human primates, which are thought to have more complex social relationships with hierarchy and that are closely related to humans, we also conducted the experiments using a social group consisting of 6 Japanese macaques (*Macaca fuscata*). The animals were 3 years old each, and the group consisted of 4 males and 2 females (Suppl. Table S1). The monkeys had been housed in a cage (4 x 5 x 3 m) as a group for approximately 1 year prior to the time experiments began. There was no kinship among the subjects, and each animal originated from a geographically different area.

No food or water restriction was given throughout the experiments in both mice and macaques.

Social rank test in mice

To determine social hierarchy of mice housed in a group, the tube rank test, which is similar to that used in other studies (Wang et al., 2011), was conducted. In this test, an apparatus consisting of a transparent plexiglass tube that is 30 cm long and 2.8 cm in diameter that is connected to transparent boxes (10 x 5 x 10 cm) at each end was used. In the middle of the tube, there was a slit through which a transparent wall was inserted to create a partition. First, mice were trained to go across the tube from one end to the other. Mice were placed into the box on one side, and a reward (a piece of cereal) was placed in the box on the other side. When mice went through the tube and consumed the reward, another reward was placed in the box on the other side. Therefore, mice passed through the tube to alternate between one box and the other box. Training was continued until mice went across the tube without stopping in the middle for more than 5 times consecutively. Test trials began after training. In the test trials, a pair of mice from the same group were taken and simultaneously placed with one mouse into each of the boxes on either side of the tube. A partition wall was inserted at the middle of the tube. When mice from each side reached the middle of the tube, the partition wall was removed. The mouse that caused the other to retreat was designated as the "winner", and the mouse that was retreated out of the tube was designated as the "loser". If no movement of either mouse was observed after 5 minutes, both mice were removed from the tube, and the trial was designated as a "draw". Tournaments of all possible combinations of matches by pairs of mice in each group (e.g. in a group of 4 mice

denoted as "A-D", combinations are 6 pairs of A-B, A-C, A-D, B-C, B-D, C-D) were conducted once per day, 5 times (5 trials). A win or a loss was scored by +1 or 0, respectively. In the case of a draw, both mice were scored as 0; however, this result was very uncommon. Social dominance was then quantified by David's score (DS) (David, 1987). DS is defined as "*...The proportion of wins by individual i in his interactions with another individual j, (P_{ij}) is the number of times that i defeats j, (α_{ij}) divided by the total number of interactions between i and j (n_{ij}), i.e. $P_{ij}=\alpha_{ij}/n_{ij}$. The proportion of losses by i in interactions with j, $P_{ji}=1-P_{ij}$...DS for each member, i, of a group is calculated with the formula: $DS=w+w_2-l-l_2$, where w represents the sum of i's P_{ij} values, w_2 represents the summed w values (weighted by the appropriate P_{ij} values) of those individuals with which i interacted, l represents the sum of i's P_{ji} values and l_2 represents the summed l values (weighted by the appropriate P_{ji} values) of those individuals with which i interacted..."* (Gammell et al., 2003). In our study, the tube test was conducted with four mice in a group and with 5 trials against each opponent. In this condition, for example, the following potential scenario is considered: 1st rank mice winning all trials against 3rd and 4th rank mice but only winning 3 out of 5 trials against 2nd rank mice; 2nd rank mice winning all trials against 3rd and 4th rank mice; and 3rd rank mice winning 3 out of 5 trials against 4th rank mice. The results can then be summarized as shown in the Suppl. Table S2. In this specific example, DS for 1st to 4th rank is calculated as $DS_{1st}=4.4$, $DS_{2nd}=3.6$, $DS_{3rd}=-3.6$, and $DS_{4th}=-4.4$, respectively.

Administration of the DA D1 receptor antagonist SCH23390 (SCH) at the dose of 0.1 mg/kg dissolved in 0.3 ml of 0.9% saline was given to mice intraperitoneally. This dose of the drug was used for the following reasons; (1) in other studies, systemic drug administration at this dose or lower has been shown to cause cognitive impairments in rodents (Murphy et al., 1996; Bourne, 2001), (2) the dose of drug administration was matched between mice and macaques, and (3) the drug is a short-acting compound with an elimination half-life of less than 30 min (Bourne, 2001) such that higher drug doses were preferred to maintain prolonged effects, and (4) we also found that higher drug doses than 0.1 mg/kg caused a significant amount of immobility in the drug-treated animals both in their home cages and during behavioral tests. As a control, an equivalent volume of saline (SAL) was administered. Twenty five groups of 4 mice each (100 mice total) were tested. The 20 groups were divided into 4 sets of drug administration conditions. In one set of 5 groups, the drug was administered to 1st rank mice in each group; in another set of 5 groups, the drug was administered to 2nd rank mice in each group, and so on. In these 20 groups, the drug-administered mice were returned to the groups, and housed together immediately after drug administration. In additional 5 groups in which the 2nd rank mice received drug administration, the drug-administered mice were isolated from the groups for 6 hours after drug administration, by which the drug effects were expected to be largely waned, and then returned to the groups. After training, the tube rank test for the baseline (BASE) condition was conducted to determine the social rank of each mouse in each group (Suppl. Fig. 1a). Then, SAL was given once per day for 5 days in mice at each rank in their home cages, and was followed by the tube rank test for 5 days. After confirming no change in social rank with SAL administration, SCH was given once per day for 5 days in the mouse that had received SAL beforehand. After 5 days of repeated SCH administration, the tube rank test was conducted again for another 5 days.

No SAL or SCH was administered during the tube rank test.

Social behavior test in mice

Although social affiliations has been suggested to underlie determination of social class in a hierarchy in primates (Raleigh and McGuire, 1991; Higley et al., 1996), it has remained elusive in rodents. Thus, alterations of social hierarchy by drug administration may be consequences of behavioral changes, such as enhancement of impulsivity and aggression, but also alterations of social affiliative bonds. To investigate this issue, we further examined the effects of SCH administration on motivation to socially interact with mates in mice. Indeed, social interactions with group mates has been shown to be rewarding and associated with DA transmission through D1 receptor in the corticolimbic system (Tucci et al., 2000; Skuse and Gallagher, 2009; Gunaydin et al., 2014; Felix-Ortiz et al., 2015). Motivation to socially interact with group mates was evaluated with the three-chamber sociability test modified from that used in other studies (Moy et al., 2004; Pearson et al., 2010). In this test, subject mice were placed in the middle chamber (20 x 40 x 40 cm), which was connected to two other chambers (30 x 40 x 40 cm each) on each side. The mice were allowed to freely enter into these chambers through 5 x 5 cm openings on the walls. Either (1) normal adult mice of the same gender with the test-subject mice and that had no previous contact with the test-subject mice, or (2) cage mates that were housed together with the test-subject mice, were placed in a metal mesh cage (a cylindrical shape that was 5 cm in diameter and 10 cm high) that was positioned in the center of one of the sides of the chamber. On the other side of the chamber, an identical mesh cage without mice was placed. The amount of time that the test-subject mice spent on each side of the chamber was measured for 10 minutes. Animals that spent more time in the side of the chamber with the trapped mice were considered to be more strongly motivated to interact with mates. Thus, the ratio of time spent in the social over non-social areas was calculated and expressed as an index for motivation to socially interact with mates.

A total of 56 mice were used in this test, of which 16 mice were paired with unfamiliar trapped mice (having no previous interaction), and twenty pairs of one higher- and one lower-ranked mice in the same home cages (which were also used for the tube rank test) were subjected to the test. Tests were conducted for each mouse twice over 2 days with SAL and SCH administration, respectively, on each day (i.p.). The order of SAL and SCH administration was counter-balanced. In the test with unfamiliar pairs, trapped mice were replaced with other mice for each administration. Acute SAL and SCH administrations were given 10 minutes before the start of each test.

Other behavioral tests in mice

D1 receptor signaling plays critical roles in cognitive functions, such as working memory (Zahrt et al., 1997; Seamans et al., 1998), behavioral inhibition (Rodgers et al., 1994; van Gaalen et al., 2006), and behavioral flexibility (Ragozzino, 2002). We investigated the effects of SCH administration on the associations between social rank and these non-social cognitive factors to address how alterations in them may contribute to social hierarchical changes using food foraging and elevated plus maze tests. Four groups of 4 mice each (16 mice total, (which were also used for the tube rank test), were used in these tests. In sequential order, the food foraging test was given on the first

day and then the elevated plus maze test were given on the next day to mice.

The random foraging task, which is similar to that used in other studies (Bond et al., 1981; Floresco et al., 1997; Jung et al., 1998), was conducted to examine working memory and behavioral flexibility. In this task, the radial eight-arm maze was used. Mice were placed in the central arena of a maze that was connected to eight arms that were 40 x 10 cm with walls (20 cm high). At the beginning of the test, a piece of a cereal was baited at the end of each arm. Mice were allowed to freely explore the maze for 5 minutes, or until consuming all baited cereals, whichever happened first. The number of times that mice re-entered arms that they had already visited was recorded. Repeated entries into the same arms were divided into two categories. One category was re-entries into the same arm at least two non-consecutive times (NC entrance). This pattern of entries into the same arms was measured as a reflection of working memory deficit. The other category was re-entries into the same arm consecutively (C entrance). This pattern of entries into the same arm was measured as a reflection of behavioral flexibility deficit. SCH and SAL were given to animals approximately 10 minutes before starting tests. To eliminate locomotor effects of the drugs, the ratio of the number of times of consecutive or non-consecutive re-entries into the same arm over the total number of arm entries was calculated.

The elevated plus maze task was conducted to examine inhibition of inappropriate behaviors. The maze consisted of two opened arms (10 x 50 cm) without walls and two enclosed arms with walls that were diagonally placed to the opened arms. The maze was elevated 1 meter above the ground. Mice were placed in the central crossing area of the arms, and were allowed to freely enter into the arms for 5 minutes. The elevated plus maze has typically been used to examine anxiety in many studies (Hogg, 1996). However, studies, including ours (Griebel et al., 1997; Ueno et al., 2002; Lee and Goto, 2011), have shown that the elevated plus maze can also be used to examine behavioral inhibition, because entering into the opened arms is considered to be an inappropriate behavior and thereby should be inhibited. Accordingly, in this task, instead of measuring the amount of time that animals spent in the opened and enclosed arms, we measured the number of times that mice entered into the opened and enclosed arms. SCH and SAL were given to animals approximately 10 minutes before starting tests. To eliminate locomotor effects of the drugs, the ratio of the number of opened arm entries over the number of enclosed arm entries was calculated. In addition, the possibility that drug effects may have been due to anxiety alterations rather than behavioral inhibition was excluded by the finding that the average time duration in the opened arms per entry into the arms (longer time durations in the opened arms per visit are thought to correlate with less anxiety) was not different between SAL (11.5 ± 1.71 sec) and SCH (10.7 ± 1.57 sec; paired t-test, t_{16}=0.40, p=0.695) conditions.

Behavioral observation and recording in non-human primates

Behavioral observations were conducted with the focal animal sampling method. Two observers with video cameras were approximately 1 meter away from the cage during observations. Monitoring and recording of monkey behavior was conducted for 15 minutes per day per monkey at the frequency of 3 or 4 days per week for 4 weeks (14 days of sampling) for the BASE observations, followed by another 4 weeks of observations after chronic SAL administration and then 4 additional weeks of

observations after chronic SCH administration (Suppl. Fig. 1b). These observations and recordings were started at the pre-determined time each day, such that intra-day behavioral variability was minimized. Before starting the baseline observation, animals were allowed to acclimate to the observers for 3 weeks. After completion of all behavioral observations with drug administration, the drug-treated subject was euthanized with an overdose injection of sodium pentobarbital (25 mg/kg, i.v.) followed by cardiac exsanguination. For later analysis of video recordings, 15 min recordings were segmented into 10 sec and the presence or absence of specific behaviors in each segment was counted. Locomotion was separately quantified by subtracting the amount of time that animals were motionless from the whole 15 min recording period. We measured "individual behavior" (goal-directed action, stereotypy, agonistic display, scanning, locomotion, unusual) of the drug-treated subject, and "social behavior" (affiliation, aggression, social inhibition, escape, mounting) of each animal in the group. Items of behavioral assessments and their detailed criteria are described in Table 1. Inter-rater reliabilities (Cohen's kappa) for the rates of aggression and social affiliation between the experimenters who were blinded and not blinded to the experimental conditions were 0.93 (confidence interval of 0.80-1.00) and 0.82 (confidence interval of 0.62-1.00), respectively, indicating that the criteria are reliable for behavioral assessments (McHugh, 2012).

Social rank determination in non-human primates

A typically employed index that determines social rank is the direction of aggressive attacks, are usually made from higher to lower social rank subjects (Alexander and Bowers, 1969). Thus, social rank was estimated by counting the number of aggressive attacks from one monkey to other cage mates. In non-human primates, instead of the number of wins/losses in the tube test in mice, the number of aggressive attacks from an initiator to a receiver was used for calculations of DS.

Another index for social rank is food incentive priority (Richards, 1974). Thus, we also conducted a food priority test to further determine social rank. In this test, food presentation (a portion of a sweet potato) was given at roughly equal distance from all subjects, and the order of obtaining a food was recorded. After one subject accessed and consumed a food, the next sweet potato portion was presented immediately. This process was repeated until the last subject obtained a piece of a sweet potato. However, to emphasize the priority for accessing a food, the portioned size of the food was consecutively reduced to be approximately two-thirds smaller than the formerly presented food portion (e.g., if the first food portion is ~15 cm^3, it would be ~10 cm^3 for the second, ~7 cm^3 for the third, and so on). Ten trials at the frequency of one trial per day were conducted in each of the control and drug administration conditions. Quantification of social rank was attempted by scoring (food priority score or FPS) for the orders of food acquiring from 6 to 1 points with 6 points for the first access, 5 points for the second access, 4 points for the third access, and so on.

Drug administration in non-human primates

The D1 receptor antagonist SCH23390 was administered in the subject that was at 2nd rank in the social group, based on the observation that the increase of social rank with SCH administration was the largest in 2nd rank subjects in mice. The drug was delivered by subcutaneous implantation of an ALZET® osmotic pump (2ML4model,

~2.5 μl/hr diffusion rate), with which drug delivery was expected to persist for up to 4 weeks (Hill et al., 2013). The concentration of SCH was adjusted to be approximately 0.1 mg/kg/day. This dose of SCH was used because (1) the dose was matched between mice and macaques, (2) systemic drug administration at this dose has been shown to cause cognitive impairments in other macaque studies (Arnsten et al., 1994; Murphy et al., 1996), and (3) this dose of SCH administration did not cause drowsiness nor affect locomotion. As a control treatment, an equivalent volume of 0.9% saline in an osmotic pump was also implanted for 1 month before the drug was administered. For implantation of the pumps, the monkey was anesthetized with ketamine (5.0 mg/kg, i.m.) and medetomidine (0.05 mg/kg, i.m.). Then, after a small incision was made on the skin of the left and right (for each pump with saline and the drug, respectively) upper-back of the subject, the pump was implanted followed by sutures of the incisions. After these surgeries, atipamezol (0.125 mg/kg, i.m.) was given to accelerate the recovery from anesthesia. The monkey was returned to the group immediately after recovery.

Data analysis

Data collection and statistical analyses were conducted by investigators who were not blinded to the experimental conditions. No data points were removed from statistical analysis. Sample sizes were not predetermined by statistical methods. All statistical analyses were conducted using SPSS and Statistica software. A probability value of $p<0.05$ was considered to indicate statistical significance. Drug effects on social hierarchy and affiliations were analyzed with analysis of variance (ANOVA) with repeated measures. In addition, drug effects on the linearity and steepness of the hierarchy were analyzed with linear regression analysis, with the linearity expressed as Pearson product-moment correlation coefficients, and the steepness as slopes, of linear regressions. Concurrence of social affiliations was calculated by absolute difference of normalized affiliative contacts for each observation between specific bonds (denoted as "similarity index"). Lower index values indicated with higher similarity between the contacts, with an index score=0 the similarity identical.

Stress hormone assay in non-human primates

Hair glucocorticoid (GC) accumulation has been shown to reflect chronic stress levels of animals and humans (Davenport et al., 2006; Sauve et al., 2007). To examine whether drug administration caused negative effects, which would be reflected as increased stress levels, in the drug-treated macaque and other cage mates, we collected hair samples from the scapular of each subject using a razor at the end of each experimental condition. The amount of GCs in the hair samples were then analyzed with enzyme-linked immunosorbent assay (ELISA). Hair sample preservation and GC extraction were conducted in accordance with the method described by Davenport et al. (Davenport et al., 2006). Briefly, the collected hair samples were put into 15 ml falcon tubes, and washed 3 times with 5 ml of isopropanol for 3 min per wash. The samples were then dried for 5 days under the fume hood. Once the samples were dried, they were cut into small pieces (of approximately 0.1 to 0.5 mm). Fifty milligrams of the samples were put into 1.5 ml centrifuge tubes with 1 ml of methanol. The tubes were incubated under the fume hood for 24 hours, followed by centrifugation for 30 seconds. Aliquots of methanol supernatants (0.6-ml aliquots) that contained the extracts were put

into fresh tubes and dried under the fume hood for 3 days. The dried extracts were then reconstituted with 0.4 ml of phosphate buffer, and processed using the ELISA cortisol assay kit purchased from Salimetrics (Carlsbad, CA) according to the manufacturer's instruction. After processing, ELISA plates were read using the iMark microplate reader (Bio-rad, Hercules, CA).

Supplementary Results

Stress assay in non-human primates

To examine whether any social relationship alterations caused by SCH administration into the 2nd rank subject resulted in negative outcomes, such as increased stress experience, hair GCs were quantified using ELISA. No consistent GC changes were observed in any subject under the BASE, SAL, or SCH condition (Suppl. Fig. S4a). There was also no correlation between hair GCs and stress-associated factors, such as the frequency of aggression that each subject received and the FPS (Suppl. Fig. S4b).

These results suggest that the social relationship alterations caused by SCH administration into the 2nd rank subject within the group did not result in a significant increase of stress in the drug-treated subject or the other mates.

Supplementary Table S1. Information about the Japanese macaques used in this study.

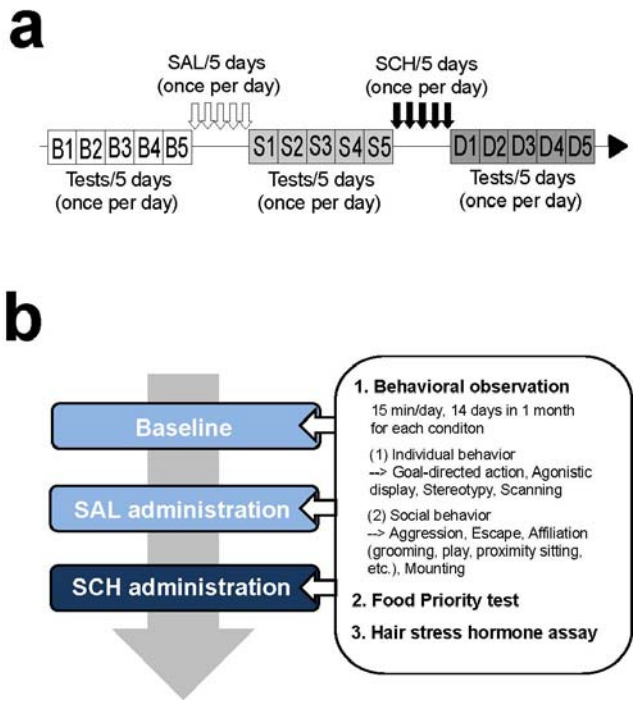
	Sex	Body weights (kg)*	Origins
A	♀	4.8	Takahama (Fukui, Japan)
B	♂	4.5	Wakasakura (Tottori, Japan)
C	♂	5.8	Takahama (Fukui, Japan)
D	♀	3.9	Takahama (Fukui, Japan)
E	♂	4.1	Takahama (Fukui, Japan)
F	♂	5.0	Takahama (Fukui, Japan)

*Body weights at the time of SCH administration to the 2nd rank subject.

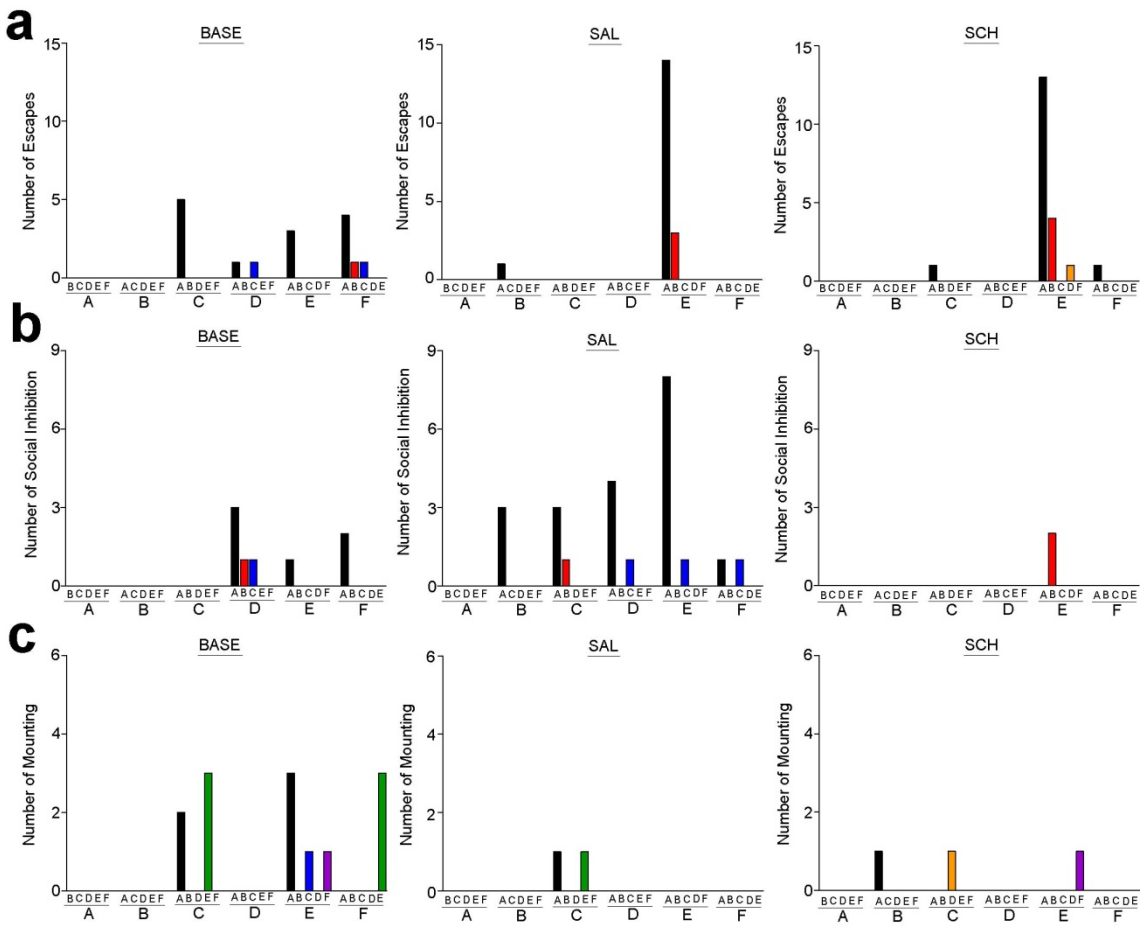
Supplementary Table S2. A table for the example of David's score calculations on the tube rank test in mice.

	A	**B**	**C**	**D**	**l**	**l_2**
A		2 (0.4)	0 (0.0)	0 (0.0)	0.4	0.24
B	3 (0.6)*		0 (0.0)	0 (0.0)	0.6	0.24
C	5 (1.0)	5 (1.0)		2 (0.4)	2.4	2.04
D	5 (1.0)	5 (1.0)	3 (0.6)		2.6	2.44
w	2.6	2.4	0.6	0.4		
w_2	2.44	2.04	0.24	0.24		

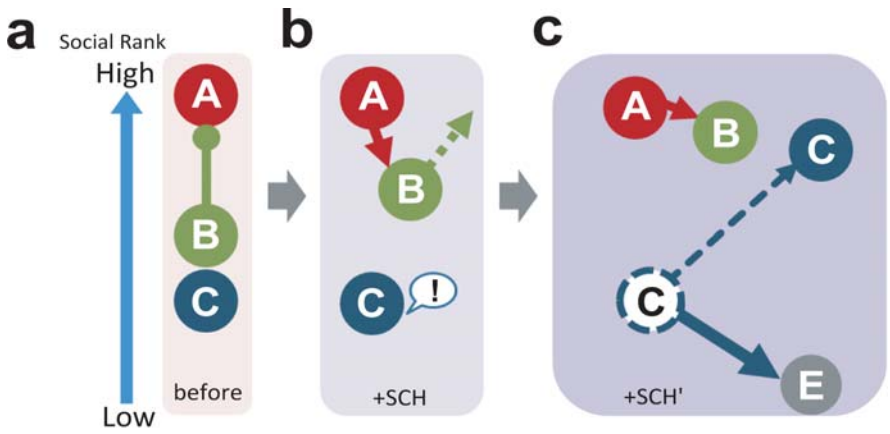
*Parentheses indicate P_{ij}.



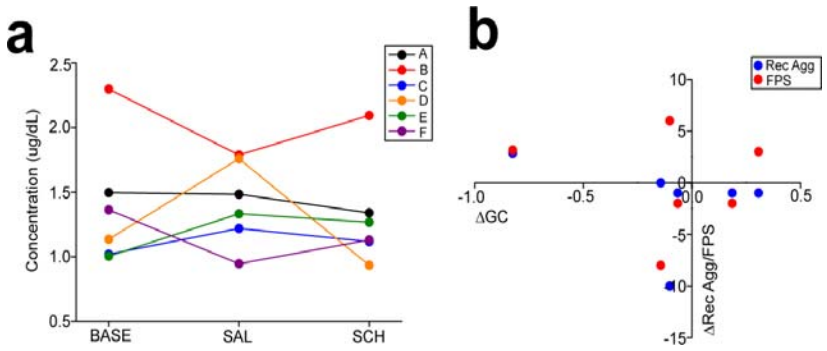
Supplementary Figure S1. Timelines of the experiments in rodents and non-human primates. (a) A diagram illustrating the timeline of the experiments in mice. B1-5, S1-5, and D1-5 indicate 5 days each of the tube rank test in the BASE, SAL, and SCH conditions, respectively. **(b)** A similar diagram illustrating the timeline of the experiments in macaques.



Supplementary Figure S2. Alterations of social behaviors with D1 antagonist administration in the 2nd rank subject in a non-human primate group. (a-c) Graphs showing (a) escape, (b) social inhibition, and (c) mounting of all subjects in the group under the BASE (left), SAL (middle), and SCH (right) conditions. SCH administration did not alter any of these social behaviors in the drug-treated subject and the other group members.



Supplementary Figure S3. Schematic diagrams describing transitions of social relationships among higher-ranked non-human primates in the group as a consequence of D1 antagonist administration in the 2nd rank subject. A striking observation was that emergence of the subject with behavioral phenotypes associated with lower DA D1 signaling in the group resulted in reconstruction of the whole group social relationships. Thus, the 3rd rank subject, which had been unrelated to the 2nd, drug-treated subject in the BASE condition, became competitive against the 1st and 2nd rank subjects. Increased affiliations were also observed not only from the 1st rank subject to the drug-treated subject but also from the 3rd to the 5th rank subjects. Moreover, these affiliative bonds (alliances) between the 1st to 2nd and between the 3rd to 5th rank subjects became concurrent under the SCH condition. Collectively, these alterations may be explained by the following scenario. **(a)** Before SCH administration, the 2nd rank subject (denoted as "B") tended to behave submissively towards the 1st rank subject (denoted as "A"), which kept the group order. **(b)** However, with SCH administration, subordinate-like behavior of the subject "B" was diminished and consequently, the subject "A" was deprived of social dominance control over other subjects in the group. To recover this condition, the subject "A" increased affiliative contacts with the subject "B". **(c)** The 3rd rank subject (denoted as "C") noticed the alteration in the relationship between the subjects "A" and "B", and made an alliance by increasing affiliative contacts with one of the lower-ranked subjects ((5th rank; denoted as "E") to cope with the higher-ranked subjects. A process similar to this model has also been reported in the field research of free-ranging monkeys such as, when social order in a group becomes unstable, a lower rank subject intensifies affiliations with a specific partner in the group to form an alliance to compete with higher-ranked subjects (Gouzoules, 1980).



Supplementary Figure S4. No chronic stress alterations in the 2nd rank macaque with D1 antagonist administration and other cage mates in the group. **(a)** A graph showing quantification of hair GCs in each subject under the BASE, SAL, and SCH conditions. **(b)** A graph showing no correlations in the alterations, i.e., subtractions of the SAL from the SCH conditions, between GCs (ΔGC) and the number of aggressions that each subject received (ΔRec Agg; blue circles) or the food priority score (ΔFPS; red circles).

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