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ARTICLE

Nucleus accumbens dichotomically controls social dominance in male mice

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Social dominance versus social submissiveness is a basic behavioral trait of social animals such as human beings and laboratory mice. The brain regions associated with this behavior have been intensely investigated, and early neuroimaging research on human subjects implies that the nucleus accumbens (NAc) might be involved in encoding social dominance. However, the underlying circuitry and synaptic mechanism are largely unknown. In this study, by introducing lesions to both NAc subregions, the shell and core, a causal relationship is established between social dominance and both NAc subregions. A further electrophysiology investigation on the circuitry of these two subregions revealed that the postsynaptic strength of excitatory synapses onto the medium spiny neurons that express the D1 dopamine receptors in the shell is negatively correlated, and the postsynaptic strength of excitatory synapses onto the medium spiny neurons that express the D2 dopamine receptors in the core is positively correlated, with social dominance. Correspondingly, a DREADD investigation revealed that the activities of these respective medium spiny neurons suppress and promote social dominance. These findings identify a neural substrate for social dominance, implying the potential for a therapeutic strategy for treating related psychiatric disorders.

INTRODUCTION

Social organization might be one important factor that has led to human beings' successful domination of the earth. Within human social organization during the pre-civilization era, individuals organized into a hierarchical structure [1], competing for food, territories and sexual partners, a practice that has played a pivotal role in directing human evolution [2–4]. In the modern egalitarian society, the hierarchical structure manifests in more subtle forms, such as socioeconomic status in society or peer competition and bullying in work places and schools. Indeed, hierarchical social status in the modern society has been regarded as the most important factor determining one's physical and mental health [5–11]. Therefore, understanding the biological mechanism underlying hierarchical social status, more specifically, social dominance versus social submissiveness, is useful both socioeconomically and biomedically.

Social dominance versus social submissiveness is established among conspecifics by their direct physical competition, dominance physical-cue learning, or transitive inference of the hierarchical structure [4]. The perception of dominance is a process of learning "prediction errors", upon which a dominant position eventually earned is rewarding, and heavily affects emotion [12, 13]. The ventral striatum nucleus accumbens (NAc) sits in the limbic-motor interface, receiving excitatory glutamatergic projections from the prefrontal cortex, thalamus, hippocampus and amygdala, and modulatory dopaminergic projections from the ventral tegmental area [14–16], and acts as a node converting motivational and affective information into motor action, a dynamic process finely adjusted by prediction errors [17–19]. As

such, it is meaningful to ask whether the NAc plays any role in social dominance.

Early neuroimaging research on human subjects demonstrated that neural activity in the NAc increased when a test subject viewed another higher-ranked subject [20–22], engaged in competition rather than collaboration [22], or won competitions in a social context [23, 24], implying that the NAc might be involved in encoding social dominance.

The NAc can be roughly divided into the shell and core subregions, which have distinct afferent and efferent brain regions and thereby encode relatively distinct behaviors [17]. Nevertheless, both the shell and core share similar local circuitry. The projection neurons in the NAc are GABAergic medium spiny neurons (MSNs), which constitute 95–98% of the striatal neuronal population and fall into two classes based on expression profile of receptors and signal molecules: one expressing the dopamine D1 receptor (D1R), the M4 acetylcholine receptor, substance P and dynorphin, and the other expressing the dopamine D2 receptor (D2R), the adenosine A2a receptor (A2aR) and enkephalin [25–28]. Both the D1R- and D2R-expressing MSNs (denoted as D1R-MSNs and D2R-MSNs, respectively) are modulated by dopaminergic inputs from the ventral tegmental area (VTA), but, as the D1R and D2R are respectively coupled to the excitatory Gs/olf and inhibitory Gi/o proteins, dopamine exerts opposing effects on their activities [28–31]. This dichotomy also manifests behaviorally. Indeed, a large body of research has demonstrated that the two groups of MSNs play opposing roles in striatum-related behaviors [32–36].
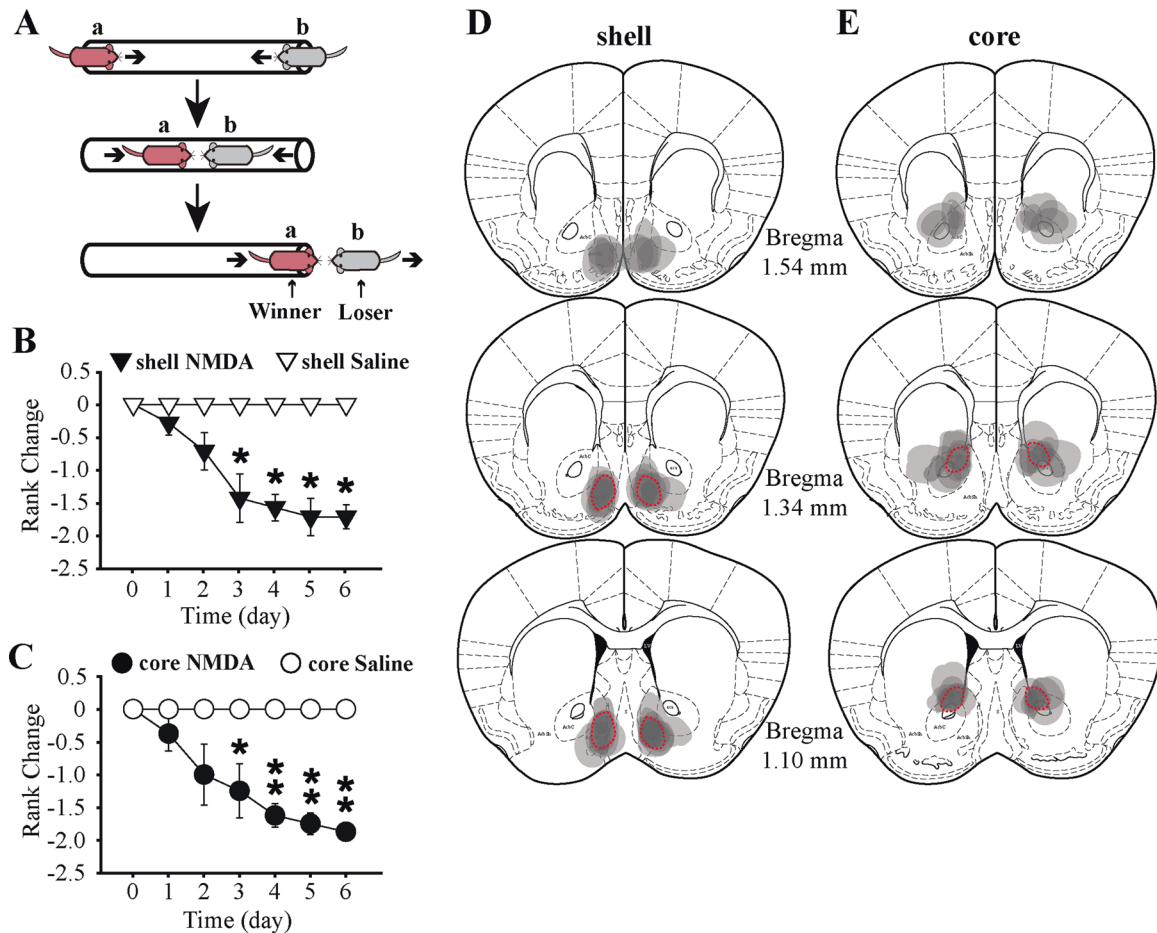
Fig. 1 **Lesion introduced to the NAc shell or core reduces social dominance. A** The social rank was determined by the tube test, which is schematically illustrated. **B**, **C** The mice injected with NMDA into the NAc shell (**B**) or core (**C**) gradually reduced their ranks relative to the mice injected with saline into the respective NAc subregion over the six days after surgery with statistical significance emerging 3 days after surgery (*$p < 0.05$, **$p < 0.01$, $n = 6$–8). **D**, **E** Only mice with lesion at the correct location in the NAc shell (**D**) or core (**E**), represented by gray blots displayed on the coronal maps, were included for the final data analysis. The lesioned areas common to all tested mice in each group are encircled in red.

Social dominance also exists in other social animals, such as laboratory mice living in an enclosure, manifesting itself as fighting, and competing for food, territories and sexual partners, which might be similar to human social organization during the pre-civilization era. Laboratory mice in a group actually form a linear hierarchical rank [37], which renders them an ideal animal model for the investigation of social dominance. In this study, laboratory mice were used to establish the role that the local neuronal circuitry, specifically the D1R-MSNs and D2R-MSNs in the shell and core subregions of the NAc, plays in encoding social dominance. It was revealed that the postsynaptic strengths of excitatory synapses onto the shell D1R-MSNs and the core D2R-MSNs are respectively negatively and positively correlated with social dominance; and correspondingly, their activities respectively suppress and promote social dominance.

MATERIALS & METHODS
Animals
Strain. Male, adult (10–16 weeks old), C57BL/6, Drd1-Cre (MMRRC, Strain name: B6.FVB(Cg)-Tg(Drd1-Cre)EY262Gsat/Mmucd; Stock number: 030989-UCD), Adora2a-Cre (MMRRC, Strain name: B6.FVB(Cg)-Tg(Adora2a-Cre)KG139Gsat/Mmucd, Stock number: 036158-UCD) and Drd2-EGFP (MMRRC, Strain name: Tg(Drd2-EGFP)S118Gsat/Mmnc, Stock number: 000230-UNC) [38] mice

were used in this study. All transgenes were maintained hemizygously. The Adora2a-Cre, rather than the Drd2-Cre, strain of mice was employed for selectively manipulating the D2R-MSNs, because in the striatum, the *adora2a* gene is active only in the D2R-MSNs, whereas the *drd2* gene is active in non-MSNs as well as the D2R-MSNs [26, 27].

Maintenance conditions. Mice were maintained in a 12 h light/12 h dark cycle in a temperature (21–25 °C)- and humidity (50–65%)-controlled environment, with food and water ad libitum. All procedures were conducted according to ethical guidelines approved by the Medical Animal Care & Welfare Committee of Shantou University Medical College.

Complete Materials & Methods are contained in the Supplementary Information.

RESULTS
In this research, the tube test (Fig. 1A), which is a well established and widely accepted method [37, 39, 40], was employed to measure social rank.

### Lesion introduced to the NAc shell or core reduces social dominance
To determine whether there is a causal relationship between social rank and either subregion of the NAc, NMDA lesion was

color code: rank 1, rank 2, rank 3, rank 4
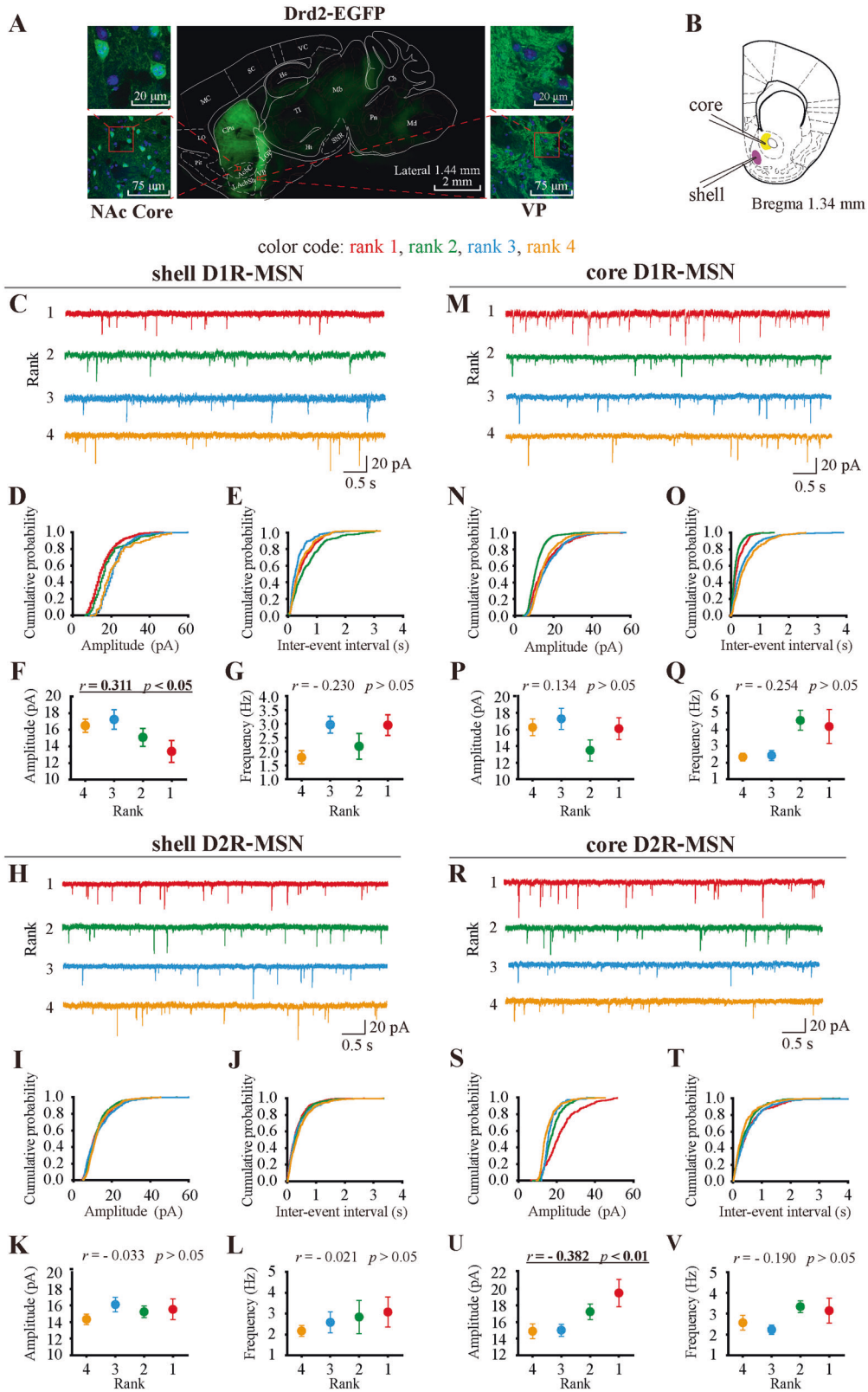
introduced to either the shell or core of the NAc. In a group of four mice ranked from 1 (the highest social rank) to 4 (the lowest social rank), the two higher-ranked mice (ranks 1 and 2) received NMDA lesions, while the two lower-ranked mice (ranks 3 and 4) received saline as a control. As shown in Fig. 1, regardless of whether the

lesion was introduced to the shell or core (Fig. 1D, E), the lesioned mice gradually reduced their ranks relative to the control mice after NMDA injection, although the change in rankings started as soon as three days after injection (one-sample signed rank test, shell: $p < 0.05$, $n = 7$, 6; core: $p < 0.05$ or $p < 0.01$, $n = 8$, 6) (Fig. 1B,

Fig. 2 Postsynaptic strengths of excitatory synapses onto the shell D1R-MSNs and the core D2R-MSNs are respectively negatively and positively correlated with social rank. A The strain of the Drd2-EGFP mice was confirmed by imaging sagittal sections, in which fluorescence concentrates at the caudate putamen (CPu), lateral NAc shell (LAcbSh), NAc core (AcbC), lateral globus pallidus (LGP) and ventral pallidum (VP), but not at the substantia nigra pars reticulata (SNR) (**A**, the large panel in the middle). Further imaging at the cellular level revealed that fluorescence is expressed mostly within cell bodies in the AcbC (**A**, the small panels on the left), but expressed densely only in the fibrous tissue at the pericellular space in the VP (**A**, the small panels on the right). These features at both rough and cellular levels imply that GFP is expressed in the indirect-pathway D2R-MSNs of the NAc, confirming the strain of Drd2-EGFP mice. (The major surrounding brain regions: piriform cortex (Pir), lateral orbital cortex (LO), motor cortex (MC), somatosensory cortex (SC), visual cortex (VC), hippocampus (Hc), cerebellum (Cb), midbrain (Mb), thalamus (Tl), hypothalamus (Ht), pons (Pn) and medulla (Md)). **B** After the tube tests were completed, sEPSCs were recorded on the GFP-negative neurons (D1R-MSNs) and GFP-positive neurons (D2R-MSNs) in the NAc shell and core. **C–G** In the shell D1R-MSNs, the sEPSC amplitude is negatively correlated with social rank (Spearman correlation, $n = 13$–16 each rank). On the other hand, no correlation was found between the sEPSC frequency and social rank (Spearman correlation, $n = 13$–16 each rank). **H–L** In the shell D2R-MSNs, no correlation was found between social rank and the sEPSC amplitude or frequency (Spearman correlation, $n = 13$–17 each rank). **M–Q** In the core D1R-MSNs, no correlation was found between social rank and the sEPSC amplitude or frequency (Spearman correlation, $n = 14$–17 each rank). **R–V** In the core D2R-MSNs, the sEPSC amplitude is positively correlated with social rank (Spearman correlation, $n = 12$–15 each rank). On the other hand, no correlation was found between the sEPSC frequency and social rank (Spearman correlation, $n = 12$–15 each rank).
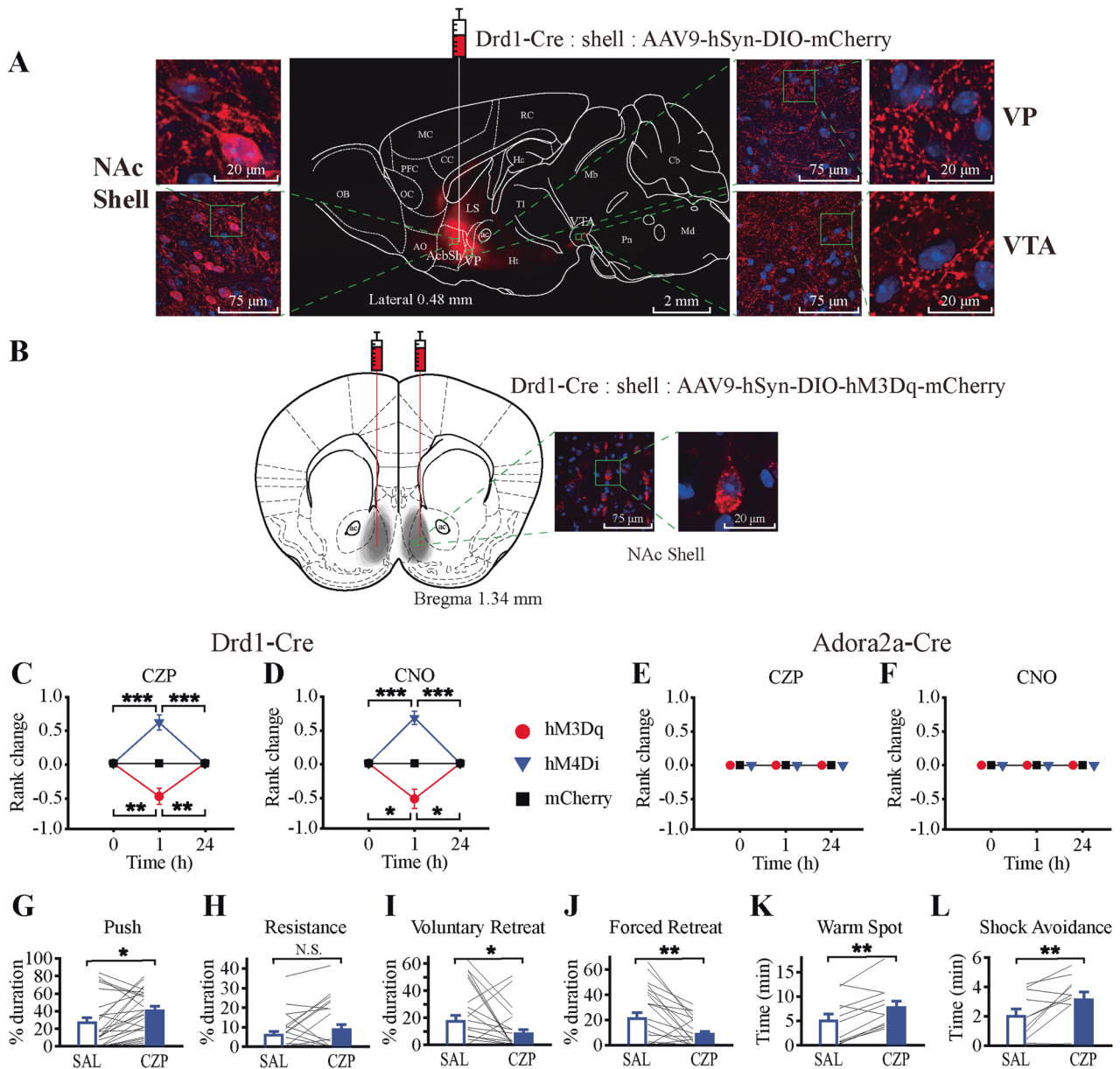
Fig. 3 Chemogenetic activation or suppression of the shell D1R-MSNs respectively reduces or promotes social dominance. A The identity of the Drd1-Cre mice was confirmed by injecting the AAV9-hSyn-DIO-mCherry virus into the NAc shell and imaging sagittal sections, in which fluorescence concentrates at the injection site the NAc shell (AcbSh), and the expected projection sites, the ventral pallidum (VP) and the ventral tegmental area (VTA) (**A**, the large panel in the middle). Further imaging at the cellular level revealed that fluorescence is expressed mostly within cell bodies in the NAc shell (**A**, the small panels on the left), but expressed at the synaptic puncta in the pericellular space in the VP and VTA (**A**, the small panels on the right). The features at both rough and cellular levels imply that mCherry is expressed in the direct-pathway D1R-MSNs of the NAc, confirming the strain of the Drd1-Cre mice. (The major surrounding brain regions: olfactory bulb (OB), orbital cortex (OC), motor cortex (MC), retrosplenial cortex (RC), cingulate cortex (CC), prefrontal cortex (PFC), hippocampus (Hc), cerebellum (Cb), midbrain (Mb), lateral sepal nucleus (LS), thalamus (Tl), pons (Pn), medulla (Md), anterior olfactory nucleus (AO), anterior commissure (ac) and hypothalamus (Ht)). **B** Only mice with correct injection sites were included in the final data analysis. At the cellular level, the mCherry fluorescence was found within the cell bodies of the NAc shell on coronal sections of the Drd1-Cre mice (injected with the AAV9-hSyn-DIO-hM3Dq-mCherry virus into the NAc shell in the example demonstrated in the small panels on the right). **C–F** The Drd1-Cre and Adora2a-Cre mice injected with viruses expressing the hM3Dq, hM4Di, or mCherry protein in the NAc shell were administered clozapine (CZP) or clozapine N-oxide (CNO), and tube test ranks relative to the respective mice administered saline were measured 1 h and 24 h later. The social ranks were significantly reduced, increased or remained constant 1 h after CZP administration respectively in the hM3Dq-, hM4Di- or mCherry-expressing Drd1-Cre mice, but restored to the basal level 24 h later (**C**, **$p < 0.01$, ***$p < 0.001$, $n = 18, 29, 19$). A similar effect was also found after CNO administration (**D**, *$p < 0.05$, ***$p < 0.001$, $n = 13, 29, 19$). On the other hand, the social ranks of hM3Dq-, hM4Di- or mCherry-expressing Adora2a-Cre mice were affected by neither CZP (**E**, $p > 0.05$ in all cases, $n = 21, 20, 20$) nor CNO administration (**F**, $p > 0.05$ in all cases, $n = 18, 20, 20$). **G–J** Further analysis of the actions performed during the tube tests by the Drd1-Cre mice expressing the hM4Di receptor in the NAc shell demonstrated that CZP administration, relative to saline (SAL) administration, significantly increased the percentage of duration mice spent on the push action (**G**), decreased the percentage of duration mice spent on both the voluntary retreat action (**I**) and forced retreat action (**J**), but exerted no effect on the percentage of duration mice spent on the resistance action (**H**) (*$p < 0.05$, **$p < 0.01$, N.S.: no significance, $p > 0.05$, $n = 25$ each). **K–L** The effect of chemogenetic manipulation on further competition tests for evaluating social rank, the warm-spot tests and shock-avoidance tests, was also determined in the Drd1-Cre mice expressing the hM4Di receptor in the NAc shell. CZP administration, relative to SAL administration, significantly increased the duration in which mice occupied the warm spot in the warm spot tests (**$p < 0.01$, $n = 11$) (**K**), or the safe platform in the shock-avoidance tests (**$p < 0.01$, $n = 11$) (**L**).

C). These results imply that both shell and core possibly causally regulate social rank.

Postsynaptic strengths of excitatory synapses onto the shell D1R-MSNs and the core D2R-MSNs are respectively negatively and positively correlated with social rank

Next, to determine whether any synaptic plasticity in the NAc encodes social rank, a tube test was performed on each group of mice to measure social ranks, and spontaneous EPSCs (sEPSCs) of the D1R-MSNs and D2R-MSNs in both the shell and core were subsequently recorded (Fig. 2B). The D1R-MSNs and D2R-MSNs were distinguished by using a transgenic mouse strain that expresses GFP in the D2R-MSNs (Drd2-EGFP mice) (Fig. 2A). As the large majority of the GFP-negative cells are D1R-MSNs, the GFP-negative and GFP-positive neurons were recorded to sample the D1R-MSNs and D2R-MSNs, respectively. Detailed criteria for sampling the D1R-MSNs and D2R-MSNs are described in the *Supplementary Materials & Methods* section.

Data demonstrate that the amplitudes, but not the frequencies, of the sEPSCs were negatively and positively correlated with social rank in the shell D1R-MSNs and in the core D2R-MSNs, respectively (Fig. 2C–G, R–V). On the other hand, no significant correlation was found between social rank and either the amplitudes or frequencies of the sEPSCs, in the shell D2R-MSNs (Fig. 2H–L) or core D1R-MSNs (Fig. 2M–Q).

As such, it is suggested that the postsynaptic strength of excitatory synapses onto the NAc MSNs might encode social rank.

Chemogenetic activation or suppression of the shell D1R-MSNs respectively reduces or promotes social dominance

To further confirm whether the synaptic strength of excitatory synapses onto the NAc MSNs causally regulates social rank, the DREADD (Designer Receptor Exclusively Activated by Designer Drugs) method [41–43] was used to manipulate the activity of MSNs, the effect of which on social rank was subsequently tested. To achieve this, the excitatory hM3Dq receptor was expressed selectively in the shell D1R-MSNs by injecting the AAV9-hSyn-DIO-hM3Dq-mCherry virus into the shell of Drd1-Cre mice (Fig. 3A, B). The hM3Dq agonist, clozapine (CZP) (0.01 mg/kg) [44], was then administered to activate the D1R-MSNs, one mouse in a group each time. It was demonstrated that

CZP temporarily reduced social ranks (one-sample signed rank test, $p < 0.01$, $n = 18$), which returned to their original positions after the drug was cleared 24 h after administration (Fig. 3C). Conversely, suppression of the shell D1R-MSNs by using a similar manipulation with the inhibitory hM4Di receptor increased social ranks (one-sample signed rank test, $p < 0.001$, $n = 29$), which also returned to their original positions after the drug was cleared 24 h after administration (Fig. 3C). As a control, manipulation with the mCherry protein did not affect social ranks (one-sample signed rank test, $p > 0.05$, $n = 19$) (Fig. 3C).

During tube test competitions, mice win competitions by dominant behaviors such as pushing (action: push) or obstructing (action: resistance) their rivals, or a combination of both. The push and resistance actions respectively represent the active and passive forms of dominant behaviors. Correspondingly, mice lose competitions by submissive behaviors such as voluntarily withdrawing (action: voluntary retreat) from, or being pushed out (action: forced retreat) of, the tube, or a combination of both. The voluntary retreat and forced retreat actions respectively represent the active and passive forms of submissive behaviors.

Analysis of the tube tests of the CZP-treated shell-D1R-MSN-hM4Di-expressing mice revealed that CZP treatment significantly increased the relative duration spent on the push action (paired t-test, $t_{24} = 2.77$, $p < 0.05$, $n = 25$) (Fig. 3G), and correspondingly decreased the relative duration spent on the voluntary and forced retreat actions (paired t-test, $t_{24} = 2.15$, $p < 0.05$; $t_{24} = 3.72$, $p < 0.01$, respectively; $n = 25$) (Fig. 3I, J). However, CZP exerted no significant effect on the relative duration spent on the resistance action (paired t-test, $t_{24} = 1.58$, $p > 0.05$, $n = 25$) (Fig. 3H). These data confirm that suppression of the shell D1R-MSNs promotes social rank by boosting the dominant behaviors (the active form, more specifically) and inhibiting submissive behaviors (both the active and passive forms, more specifically) in mice.

To confirm this conclusion, CZP-treated shell-D1R-MSN-hM4Di-expressing mice were subjected to other competition tests to determine social rank: the warm-spot and shock-avoidance tests. It was demonstrated that CZP treatment increased the relative duration mice spent at the warm-spot
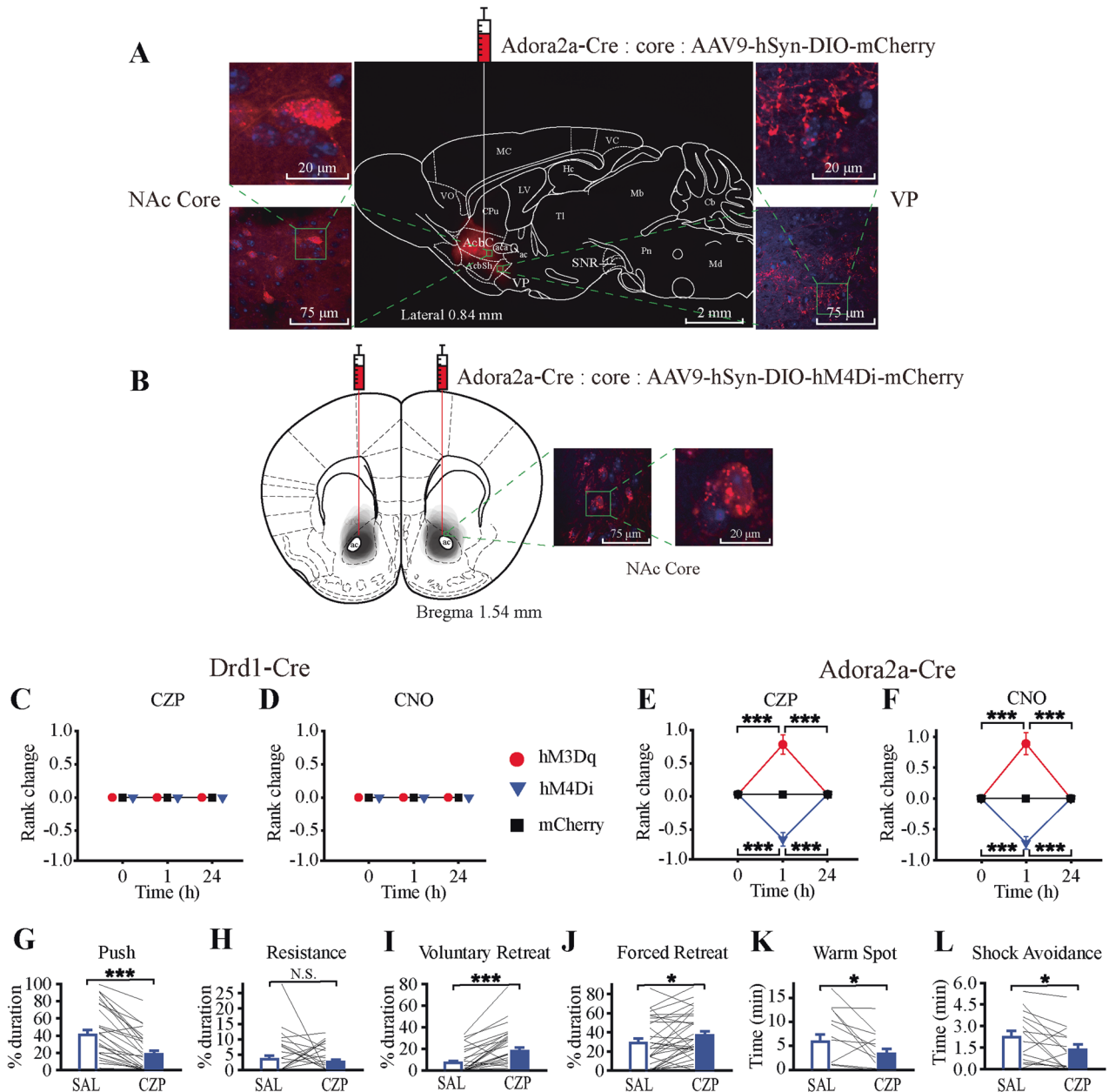
(paired t-test, $t_{10} = 3.83$, $p < 0.01$, $n = 11$) (Fig. 3K) or safe-platform (paired t-test, $t_{10} = 2.98$, $p < 0.01$, $n = 11$) (Fig. 3L) in the respective tests, further confirming that suppression of the shell D1R-MSNs promotes dominance.

It should be noted that any CZP-induced changes in the behaviors revealed in the tube test, warm-spot test or shock-avoidance test, could be attributable to changes in social dominance, the subject of this study, but could also be artifacts arising from CZP-induced changes in locomotor activity or muscular strength. For example, apparent CZP-induced wins in the tube tests could be attributable to higher locomotor activity or muscular strength, rather than higher social rank. To eliminate the possibility of these artifacts, open field tests and front paw grip strength measurements were performed on the CZP-treated shell-D1R-MSN-hM4Di (or hM3Dq or mCherry)-expressing mice. CZP did not exert any significant effect on the open field movement speed (Fig. S1A) or grip strength (Fig. S1C) in any of the groups tested. These data further confirm

that manipulating the activity of the shell D1R-MSNs affects social dominance.

Besides the shell D1R-MSNs, the role of the other group of shell MSNs, the D2R-MSNs, in social dominance was also tested. To do so, manipulations similar to those in the case of shell D1R-MSNs were performed, except that an Adora2a-Cre mouse strain was employed in place of the Drd1-Cre mouse strain, in order to enable selective manipulation of the D2R-MSNs. In sharp contrast to the results for the shell D1R-MSNs, CZP treatment exerted no significant effects on any group of mice expressing either the hM3Dq, hM4Di or mCherry protein in the shell D2R-MSNs, in any behavioral tests including the tube test (one-sample signed rank test, $p > 0.05$ in all cases, $n = 21$, 20, 20) (Fig. 3E), open field locomotor test (Fig. S1B) or the front paw grip strength measurement (Fig. S1D). These data imply that the shell D2R-MSNs do not play a major role in social dominance.

As a control, CZP was also administered to wild-type mice. This treatment did not change the tube test ranking, open field

Fig. 4 Chemogenetic activation or suppression of the core D2R-MSNs respectively promotes or reduces social dominance. A The strain of the Adora2a-Cre mice was confirmed by injecting the AAV9-hSyn-DIO-mCherry virus into the NAc core and imaging sagittal sections, in which fluorescence concentrates at the injection site the NAc core (AcbC), and the expected projection site the ventral pallidum (VP), but not the substantia nigra pars reticulata (SNR) (**A**, the large panel in the middle). Further imaging at the cellular level revealed that fluorescence is expressed mostly within cell bodies in the NAc core (**A**, the small panels on the left), but expressed at the synaptic puncta in the pericellular space in the VP (**A**, the small panels on the right). The features at both rough and cellular levels imply that the mCherry protein is expressed in the indirect-pathway D2R-MSNs of the NAc, confirming the strain of the Adora2a-Cre mice. (The major surrounding brain regions: the ventral orbital cortex (VO), motor cortex (MC), visual cortex (VC), caudate putamen (CPu), lateral ventricle (LV), hippocampus (Hc), cerebellum (Cb), midbrain (Mb), thalamus (Tl), pons (Pn), medulla (Md), accumbens shell (AcbSh), anterior commissure (ac), anterior commissure and anterior part (aca)). **B** Only mice with correct injection sites were included in the final data analysis. At the cellular level, the mCherry fluorescence was found within the cell bodies of the NAc core on coronal sections of the Adora2a-Cre mice (injected with the AAV9-hSyn-DIO-hM4Di-mCherry virus into the NAc core in the small panels on the right). **C–F** The Drd1-Cre and Adora2a-Cre mice injected with viruses expressing the hM3Dq, hM4Di, or mCherry protein in the NAc core were administered clozapine (CZP) or clozapine N-oxide (CNO), and tube test ranks relative to the respective mice administered saline were measured 1 h and 24 h later. The social ranks were significantly increased, reduced or remained constant 1 h after CZP administration in the hM3Dq-, hM4Di- or mCherry-expressing Adora2a-Cre mice, respectively, but returned to the basal level 24 h later (***$p < 0.001$, $n = 26, 36, 20$) (**E**). A similar effect was also found after CNO administration (***$p < 0.001$, $n = 18, 36, 20$) (**F**). On the other hand, the social ranks of hM3Dq-, hM4Di- or mCherry-expressing Drd1-Cre mice were affected by neither CZP ($p > 0.05$ in all cases, $n = 24, 19, 19$) (**C**) nor CNO administration ($p > 0.05$ in all cases, $n = 19$ each) (**D**). **G–J** Further analysis of the actions performed during the tube tests by the Adora2a-Cre mice expressing the hM4Di receptor in the NAc core, demonstrated that CZP administration, relative to saline (SAL) administration, significantly decreased the percentage of duration mice spent on the push action (**G**), increased the percentage of duration mice spent on both the voluntary retreat action (**I**) and forced retreat action (**J**), but exerted no effect on the percentage of duration mice spent on the resistance action (**H**). (*$p < 0.05$, ***$p < 0.001$, N.S.: no significance, $p > 0.05$, $n = 31$ each). **K, L** The effect of chemogenetic manipulation on further competition tests for evaluating social rank, the warm-spot tests and shock-avoidance tests, was also determined in the Adora2a-Cre mice expressing the hM4Di receptor in the NAc core. CZP administration, relative to SAL administration, significantly decreased the time during which mice occupied the warm spot in the warm-spot tests (*$p < 0.05$, $n = 16$) (**K**), or the safe platform in the shock-avoidance tests (*$p < 0.05$, $n = 16$) (**L**).

locomotor activity or front paw grip strength (Fig. S1E–G), confirming the behavioral effects described above are attributable to the specific action of CZP on the hM3Dq or hM4Di receptors.

Another compound, clozapine N-oxide (CNO), which was once presumed an inert drug specifically acting on the exogenously-introduced hM3Dq and hM4Di receptors, but has recently been proven to exert this pharmacological effect via its metabolite CZP [44], had been previously widely used in place of CZP [41–43]. To make this research comparable to much previous research, CNO was also administered in place of CZP, and it was demonstrated that CNO produced results similar to those of CZP in the tube tests for both Drd1-Cre and Adora2a-Cre mice expressing either the hM3Dq, hM4Di, or mCherry proteins in either the shell D1R-MSNs (one-sample signed rank test, $p < 0.05$, $n = 13$; $p < 0.001$, $n = 29$; or $p > 0.05$, $n = 19$, respectively) (Fig. 3D) or D2R-MSNs (one-sample signed rank test, $p > 0.05$ in all cases, $n = 18, 20, 20$, respectively) (Fig. 3F).

Chemogenetic activation or suppression of the core D2R-MSNs respectively promotes or reduces social dominance
An experiment was also performed in parallel to address the question of whether the D1R-MSNs or D2R-MSNs in the core area play any role in social dominance. Manipulations, similar to those used in the investigation of the shell MSNs, were conducted, except that the viruses were injected into the core area (Fig. 4A, B). The tube test results demonstrated that CZP- and CNO-induced activation or suppression of the core D2R-MSNs promoted or reduced social rank, respectively (one-sample signed rank test, $p < 0.001$, $n = 26, 36, 18, 36$ for CZP-hM3Dq, CZP-hM4Di, CNO-hM3Dq, CNO-hM4Di, respectively; $p > 0.05$, $n = 20, 20$ for CZP-mCherry, CNO-mCherry, respectively) (Fig. 4E, F); whereas manipulation of the activity of the core D1R-MSNs exerted no significant effect (one-sample signed rank test, $p > 0.05$ in all cases; $n = 24, 19, 19, 19, 19, 19$ for CZP-hM3Dq, CZP-hM4Di, CZP-mCherry, CNO-hM3Dq, CNO-hM4Di, CNO-mCherry, respectively) (Fig. 4C, D). Further analysis of the core-D2R-MSN-hM4Di-expressing mice's actions in the tube test indicated that CZP-treatment-induced rank demotion was attributable to a decrease in the relative duration spent on the push action (paired t-test, $t_{30} = 6.31$, $p < 0.001$, $n = 31$) (Fig. 4G), and an increase in the relative duration spent on both the

voluntary and forced retreat actions (paired t-test, $t_{30} = 4.61$, $p < 0.001$; $t_{30} = 2.22$, $p < 0.05$, respectively, $n = 31$) (Fig. 4I, J), but not attributable to the resistance action, which was not significantly changed by the CZP treatment (paired t-test, $t_{30} = 0.73$, $p > 0.05$, $n = 31$) (Fig. 4H). Moreover, the CZP-treated core-D2R-MSN-hM4Di-expressing mice also demonstrated a reduction in the relative duration occupying the warm spot or safe platform respectively in the warm-spot (paired t-test, $t_{15} = 2.31$, $p < 0.05$, $n = 16$) (Fig. 4K) or shock-avoidance (paired t-test, $t_{15} = 2.57$, $p < 0.05$, $n = 16$) (Fig. 4L) test. In addition, CZP treatment exerted no significant effects on open field locomotor activity (Fig. S2A, B) or front paw grip strength (Fig. S2C, D), for both groups of the core-D1R-MSN-hM3Dq (or hM4Di or mCherry)-expressing and core-D2R-MSN-hM3Dq (or hM4Di or mCherry)-expressing mice. Taken together, these data suggest that chemogenetic activation or suppression of the core D2R-MSNs promotes or reduces social dominance, whereas similar manipulation of the core D1R-MSNs exerts no significant effect. These results are in sharp contrast to the results obtained for MSNs in the shell in terms of the types of MSN and the direction of effect (promotion or demotion of social ranks), where chemogenetic activation or suppression of the shell D1R-MSNs respectively reduces or promotes social dominance, whereas similar manipulation of the shell D2R-MSNs exerts no significant effect, as described in the previous section.

CZP increases or decreases the excitability of NAc MSNs respectively expressing the hM3Dq or hM4Di receptor
To verify the pharmacological effect of CZP at the ex vivo cellular level, brain slice recordings were performed on mice with the hM3Dq, hM4Di or mCherry protein selectively expressed in the shell D1R-MSNs, shell D2R-MSNs, core D1R-MSNs or core D2R-MSNs (Fig. 5A).

Current-clamp recordings revealed that CZP activation of the excitatory Gq-coupled hM3Dq receptors expressed in all four groups of MSNs increased intrinsic excitability, which manifested as significantly higher numbers of spikes when neurons were excited by injected currents at given amplitudes (two-way repeated-measures ANOVA, $F_{1,6} = 41.8$ for shell D1R-MSNs, $F_{1,8} = 64.5$ for core D1R-MSNs, $F_{1,5} = 95.2$ for shell D2R-MSNs, $F_{1,6} = 73.4$ for core D2R-MSNs; $p < 0.001$ for all cell types; $n = 6–9$) (Fig. 5C, D,
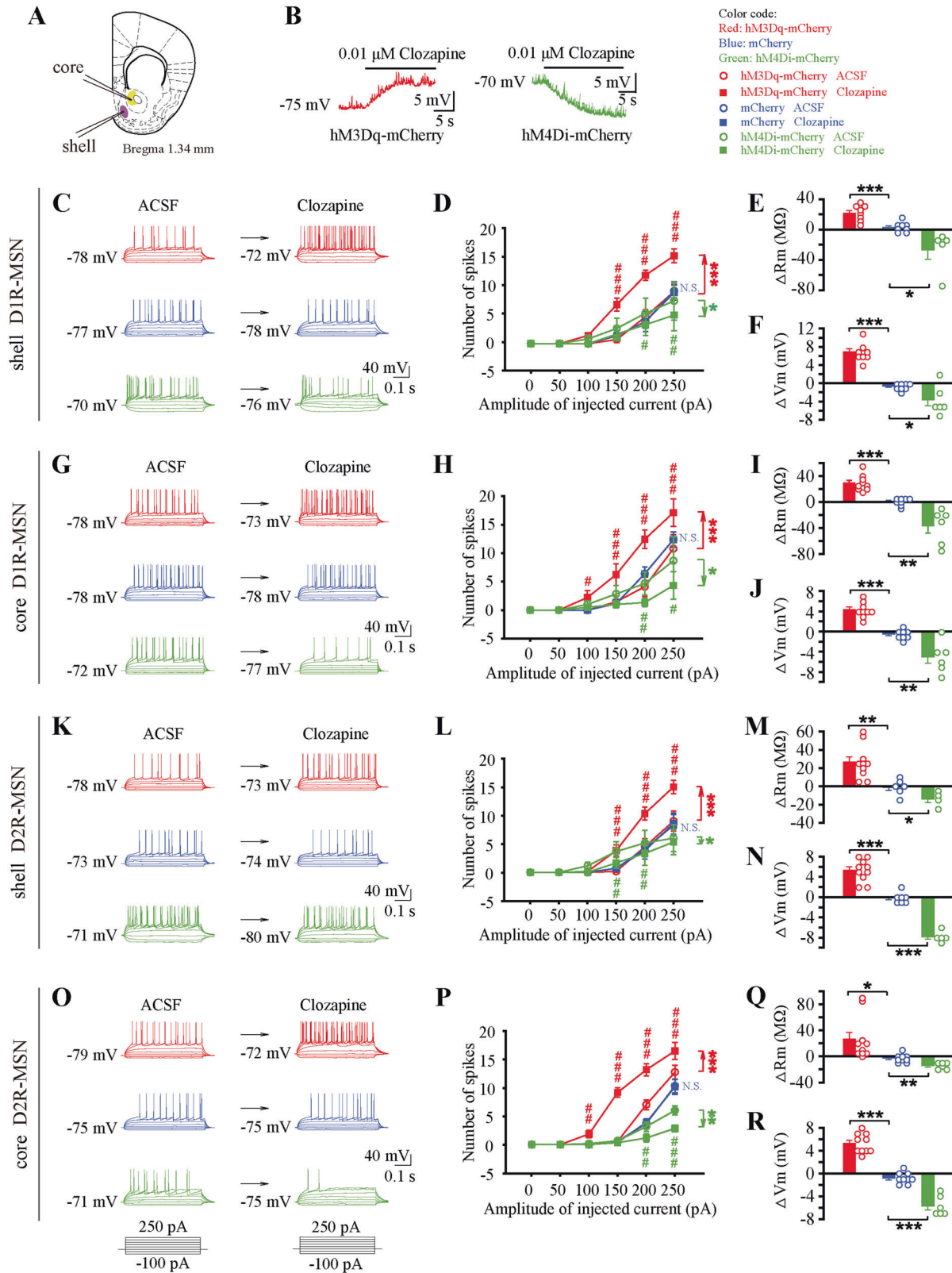
G, H, K, L, O, P). Activation of the hM3Dq receptors also significantly increased the input resistance (one-way ANOVA, $F_{1,14} = 18.1$ and $p < 0.001$ for shell D1R-MSNs, $F_{1,15} = 36.5$ and $p < 0.001$ for core D1R-MSNs, $F_{1,14} = 11.5$ and $p < 0.01$ for shell D2R-MSNs, $F_{1,17} = 6.76$ and $p < 0.05$ for core D2R-MSNs; $n = 8–10$) (Fig. 5E, I, M, Q) and

depolarized the membrane (one-way ANOVA, $F_{1,14} = 96.2$ for shell D1R-MSNs, $F_{1,15} = 61.8$ for core D1R-MSNs, $F_{1,15} = 37.4$ for shell D2R-MSNs, $F_{1,17} = 88.4$ for core D2R-MSNs; $p < 0.001$ for all cell types; $n = 8–10$) (Fig. 5B, F, J, N, R). In contrast, CZP activation of the inhibitory Gi-coupled hM4Di receptors induced

Fig. 5 CZP increases or decreases the excitability of MSNs respectively expressing the hM3Dq or hM4Di receptors, in both the shell and core. The current-clamp recordings were performed on NAc slices prepared from the Drd1-Cre and Adora2a-Cre mice that were injected with viruses expressing the hM3Dq, hM4Di or mCherry proteins in the NAc shell or core. **A** The recording sites in the NAc shell (violet blot) or core (yellow blot) at Bregma 1.34–1.54 mm are displayed on the coronal map. **B–R** The application of CZP exerted similar effects on shell D1R-MSNs, core D1R-MSNs, shell D2R-MSNs and core D2R-MSNs, which are summarized as follows: (1) The excitability, which is determined by the number of action potentials induced by the current of a given amplitude, was significantly increased in the neurons expressing the hM3Dq receptor (***$p < 0.001$, $n = 6$–9), decreased in the neurons expressing the hM4Di receptor (*$p < 0.05$, **$p < 0.01$, $n = 6$ each), and did not change in the neurons expressing the mCherry protein (N.S.: no significance, $n = 7$–8). The step-current induced action potential traces (**C, G, K, O**) and relationship between the amplitude of injected currents and the number of action potential spikes (**D, H, L, P**) are displayed. (post hoc test: #$p < 0.05$, ##$p < 0.01$, ###$p < 0.001$). (2) The input resistance was significantly increased in the neurons expressing the hM3Dq receptor (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, $n = 8$–10), and decreased in the neurons expressing the hM4Di receptor (*$p < 0.05$, **$p < 0.01$, $n = 4$–6), compared to that in the neurons expressing the mCherry protein ($n = 6$–9) (**E, I, M, Q**). (3) The membrane potential was significantly depolarized in the neurons expressing the hM3Dq receptor (***$p < 0.001$, $n = 8$–10), and hyperpolarized in the neurons expressing the hM4Di receptor (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, $n = 5$–6), compared to that in the neurons expressing the mCherry protein ($n = 7$–9) (**F, J, N, R**). Representative voltage traces obtained from a shell D2R-MSN expressing the hM3Dq receptor, and a core D2R-MSN expressing the hM4Di receptor, are displayed (**B**).

electrophysiological effects in directions opposite to those found in the case of CZP activation of the hM3Dq receptors (Intrinsic excitability: two-way repeated-measures ANOVA, $F_{1,5} = 6.76$ and $p < 0.05$ for shell D1R-MSNs, $F_{1,5} = 7.68$ and $p < 0.05$ for core D1R-MSNs, $F_{1,5} = 9.32$ and $p < 0.05$ for shell D2R-MSNs, $F_{1,5} = 24.5$ and $p < 0.01$ for core D2R-MSNs; $n = 6$ each. Input resistance: one-way ANOVA, $F_{1,11} = 9.12$ and $p < 0.05$ for shell D1R-MSNs, $F_{1,12} = 15.0$ and $p < 0.01$ for core D1R-MSNs, $F_{1,8} = 5.43$ and $p < 0.05$ for shell D2R-MSNs, $F_{1,13} = 14.2$ and $p < 0.01$ for core D2R-MSNs; $n = 4$–6. Membrane potential: one-way ANOVA, $F_{1,12} = 6.90$ and $p < 0.05$ for shell D1R-MSNs, $F_{1,12} = 15.4$ and $p < 0.01$ for core D1R-MSNs, $F_{1,10} = 147$ and $p < 0.001$ for shell D2R-MSNs, $F_{1,13} = 48.9$ and $p < 0.001$ for core D2R-MSNs; $n = 5$–6.) (Fig. 5B–R).

It is worth noting that the electrophysiological effects of the hM4Di receptor activation, especially its effects on intrinsic excitability, were less dramatic than those of the hM3Dq receptor activation (Fig. 5D, H, L, P). This difference might be attributable to the fact that MSNs have very hyperpolarized resting membrane potentials [26], and suppression of their excitability by the hM4Di receptor activation might be limited by a floor effect. However, it seems that manipulation of the hM4Di receptor in the MSNs, in order to modulate the tube test behavior, was as effective as manipulation of the hM3Dq receptor in the MSNs (Figs. 3C, D; 4E, F). This apparent paradox could possibly be explained by the fact that the activation of either the hM3Dq-Gq or hM4Di-Gi axis, in addition to modulating membrane excitability, also induces a complex cellular signal cascade leading to a modulation of the whole cellular reaction, which might not be limited by any floor effect. In addition, the hM4Di activation at the output terminals may also directly inhibit the GABA release of MSNs at their synapses, either onto other downstream neurons via projection outputs or onto other MSNs via collateral outputs [45].

DISCUSSION
The role of the NAc in social dominance
Brain regions associated with social dominance have been intensely investigated and, so far, several have been identified, such as the amygdala, hippocampus, hypothalamus, intraparietal sulcus, prefrontal cortex and striatum [46]. Despite this, knowledge of causal relationships between social dominance and the brain regions, and of the underlying circuitry and synaptic basis is limited. In this study, a causal relationship was found between social dominance and NAc circuitry, which aligns with the notion that the NAc plays an essential role in social behaviors [47–51], such as social attachment [52, 53] and social comparison [54].

The role of NAc D1Rs and D2Rs in social dominance
Previous research has focused on the role of D1Rs and D2Rs in social dominance, which has hinted at the striatal circuitry that mediates social dominance.

For example, it has been shown that D2R expression in the striatum is increased in dominant rodents, non-human primates and humans [55–59], which seems to contradict the results obtained in this study that suppression of NAc core D2R-MSNs reduces social dominance, considering that D2R activation via the Gi signal also suppresses D2R-MSNs. This inconsistency can be interpreted as a homeostatic compensation mechanism, i.e., the differential D2R expression level is a consequence, rather than a cause, of social dominance [55, 58]. On the other hand, systemic administration of a D2R antagonist reduces social ranks in dominant rodents and primates [60], which contradicts the data reported in this study, but cannot simply be explained by the D2R homeostatic compensation mechanism. This inconsistency could however be attributable to the lack of specificity of systemic administration of D2R antagonists.

Previous investigation of the role that D1Rs play in social dominance has produced inconclusive results. Positron emission tomography research has revealed that the D1R binding potential in the ventral striatum is negatively correlated with aggression [59, 61], a typical trait of dominant behaviors. In addition, systemic administration of a D1R antagonist generally promotes social dominance [62]. These results are consistent with the data presented in this study that activity of shell D1R-MSNs is causally negatively correlated with social dominance. Paradoxically, it has also been shown that intra-NAc-shell infusion of a D1R agonist facilitates social dominance [63], which contradicts the data presented in our study that NAc shell D1R-MSNs negatively regulate social dominance. This contradiction could possibly be attributable to the different NAc subregions involved—specifically, the NAc shell region in the previous study [63] is more posterior than the one in our study.

Our study reveals that the NAc shell D1R-MSNs and core D2R-MSNs play a negative and positive role, respectively, in social dominance. The D1R-MSNs and D2R-MSNs in the striatum have been conventionally respectively designated as the direct pathway and indirect pathway, which mediate the "Go" and "NoGo" behaviors, respectively. Generally, the direct pathway plays a positive role in appetitive behaviors such as reinforcement, reward, and drug addiction; whereas the indirect pathway plays a negative role in such cases [33–35, 64–70]. Conversely, the direct pathway plays a negative role in aversive behaviors such as avoidance, punishment, anhedonia, and stress; whereas the indirect pathway plays a positive role in such cases [71, 72]. However, the data presented in this study do not seem to align with this conventional dogma, if it is assumed that dominance is an appetitive "Go" behavior and that submissiveness is an aversive "NoGo" behavior. Indeed, recent work has challenged the conventional designation of "Go" and "NoGo" behaviors respectively to the direct and indirect pathways [73–75], which is partially attributable to the oversimplified model for these two pathways. In fact, the

assignment of the D1R-MSNs and D2R-MSNs solely to the direct and indirect pathways, respectively, at least in the NAc, has been challenged [73, 75–77].

It is noteworthy that previous research suggests that D1R-MSNs in NAc shell or core positively regulate aggression [78, 79], which apparently contradicts the result reported in our study showing that shell D1R-MSNs negatively regulate social dominance (Fig. 3). This contradiction might be attributable to differential basal aggression levels of mice between the studies — mice with a C57BL background, which were used in this study on social dominance, are known to barely demonstrate any aggressive behaviors [80]; whereas the C57BL mice used in the previous studies on aggression were either crossed with aggression-prone CD-1 mice or provoked (and screened) to demonstrate frequent aggressive behaviors [78, 79]. In support of this possible explanation, it has been shown that regulating the NAc activity (i.e., overexpressing ΔFosB in the NAc) promotes aggression in aggressive mice but not in non-aggressive mice [79]. Regardless, further research is needed to reconcile these different results.

The circuitry and synaptic mechanism of NAc underlying the concomitance of social dominance and chronic stress in rodents

It has been recently reported that dominant mice are more susceptible to chronic social defeat stress [81]. Conversely, stress induced by neonatal social isolation leads to social dominance [82]. The expression of chronic stress has long been known to be encoded partly by the NAc [83]. Indeed, chronic social defeat stress is correlated with decreased and increased presynaptic strengths of excitatory synapses respectively onto NAc D1R-MSNs and D2R-MSNs [71], and with a reduced calcium transient in NAc D1R-MSNs [84]. On the other hand, the data presented in our study indicate that decreased and increased postsynaptic strengths of excitatory synapses respectively onto shell D1R-MSNs and core D2-MSNs are causally involved in social dominance. The consistency of the changes in synaptic strength underlying chronic stress and social dominance, despite arising from distinct synaptic components (presynaptic and postsynaptic, respectively), imply that chronic stress and social dominance may facilitate the expression of each other by providing supportive synaptic plasticity to each other. This can explain the concomitance of stress susceptibility and social dominance [81, 85]. However, the distinct origins of the NAc synaptic plasticity in chronic stress and social dominance imply that these two behaviors are not simply of the same neural process.

Finally, it might be counterintuitive that the circuitry and synaptic mechanism of the NAc underlying social dominance (rather than social submissiveness) aligns with that underlying stress, because the concomitance of social submissiveness and stress is deeply rooted based on our experience in modern human society [63, 85–87]. Further research is needed to reconcile this contradiction.

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AUTHOR CONTRIBUTIONS
QS conceived, designed and supervised the project. QS, YH, SC, and YT conducted the experiments and analyzed data. QS interpreted the data, drafted and revised the

paper, communicated with the editors and reviewers, and handled publication. QS is the senior author of this paper.

COMPETING INTERESTS
The authors declare no competing interests.

ADDITIONAL INFORMATION
Supplementary information The online version contains supplementary figures and materials & methods available at https://doi.org/10.1038/s41386-021-01220-1.

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