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Review

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Neural substrates for regulating self-grooming behavior in rodents

Guanqing LI[1,2,3*], Chanyi LU[4*], Miaomiao YIN[5], Peng WANG[6], Pengbo ZHANG[7], Jialiang WU[1,2], Wenqiang WANG[1,2,3], Ding WANG[1,2], Mengyue WANG[1,2,8], Jiahan LIU[1,2,3], Xinghan LIN[1,2], Jian-Xu ZHANG[1,2], Zhenshan WANG[3✉], Yiqun YU[9,10,11✉], Yun-Feng ZHANG[1,2✉]

[1]*State Key Laboratory of Integrated Management of Pest Insects and Rodents, Institute of Zoology, Chinese Academy of Sciences, Beijing 100101, China*
[2]*CAS Center for Excellence in Biotic Interactions, University of Chinese Academy of Sciences, Beijing 100101, China*
[3]*School of Life Sciences, Hebei University, Baoding 071002, China*
[4]*State Key Laboratory of Molecular Development Biology, Institute of Genetics and Developmental Biology, Chinese Academy of Sciences, Beijing 100101, China*
[5]*Department of Rehabilitation Medicine, Tianjin Huanhu Hospital, Tianjin 300350, China*
[6]*Medical Center for Human Reproduction, Beijing Chao-Yang Hospital, Capital Medical University, Beijing 100101, China*
[7]*Department of Gastrointestinal Surgery, the People's Hospital of Zhaoyuan City, Zhaoyuan 265400, China*
[8]*School of Life Sciences, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei 230026, China*
[9]*Department of Otolaryngology, Eye, Ear, Nose & Throat Hospital, Fudan University, Shanghai 200031, China*
[10]*Ear, Nose & Throat Institute, Eye, Ear, Nose & Throat Hospital, Fudan University, Shanghai 200031, China*
[11]*Clinical and Research Center for Olfactory Disorders, Eye, Ear, Nose & Throat Hospital, Fudan University, Shanghai 200031, China*

Abstract: Grooming, as an evolutionarily conserved repetitive behavior, is common in various animals, including humans, and serves essential functions including, but not limited to, hygiene maintenance, thermoregulation, de-arousal, stress reduction, and social behaviors. In rodents, grooming involves a patterned and sequenced structure, known as the syntactic chain with four phases that comprise repeated stereotyped movements happening in a cephalocaudal progression style, beginning from the nose to the face, to the head, and finally ending with body licking. The context-dependent occurrence of grooming behavior indicates its adaptive significance. This review briefly summarizes the neural substrates responsible for rodent grooming behavior and explores its relevance in rodent models of neuropsychiatric disorders and neurodegenerative diseases with aberrant grooming phenotypes. We further emphasize the utility of rodent grooming as a reliable measure of repetitive behavior in neuropsychiatric models, holding promise for translational psychiatry. Herein, we mainly focus on rodent self-grooming. Allogrooming (grooming being applied on one animal by its conspecifics via licking or carefully nibbling) and heterogrooming (a form of grooming behavior directing towards another animal, which occurs in other contexts, such as maternal, sexual, aggressive, or social behaviors) are not covered due to space constraints.

Key words: Grooming; Repetitive behavior; Syntactic chain; Cephalocaudal progression; Neuropsychiatric disorders

1 Introduction

Grooming is an evolutionarily conserved repetitive behavior (Fentress, 1968a, 1968b; Spruijt et al., 1988, 1992; Leonard et al., 2005) that is common in various animals, including humans (Cohen-Mansfield and Jensen, 2007; Prokop et al., 2014). It has multifaceted roles including hygiene maintenance, thermoregulation, de-arousal, and stress reduction (Smolinsky et al., 2009; Kalueff et al., 2016), as well as social behaviors via chemosensory communications (Harriman and Thiessen, 1985; Ferkin and Leonard, 2010; Hobbs et al., 2012; Zhang et al., 2022). In rodents, grooming behavior involves a sequenced structure, known as the syntactic chain with four phases that comprise repeated stereotyped movements sequentially progressing from the nose (phase I) to the face (phase II), to the head (phase III), and finally ending with body licking

✉ Zhenshan WANG, zswang@hbu.edu.cn
Yiqun YU, yu_yiqun@fudan.edu.cn
Yun-Feng ZHANG, yfzhang@ioz.ac.cn
* The two authors contributed equally to this work
Zhenshan WANG, https://orcid.org/0000-0002-1478-1739
Yiqun YU, https://orcid.org/0000-0001-5256-7082
Yun-Feng ZHANG, https://orcid.org/0000-0001-6324-4115

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(phase IV), typically defined as a cephalocaudal progression. Phase I (paw, nose grooming) is characterized with series of elliptical strokes tightly around the nose. Phase II (face grooming) is composed of series of unilateral strokes (each made by one paw) that reach up the mystacial vibrissae to below the eye. Phase III (head grooming) is typically shown as series of bilateral strokes made by both paws simultaneously. Paws reach back and upwards, usually ascending high enough to pass over the ears. Phase IV (body licking) is preceded by a postural cephalocaudal transition from paw/head grooming to body grooming (Berridge et al., 2005; Kalueff et al., 2007, 2016). It is noteworthy that tail/genital grooming, as a part of a cephalocaudal grooming pattern, is also frequently observed in rodents. Rostral grooming is composed of forepaw (preliminary rostral grooming) and head grooming. Caudal grooming is arbitrarily defined as comprising body, legs, and tail/genital grooming (Kalueff et al., 2007). The syntactic grooming chain is regulated by specific brain areas such as the basal ganglia (Aldridge, 2005). A plethora of evidence demonstrates that lesions of the dorsolateral striatum impair the completion of syntactic grooming chains (Berridge, 1989; Berridge and Whishaw, 1992; Cromwell and Berridge, 1996), indicating that an intact striatum is indispensable in the correct performance of grooming chains. Since the serial structure of this chain is repetitive and consistent in terms of order and time, once the first phase (phase I) begins, the entire remaining sequential pattern reliably continues through all four phases. Approximately 10%–15% of all observed self-grooming behaviors in rodents exhibit such intact syntactic chain pattern, and the remainder usually follow less predictable sequential patterning rules (Kalueff et al., 2007).

In the temporal allocation system of multiple behaviors, grooming behavior is a low-priority one that is not time-locked to urgent external behavioral requirements. Grooming behavior usually fills the time intervals left by high-priority functions (Mul et al., 2013). In laboratory rearing conditions, rats spend 25%–40% of their awake time involved in grooming behavior, with most of the behavior seen just before and after the diurnal period of low activity (Bolles, 1960). In addition, the occurrence of grooming behavior is context-dependent, under either relaxed or stressed condition. There is evidence showing that rodents perform grooming frequently right after a sequence of eating, drinking, exploratory behavior (Bolles, 1960; Mul et al., 2013), or mating (Karigo and Deutsch, 2022), which is probably due to the post-rewarding effects resulting from feeding and drinking, or the need for post-copulatory hygiene of the genital area. Actually, grooming behavior per se could induce rewarding effects in rodents. This could be supported by our recent work disclosing that, in the post conditioning session of the conditioned place preference test, D3-Cre/ChR2 mice prefer to spend more time in the chamber paired with more grooming mice triggered by the activation of ventral striatal islands of Calleja dopamine receptor 3 (D3)-expressing neurons compared to the chamber paired with less grooming mice. However, when the same test was performed with a collar around the neck of D3-Cre/ChR2 mice to block self-directed orofacial grooming by preventing the forepaws from contacting the face and head, the conditioned place preference caused by the stimulation of D3 neurons disappeared, suggesting that grooming behavior elicited by the activation of D3 neurons is necessary for the rewarding effect (Zhang et al., 2023).

Rodents also exhibit abundant grooming behavior in a stressed context (Spruijt et al., 1992; Kalueff and Tuohimaa, 2004, 2005b). Indeed, grooming behavior happens during (and following) exposure to distinct types of stressful situations/stimuli (Spruijt et al., 1992; van Erp et al., 1994). Generally, rodent grooming behavior is indicative of their state of stress resilience. For example, by selecting male mice with high immobility (HI) and low immobility (LI) traits in the tail suspension test and using the repeated restraint stress paradigm, HI animals (low resilience to stress) show an increased frequency and decreased duration of grooming behavior in a familiar environment compared to LI animals (high resilience). In contrast, in a novel environment, stress increases the frequency and duration of grooming behavior in HI versus LI animals (Reis-Silva et al., 2019). In a study on inbred Roman low- and high-avoidance rats (RLA-I and RHA-I), and the outbred National Institutes of Health Genetically Heterogeneous Rat Stock (NIH-HS), grooming behavior was compared under different conditions (Estanislau et al., 2013). No differences were observed in the home cage. In contrast, when tested in a novel environment, RHA-I rats exhibited less grooming behavior than the other rats. In addition, in the two-way active avoidance training test, after avoidance responses

appeared, differences among the strains were opposite to those observed in novelty tests. This evidence reveals that grooming behavior varies robustly under testing situations involving different levels of aversiveness. Rodents may recruit the involvement of the hypothalamic-pituitary-adrenal (HPA) axis to appropriately orchestrate stress-induced grooming behavior depending on distinct stressed contexts, which is supported by the fact that corticosterone-induced HPA disruption blunts acute stress-induced grooming behavior in a novel environment (Kinlein et al., 2019).

In rodents, multiple brain centers/neural circuits are specifically recruited for the control of stress-triggered grooming behavior. For example, a di-synaptic circuit linking the hippocampal ventral subiculum to the ventral lateral septum (LSv) and then the lateral hypothalamus tuberal nucleus regulates stress-induced grooming behavior with positive affective valence, suggesting the potential contribution of grooming behavior to post-stress de-arousal with adaptive value (Mu et al., 2020). In addition, grooming behavior can help rodents relieve the negatively affective state resulting from external stress. One recent study reveals that the subthalamo-parabrachial glutamatergic pathway is involved in body-restraint and foot-shock stress-induced grooming behaviors (Jia et al., 2023). Similarly, it is reported that the circuit linking the central amygdala to the medial paralemniscal nucleus (MPL) and the ventral tegmental area (VTA) controls grooming behavior and post-stress anxiety alleviation, suggesting that rodents did gain relief and pleasure during and after the typical repetitive behavior—grooming (Sun et al., 2022). Except for the aforementioned neural substrates specifically responsible for the regulation of stress-induced grooming behavior, a variety of other elaborated neural circuits are also engaged in the control of grooming behavior, which are detailed in the following sections.

2 Neural substrates underlying grooming behavior

The performance of the proper functions of neural circuits relies heavily on mutual interactions among specific brain centers (Fig. 1). Several brain regions, such as the lateral septum (LS) (Mu et al., 2020), the prefrontal cortex (PFC) (Ahmari et al., 2013; Burguière et al., 2013; Pinhal et al., 2018), the amygdala (Hong et al., 2014; Alò et al., 2015), the hypothalamus (Dunn et al., 1987; Dunn, 1988; Roeling et al., 1993; Kruk et al., 1998; Mangieri et al., 2018; Mu et al., 2020), the brainstem (Berntson et al., 1988; Berridge, 1989; Spruijt et al., 1992), the periaqueductal gray (PAG) (Gao et al., 2019), the cerebellum (Berridge and Whishaw, 1992), the MPL (Sun et al., 2022), and the spinal cord (Xie et al., 2022), are responsible for the control of grooming behavior. We describe how these brain areas are involved in the regulation of grooming behavior below.

The LS is a major relay connecting several brain regions, and its crucial role in the regulation of grooming has been broadly reported (Xu et al., 2019, 2023; Mu et al., 2020). There is evidence that the activation of the LSv projecting paraventricular hypothalamus (PVH) melanocortin receptor 4 (PVH^{Mc4R}) neurons promotes stress-related self-grooming in mice (Xu et al., 2023) (Table 1). Another study focusing on the PVH to LSv pathway showed that the weak optogenetic activation of PVH glutamatergic terminals in LSv elicits stress-related self-grooming, which is distinct from the strong photostimulation condition that causes fear-related escape jumping behavior (Xu et al., 2019). Additionally, the circuit from the hippocampal ventral subiculum to the LS has pinpointed the important role of the LS in the control of grooming, and the activation of this pathway could trigger delayed but robust excessive grooming behavior (Mu et al., 2020). It is assumed that the LS controls grooming behavior in rodents through orchestrating neurons expressing specific receptors, for example, the corticotropin-releasing factor (CRF) receptors. This hypothesis has been corroborated by the evidence that infusions of CRF_1/CRF_2 agonist urocortin into the LS reliably enhanced grooming behavior in food-restricted male Sprague-Dawley rats (Bakshi et al., 2007) (Table 1).

Grooming behavior is also modulated by the limbic circuitry, including the amygdala and the hypothalamus, as well as cortical areas such as the PFC. Stress-induced grooming behavior specifically predicts enhanced motivation to self-administer cocaine in rats, which is related to dopamine release in the amygdala and medial PFC (mPFC) (Homberg et al., 2002). In addition, the extended amygdala is composed of the medial and lateral divisions. The medial part includes the medial nucleus of the amygdala

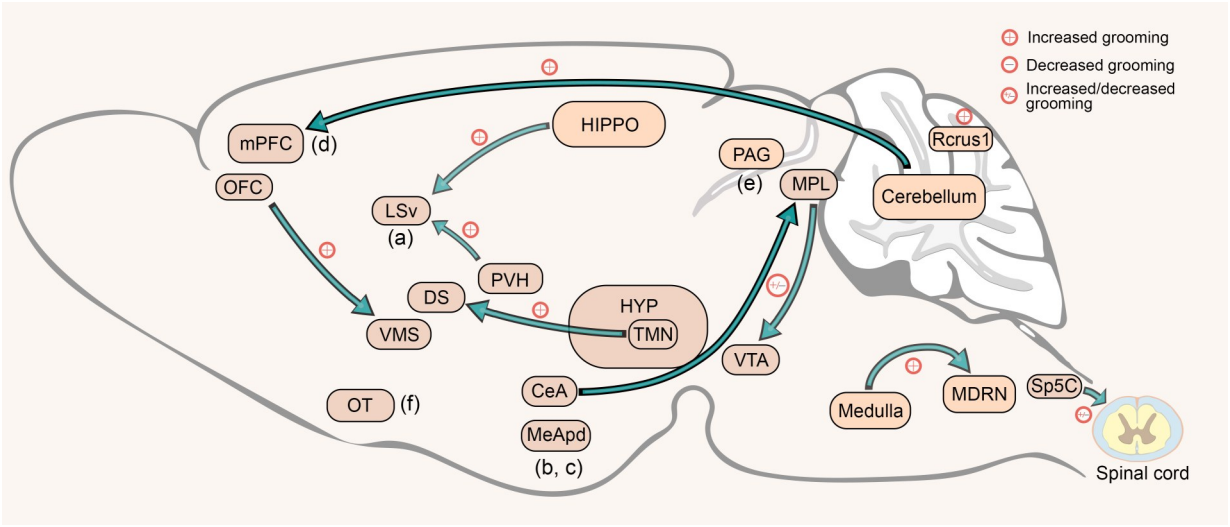

Fig. 1 Neural circuits involved in the regulation of rodent self-grooming. Activation of the LSv-projecting PVH^{Mc4R} neurons promoted stress-related self-grooming in mice (Xu et al., 2023), and weak optogenetic activation of PVH glutamatergic terminals in LSv also elicited stress-related self-grooming (Xu et al., 2019). Activation of the hippocampal ventral subiculum to LS triggered robust excessive grooming behavior in rats (Mu et al., 2020). Repeated photostimulation of the OFC-to-VMS projections induced increased grooming in mice (Ahmari et al., 2013). Specific ablation or chemogenetic silencing of histaminergic neurons in the TMN of the HYP enhanced grooming in mice, and the TMN to DS pathway took charge of the modulation of grooming behavior (Rapanelli et al., 2017). Optogenetic stimulation of lateral rostral medulla neurons projecting to the dorsal part of MDRN induced grooming or hand-to-mouth movements in mice (Ruder et al., 2021). The excitatory somatostatin-positive neurons in the MPL bidirectionally regulated grooming in mice via the CeA-MPL-VTA pathway (Sun et al., 2022). Circuitry linking the cerebellum and the mPFC has been documented in regulating grooming in mice. Inhibition of Rcrus1 PCs induced grooming, which, however, could not be rescued by gain-of-function of Rcrus1 PCs (Kelly et al., 2020). Cervical spinal cord projecting Cbln2$^+$-expressing neurons in Sp5C bidirectionally regulated repetitive orofacial grooming in mice (Xie et al., 2022). (a) Infusions of CRF$_1$/CRF$_2$ agonist urocortin into the LS enhanced grooming in food-restricted male Sprague Dawley rats (Bakshi et al., 2007). (b) Activation of glutamatergic and GABAergic neurons, respectively, in the MeApd promoted and inhibited grooming in mice (Hong et al., 2014). (c) In the MeApd of female mice, photoexcitation of VGluT2 neurons increased self-grooming, and photoinhibition of VGAT neurons did not influence grooming (Johnson et al., 2021). (d) VMAT2-conditioned knockout mice exhibited excessive grooming accompanied by a pronounced reduction of dopamine levels in the mPFC (Petrelli et al., 2023). (e) Activation of Tac1-expressing neurons in the lateral and ventrolateral PAG (l/vlPAG) triggered grooming in mice (Gao et al., 2019). (f) Ventral striatal islands of Calleja D3 neurons bidirectionally controlled grooming in mice (Zhang et al., 2021). Cbln2, cerebellin-2; CeA, central nucleus of the amygdala; CRF, corticotropin-releasing factor; D3, dopamine receptor 3; DS, dorsal striatum; GABAergic, γ-aminobutyric acid (GABA)-ergic; HIPPO, hippocampus; HYP, hypothalamus; LSv, ventral lateral septum (LS); MDRN, medullary reticular nucleus; MeApd, posterior dorsal part of the medial amygdala; mPFC, medial prefrontal cortex; MPL, medial paralemniscal nucleus; OFC, orbitofrontal cortex; OT, olfactory tubercle; PAG, periaqueductal gray; PCs, Purkenje cells; PVH^{Mc4R}, paraventricular hypothalamus (PVH) melanocortin receptor 4; Rcrus1, right crus 1; Sp5C, caudal part of the spinal trigeminal nucleus; Tac1, tachykinin 1; TMN, tuberomammillary nucleus; VGAT, vesicular GABA transporter; VGluT2, vesicular glutamate transporter 2; VMAT2, vesicular monoamine transporter 2; VMS, ventromedial striatum; VTA, ventral tegmental area.

(MeA) and the medial bed nucleus of the stria terminalis (BNST), and the lateral part includes the central nucleus of the amygdala (CeA) and the lateral BNST. Different subregions and even distinct neuronal types in the same division of the amygdala exert varied effects on the regulation of grooming behavior. There is evidence that glutamatergic and γ-aminobutyric acid (GABA)-ergic (GABAergic) neurons in the posterior dorsal part of the medial amygdala (MeApd) antagonistically modulate grooming behavior, with the former promoting and the latter inhibiting grooming (Hong et al., 2014). It seems that distinct neuronal types in the MeA function differently in the orchestration of grooming behavior. Interestingly, it has also been revealed that, in the MeApd in female mice, the photoexcitation of vesicular glutamate transporter 2 (VGluT2) neurons increases self-grooming without affecting the lordosis quotient (LQ), and photoinhibition of vesicular GABA transporter (VGAT) neurons specifically decreases the LQ but does not influence

Table 1 Summary of genes pertaining to grooming behavior in rodents

Gene	Species	Effects on grooming behavior
Melanocortin receptor 4 (*Mc4R*)	Mouse	Activation of $PVH^{Mc4R}\rightarrow$LSv projections promoted stress-related self-grooming (Xu et al., 2023)
Corticotropin-releasing factor (*CRF*)	Rat	Infusions of CRF_1/CRF_2 agonist urocortin into the LS enhanced grooming (Bakshi et al., 2007)
Vesicular glutamate transporter 2 (*VGluT2*)	Mouse	Photoexcitation of VGluT2-expressing neurons increased self-grooming (Johnson et al., 2021)
Vesicular monoamine transporter 2 (*VMAT2*)	Mouse	VMAT2-conditioned knockout mice exhibited excessive grooming (Petrelli et al., 2023)
Tachykinin 1 (*Tac1*)	Mouse	Activation of Tac1-expressing neurons in the lateral and ventrolateral PAG (l/vlPAG) triggered robust grooming (Gao et al., 2019)
Glutamate receptor-interacting proteins 1/2 (*Grip1/2*) and metabotropic glutamate receptor 5 (*mGluR5*)	Mouse	Loss of Grip1/2 in cerebellar PCs led to AMPAR-trafficking defects in these neurons and disturbances of mGluR5 signaling in cerebellum, which resulted in increased grooming (Mejias et al., 2019)
Cerebellin-2 (*Cbln2*)	Mouse	Inactivation of $Cbln2^+$ Sp5C neurons prevented orofacial grooming while activation of these neurons induced forelimb movements resembling orofacial grooming (Xie et al., 2022)
Dopamine receptor 3 (*D3*)	Mouse	Optogenetic activation of D3 neurons triggered robust grooming while inhibition or ablation of these neurons remarkably decreased total grooming time (Zhang et al., 2021)
SH3 and multiple ankyrin repeat domains (*Shank*)	Mouse	*Shank1*-mutant mice showed slightly increased grooming as adults, but not as juveniles (Sungur et al., 2014); *Shank2*-mutant females but not males showed elevated duration of grooming bouts (Schmeisser et al., 2012); *Shank3*-mutant mice had increased duration of grooming bouts (Peça et al., 2011; Wang et al., 2011; Yang et al., 2012)
Glutamic acid decarboxylase-67 (*Gad67*)	Mouse	Gad67-deficient mice exhibited enhanced stereotypic grooming (Zhang et al., 2014)
SAP90/PSD95-associated protein 3 (*Sapap3*)	Mouse	*Sapap3*-mutant mice showed robust increased grooming which could be rescued by Sapap3 re-expression in the striatum (Welch et al., 2007; Wan et al., 2014)

PVH, paraventricular hypothalamus; LSv, ventral lateral septum (LS); PAG, periaqueductal gray; PCs, Purkenje cells; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor; Sp5C, caudal part of the spinal trigeminal nucleus; SAP90, synapse-associated protein 90; PDP95, postsynaptic density protein 95.

grooming behavior (Johnson et al., 2021) (Table 1). Moreover, region-specific infusion of orexin-B into the CeA moderately enhances grooming frequency in hamsters (Alò et al., 2015), supporting the supposition that both MeA and CeA are engaged in grooming control.

The PFC interconnects with multiple brain regions, and its dysfunctions are also closely associated with abnormal grooming behavior in rodents (Petrelli et al., 2023). The internal capsule (IC) and the dorsal part of the ventral striatum (dVS) are two distinct brain areas that are potentially modulated by prefrontal cortical fibers. In a synapse-associated protein 90/postsynaptic density protein 95 (SAP90/PSD95)-associated protein 3 (*Sapap3*)-mutant mouse model, deep brain stimulation (DBS) of the IC dramatically ameliorates excessive grooming, whereas DBS of the dVS is less effective. In addition, grooming behavior is reduced rapidly after the onset of DBS of the IC and reinstates upon DBS offset (Pinhal et al., 2018). This evidence strongly suggests that the PFC executes its key role in grooming control by innervating downstream areas via its broad corticofugal fibers. In addition, the orbitofrontal cortex (OFC), as a key prefrontal region, is also heavily involved in the modulation of grooming behavior. Repeated photostimulations of OFC to ventromedial striatum (VMS) projections trigger hyperactivation of this pathway, which in turn leads to progressively increased grooming behavior in mice (Ahmari et al., 2013). In contrast, Burguière et al. (2013) reported that selective optogenetic stimulation of glutamatergic projections of the lateral orbitofronto-striatal pathway could prevent over-expression of both conditioned and spontaneous repetitive grooming behaviors in mice. The discrepancies among these studies

are probably due to distinct experimental manipulations recruited as well as different subregions of OFC studied. In addition, it is noteworthy that, in a vesicular monoamine transporter 2 (VMAT2)-conditioned knockout mouse model, mice exhibited excessive grooming behavior accompanied by a pronounced reduction of dopamine levels in the mPFC (Petrelli et al., 2023) (Table 1), implying that dopamine release control in the PFC is one potentially vital factor for orchestrating grooming behavior.

The hypothalamus is another crucial limbic brain area that is heavily implicated in the control of rodent grooming behavior (Roeling et al., 1993). The hypothalamus is traditionally considered as the "grooming center" in the brain, and the hypothalamic "grooming area" consists of parts of the hypothalamic paraventricular nucleus and parts of the dorsal hypothalamic area, as well as of the tuberomammillary nucleus (TMN), which probably interacts intensely with other grooming-related circuitries in the brain (Roeling et al., 1993; Rapanelli et al., 2017). For example, the PVH and MeApd are reciprocally connected, and the latter is an important brain area that plays key roles in modulating grooming behavior in mice (Roeling et al., 1993; Hong et al., 2014). Additionally, specific ablation or chemogenetic silencing of histaminergic neurons in the TMN of the hypothalamus remarkably enhances grooming behavior in mice and concomitantly elevates markers of neuronal activity in both the dorsal striatum and the mPFC. Further experiments delineate that the TMN to dorsal striatum pathway takes charge of the modulation of grooming behavior while the TMN to mPFC underlies the increased locomotion effect but not the grooming control (Rapanelli et al., 2017). The interaction between the hypothalamus and the pituitary system is also engaged in the regulation of grooming behavior via specific hormones such as the stress-related peptides corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH) (Dunn et al., 1979, 1987), testosterone, prolactin, and corticosterone (Kruk et al., 1998). This evidence indicates that the hypothalamus, via its broad connections with other grooming-related brain centers and acting as a crossroads, is a far underappreciated brain region that integrates the neural and endocrine regulation of grooming behavior (Spruijt et al., 1992; Kruk et al., 1998).

The brainstem circuitry is also engaged in the orchestration of grooming behavior in rodents, especially playing an indispensable role in the execution of fully patterned grooming sequences (Berridge, 1989; Kalueff et al., 2016). It is reported that the optogenetic stimulation of lateral rostral medulla neurons projecting to the dorsal part of the medullary reticular formation induces grooming behavior or hand-to-mouth movements in mice (Ruder et al., 2021), in which the induced grooming behavior seems unnatural and is not similar to normal self-grooming behavior. The PAG, as the other key subregion of the brainstem structure, also has an important role in grooming control. The activation of tachykinin 1 (Tac1)-expressing neurons in the lateral and ventrolateral PAG (l/vlPAG) triggers robust spontaneous scratching and grooming behaviors (Gao et al., 2019) (Table 1). As another potentially underlying mechanism, the PAG may modulate grooming behavior via interacting with distinct peptide components such as the ACTH and the substance P, which could trigger excessive grooming behavior by local infusion into the dorsal part of the PAG in rats (Spruijt et al., 1986; Aguiar and Brandão, 1994). Arginine vasopressin (AVP) produces enhanced grooming behavior in golden hamsters (Cormier et al., 2015), and the luteinizing hormone-releasing hormone (LHRH), as well as and the bombesin (BBS), produces enhanced grooming behavior in rats (Kyrkouli et al., 1987; Gargiulo and Donoso, 1989), when locally applied to the PAG. As another key component of the brainstem, the rostral pons is also engaged in grooming behavior. The MPL is located in the rostral pons, and the excitatory somatostatin-positive neurons in the MPL could bidirectionally regulate grooming behavior in mice via the CeA-MPL-VTA pathway (Sun et al., 2022). The aforementioned evidence reveals that distinct components of the brainstem are all actively involved in the regulation of grooming behavior, and further highlights the paramount role of the brainstem in the control of this stereotypical and repetitive behavior in rodents.

The brainstem, as a hub, connects the cerebrum to the cerebellum and the spinal cord, and the latter two are involved in grooming control. A circuitry linking the cerebellum and the mPFC, starting from the cerebellar cortical areas right crus 1 (Rcrus1) and posterior vermis through the cerebellar nuclei and ventromedial thalamus, and culminating in the mPFC, has been documented as regulating grooming behavior in mice. This reveals that the inhibition of Rcrus1

Purkenje cells (PCs) induces both social impairments and grooming behavior, which, however, could not be rescued by the gain-of-function of Rcrus1 PCs (Kelly et al., 2020). These results suggest that dysfunctions of PCs in the cerebellum are closely related to abnormal grooming behavior. Mejias et al. (2019) demonstrated that the loss of glutamate receptor-interacting proteins 1/2 (Grip1/2) in cerebellar PCs leads to α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor (AMPAR)-trafficking defects in these neurons and disturbances of metabotropic glutamate receptor 5 (mGluR5) signaling in the cerebellum, which, in the end, results in increased repetitive grooming behavior in mice (Table 1). This finding suggests a potentially crucial role of mGluR5 in the orchestration of grooming behavior, which is supported by the evidence that the administration of 2-methyl-6-phenylethyl-pyrididine (MPEP), the mGluR5 antagonist, could significantly alleviate grooming behavior in valproic acid (VPA)-treated mice (Mehta et al., 2011). Similarly, the spinal cord-related neural circuits are also engaged in modulating grooming behavior. In the caudal part of the spinal trigeminal nucleus (Sp5C), cerebellin-2-positive ($Cbln2^+$)-expressing neurons recruit a neural pathway via projections to the cervical spinal cord to bidirectionally regulate repetitive orofacial grooming in mice. Moreover, the inactivation of $Cbln2^+$ Sp5C neurons prevents both sensory-evoked and stress-induced repetitive orofacial grooming while the activation of these neurons induces short-latency repetitive forelimb movements resembling orofacial grooming (Xie et al., 2022) (Table 1), uncovering a brain-to-spinal sensorimotor loop for repetitive grooming in mice.

In addition to the aforementioned brain areas, the basal ganglia is also involved in the patterning and execution of grooming behavior (Cromwell and Berridge, 1996; Aldridge et al., 2004; Graybiel, 2008; Burguière et al., 2015; Graybiel and Grafton, 2015; Rapanelli et al., 2017; Yu et al., 2018). Different striatal subregions and their downstream targets play distinct roles in the regulation of grooming behavior. Lesions to the dorsolateral striatum dramatically reduce syntax completion without affecting total grooming time, while lesions to the ventral pallidum, a downstream target of the ventral striatum, decrease total grooming time without affecting syntax completion (Cromwell and Berridge, 1996). Electrophysiological recordings in the dorsolateral striatum in rats reveal that neurons in this area are responsible for the entire grooming sequence pattern as a whole, especially firing in terminal phases. These neurons could discriminate between the sequential pattern and those same grooming movements produced in distinct phases outside of the syntactic chain (Aldridge et al., 1993; Aldridge and Berridge, 1998; Meyer-Luehmann et al., 2002). In contrast, neural activity in the substantia nigra pars reticulata, the other important component of the basal ganglia, appears to take charge of the initiation of the pattern, responding especially to the onset of chains (Meyer-Luehmann et al., 2002). In addition, as a key subregion of the ventral striatum and a main member of the olfactory cortices, the olfactory tubercle (OT) plays a crucial role in the regulation of grooming behavior. Our recent work shows that the ventral striatal islands of Calleja D3 neurons bidirectionally control grooming behavior in mice (Zhang et al., 2021). Optogenetic activation of OT D3 neurons triggers robust grooming behavior with short onset latency while the inhibition or ablation of these neurons remarkably decreases total grooming time, indicating a novel role of ventral striatal D3 neurons in the regulation of grooming behavior in mice. Taken together, this evidence suggests that distinct components of the basal ganglia work cooperatively in the initiation and organization of sequential patterns of grooming, rather than just implementing the elementary component movements within a pattern.

Last but not least, historic studies indicate that rodents display a sexual dimorphic phenotype in grooming behavior (Moore, 1986; Thor et al., 1988; Hill et al., 2007; Schmeisser et al., 2012). When adult Long-Evans hooded rats are exposed to a novel juvenile conspecific, males perform substantially greater self-grooming behaviors than females (Thor et al., 1988). There is evidence showing that the difference in testosterone availability during the peripubertal period is one primary reason accounting for the sex differences in the self-grooming behavior of rats (Moore, 1986). Moreover, in an aromatase knockout (ArKO) mouse model that is deficient of estrogen, males but not females develop excessive grooming behavior (Hill et al., 2007). This evidence suggests a hormonal basis for a sex dimorphic effect on grooming behavior. In addition, a dysfunctional synapse is one potential factor inducing sex differences in grooming behavior. For example, SH3 and multiple ankyrin repeat domains (Shank2), as a member of the Shank family

of synaptic proteins, plays a role in synaptogenesis, and *Shank2*-mutant females but not males exhibit an elevated duration of grooming bouts (Schmeisser et al., 2012). Unfortunately, relatively little information is available pertaining to the neural circuits underlying sex differences in grooming behavior, and more further work is warranted.

3 Grooming behavior and neuropsychiatric disorders

Repetitive behavior is a typical phenotype of some neuropsychiatric disorders including, but not limited to, autism spectrum disorder (ASD) and obsessive compulsive disorder (OCD). Grooming, as a repetitive behavior, is also frequently observed in humans and, to some extent, self-grooming in humans is similar to that seen in other animals (Cohen-Mansfield and Jensen, 2007; Prokop et al., 2014). In humans, grooming behavior, such as care-of-body-surface via applying cosmetics to the skin, plays a crucial role in body surface maintenance, and it is traditionally considered as providing functional and aesthetic benefits—we keep clean and we look good (McGlone et al., 2016). Nowadays, humans spend more time autogrooming, for example, washing, bathing, haircutting, etc., and humans seem to deviate from other primates by shifting their grooming from pure hygiene maintenance to beautification, reflecting reduced hygienic need and increased investment in mate attraction (Jaeggi et al., 2017). It is noteworthy that human self-grooming behavior can become pathological, for example, during stressful conditions or in certain neuropsychiatric disorders (Golani and Fentress, 1985; Berridge et al., 1987; Berridge and Aldridge, 2000; Kalueff et al., 2007; Ahmari et al., 2013; Roth et al., 2013) including ASD and OCD. It is generally acceptable that grooming behaviors in rodents can be used to model normal or pathological human grooming behaviors (Feusner et al., 2009). In addition, grooming behavior abnormalities are usually common symptoms in some rodent models of anxiety and depression (Smolinsky et al., 2009; Kalueff et al., 2016). Therefore, grooming may be a useful measure of repetitive behavior in rodent models of neuropsychiatric disorders, and is accordingly endowed with the value of translational psychiatry (Kalueff et al., 2016).

The inbred BTBR T+ tf/J (BTBR) mouse strain exhibits increased repetitive grooming behavior and abnormal behaviors that resemble the symptoms of ASD (Amodeo et al., 2014). The enhanced grooming in these BTBR mice could be improved via pharmacological reagents such as the muscarinic cholinergic receptor (mAChR) agonist, oxotremorine (Amodeo et al., 2014), and the glutamatergic metabotropic mGluR5 receptor antagonist, methyl-6-phenylethynyl-pyridine (MPEP) (Silverman et al., 2010), as well as the selective negative allosteric modulator of the mGluR5 receptor, 4-difluoromethoxy-3-(pyridine-2-ylethynyl)phenyl)5H-pyrrolo[3,4-b]pyridine-6(7H)-yl methanone (GRN-529) (Silverman et al., 2012). Interestingly, though co-rearing with a non-ASD strain (C57BL/6J) corrected social deficits in BTBR mice, it failed to rescue the heightened grooming behavior (Yang et al., 2011), raising the possibility that the ASD-like behavior, repetitive grooming, may be regulated by distinct brain areas with different mechanisms which are probably discrepant to those of social deficits.

Mice with mutations in *Shank* genes also display aberrant grooming behavior (Schmeisser, 2015). For example, *Shank1*-mutant mice show slightly increased levels of grooming behavior as adults, but not as juveniles (Sungur et al., 2014). *Shank2*-mutant mice demonstrate sexual dimorphic effects on grooming behavior, with females but not males showing an elevated duration of grooming bouts (Schmeisser et al., 2012). Interestingly, the influence of the *Shank2* mutation on grooming behavior is context-dependent, with enhanced grooming during a novel object recognition test but not the open field test (Won et al., 2012). Similarly, *Shank3*-mutant mice exhibit an increased duration of grooming bouts (Peça et al., 2011; Wang et al., 2011; Yang et al., 2012) (Table 1). These results reveal that the *Shank*-mutant mice are good models of ASD. Moreover, glutamic acid decarboxylase-67 (Gad67) is the GABA-synthesizing enzyme. Gad67-deficient mice show enhanced stereotypic grooming behavior and impaired spatial learning and social behavior, resembling symptoms of ASD (Zhang et al., 2014) (Table 1), suggesting that altered striatal GABAergic activity could be involved in ASD-related deficits such as aberrant grooming (Centonze et al., 2008; Chao et al., 2010).

Excessive grooming is also a key characteristic of some forms of OCD (Graybiel and Saka, 2002;

Parolari et al., 2021). *Sapap3*-mutant mice show robust increased grooming which could be rescued by *Sapap3* re-expression in the striatum (Welch et al., 2007; Wan et al., 2014) (Table 1). In rodents, since SAPAP3 is primarily expressed in the striatal glutamatergic synapses, and the striatum is a key brain region heavily engaged in the regulation of grooming, it is not surprising that mutations of *Sapap3*-induced neural substrates are responsible for the modulation of grooming behavior in these mutant models. This is supported by the finding that optogenetic stimulation of the orbitofronto-striatal pathway is sufficient to correct the excessive grooming behavior observed in the *Sapap3*-mutant mice (Burguière et al., 2013, 2015; Ahmari and Dougherty, 2015; Monteiro and Feng, 2016). Moreover, even in wild-type mice, grooming behavior is remarkably enhanced via repeatedly stimulating a nearby part of the OFC (Ahmari et al., 2013). This evidence further emphasizes the crucial role of corticostriatal circuits in the modulation of grooming behavior in rodents, which is undoubtedly useful for modelling compulsions in humans with OCD, and even related mental disorders. In addition to OCD and ASD, abnormal grooming behaviors are also depicted in some other models of neuropsychiatiric disorders such as Alzheimer's disease (AD) (Várkonyi et al., 2022) and Parkinson's disease (Paumier et al., 2013). For example, in a triple-transgenic mouse (3×Tg-AD) model of AD, it was found that the four-month-old 3×Tg-AD animals spent more time engaging in grooming behavior than the controls (Várkonyi et al., 2022). In contrast, in the Parkinson's disease model, *A53T*-mutant mice show ameliorated grooming behavior before the occurrence of parkinsonian-like phenotypes (Paumier et al., 2013). This evidence implies that grooming behavior acts as a common behavioral hallmark of these disorder models but with large variances.

Aberrant grooming behavior is also observed in rodent models of anxiety and depression (Smolinsky et al., 2009; Kalueff et al., 2016). Abnormal grooming behavior could be triggered by acute stressors (Rodríguez Echandía et al., 1987; Spruijt et al., 1987, 1988; Kalueff and Tuohimaa, 2004; Brodkin et al., 2014) and chronic anxiogenic states (Kalueff and Tuohimaa, 2004; Kalueff et al., 2007; Estanislau et al., 2013), and therefore it is considered a useful measure of stress or anxiety in a variety of experimental models and tests (Kalueff et al., 2007). Acute stress usually induces anxiety-like behaviors in rodents (Smolinsky et al., 2009). However, distinct acute stressors exert different effects on grooming behavior. In rats, both foot shock and the acute administration of the stress hormone corticosterone alleviate grooming behavior while novelty habituation produces the opposite effect (Rojas-Carvajal et al., 2023). Interestingly, acute stress via footshock mildly ameliorates complex grooming sequences while increasing cephalic grooming behavior (Rojas-Carvajal and Brenes, 2020), indicating that acute stress differentially affects grooming subtypes. Novelty stress induced by exposing rodents to an unfamiliar environment usually evokes high levels of grooming behavior (File et al., 1988; Kalueff and Tuohimaa, 2005a), and stronger stressors, for example, a 5-min pre-exposure to a predator or a bright light, also elicit robust grooming behavior in rodents (File et al., 1988; Kalueff and Tuohimaa, 2004, 2005b). Generally, the grooming microstructure of mice is considered a reliable anxiety marker, and could be leveraged as a valuable tool in the behavioral pharmacology of anxiety (Kalueff and Tuohimaa, 2005c). For example, zinc finger protein 462 (*Zfp462*)-mutant mice demonstrate anxiety-like behaviors with excessive grooming behavior (Wang et al., 2017), providing a useful tool to pinpoint potential therapeutic targets for anxiety and screen anti-anxiety drugs. With the development of more ethologically based measures of anxiety, abnormal grooming behavior has been utilized to comprehensively understand the behavioral profile of mouse strains in anxiety tests (Rodgers et al., 1997; Carobrez and Bertoglio, 2005).

The analysis of rodent grooming behavior not only serves as a powerful way to study animal stress and anxiety, but also provides an avenue for investigating depression (Smolinsky et al., 2009). In mouse models of depression, mice exhibit remarkably decreased grooming behavior in the sucrose splash test (Santarelli et al., 2003), reflecting self-care difficulties in these animals. Aberrant grooming behavior in rodents could reliably mirror symptoms in patients with depression. For example, grooming patterning rigidity in rodents is similar to behavioral perseveration in depression patients, and reduced grooming activity could, to some extent, reflect the anhedonia and poor hygiene state of patients suffering from depression (American Psychiatric Association, 2013). Compared to acute

stress, chronic mild stress is generally used to induce animal models of depression. Distinct from the "acute" nature of anxiety-induced grooming responses, the effects of depression on grooming behavior are delayed and somewhat less obvious (Smolinsky et al., 2009). Moreover, the effect of chronic mild stress on animal grooming behavior is, to some extent, controversial. Some researchers demonstrated that chronic mild stress ameliorates grooming (Piato et al., 2008; Wang et al., 2008), while other studies showed that the chronic application of strong stressors, such as olfactobulbectomy or peripheral anosmia, could trigger a remarkable increase in grooming behavior (Iu Makarchuk, 1999; Iu Makarchuk and Zyma, 2002). The discrepancies between acute and chronic stress-induced emotional state changes, accompanied by abnormal grooming behaviors in rodents, are probably, to some extent, due to varied stress levels affecting distinct brain regions and/or different neurotransmitters (Adell et al., 1988; Hellriegel and D'Mello, 1997; Jankord and Herman, 2008).

4 Grooming behavior and other diseases

Apart from acting as a hallmark of some neuropsychiatric disorders, aberrant grooming behavior also occurred in a rodent model of some other diseases including, but not limited to, Tourette's syndrome (Taylor et al., 2010), Huntington's disease (Hickey et al., 2002; Scattoni et al., 2004; Steele et al., 2007; André et al., 2011), and familial Danish dementia (Vidal et al., 2009), as well as Krabbe disease (Scruggs et al., 2013). For example, in a quinolinic acid injection-induced rat model of Huntington's disease, abnormal hyper-grooming was observed in the early stages of the disease (Scattoni et al., 2004). In addition, abnormal grooming behavior is frequently observed in rodent models of itch and pain. It is demonstrated that house dust mite allergen-induced scratching behavior (itch) is positively correlated with grooming behavior in BALB/c mice (Anggraeni et al., 2023). Similarly, the activation of Tac1-expressing glutamatergic neurons in the l/vlPAG triggers robust spontaneous scratching and grooming behaviors (Gao et al., 2019). This evidence suggests that unnatural grooming behavior is probably an accompanied behavior of itch-induced scratching behavior and could, to some extent, be considered a derivative of the latter. Pain is also closely associated with grooming behavior in rodents. Grooming is one kind of surrogate behavior that is used to indirectly assess painful states, which can be achieved through the grooming transfer test (Turner et al., 2019) and facial grooming method (Liu et al., 2023). Despite aforementioned evidence, it is worth noting that, in rodents, itch behavior is distinct from pain or grooming (Meixiong and Dong, 2017). Moreover, abnormal grooming behavior is also reported in a rodent model of some other neurodegenerative diseases (Glynn et al., 2005; Bubeníková -Valesováet al., 2006) and even cancers such as gastric cancer (Heideman et al., 2004; Song et al., 2010). It is disclosed that female severe combined immune-deficient mice inoculated intraperitoneally with human gastric cancer cells develop peritoneal tumors and exhibit poor grooming behavior (Song et al., 2010). Collectively, this evidence suggests that grooming behavior is an available and useful measurement for modelling various neurodegenerative disorders and even other diseases including cancers, and also for uncovering corresponding pathobiological mechanisms.

5 Perspectives and concluding remarks

Although great advances have been made in understanding the neurobiology of grooming behavior in the past few decades, much more work is still warranted, given the high level of behavioral complexity and organization of this evolutionarily conserved behavior. Several key research questions remain to be addressed: (1) How can we develop more automated paradigms/platforms to analyze grooming behavior in a more precise, objective, and efficient way? (2) What are the exact neuromorphological endophenotypes of corresponding brain regions under both normal and aberrant grooming behaviors? (3) How do environmental factors interact with genes specifically pertaining to grooming behavior? (4) What are the potential associations between the distinctly paralleled neural circuits responsible for grooming behavior? (5) How do we apply large-scale bioinformatics and pathway analyses to study the complex grooming microstructure?

Research on rodent grooming behavior, especially dissecting the neural substrates responsible for this evolutionarily conserved behavior, has provided valuable information on the pathophysiology of some neuropsychiatric disorders and neurodegenerative

diseases and, therefore, has great value for translational psychiatry. In the future, it will be very helpful to develop more rodent models of grooming that could be easily manipulated, allowing for a thorough examination of human-related diseases and the underlying mechanisms. Meanwhile, conducting more elaborate investigations on neural circuitries, genetic determinants, and associated molecular pathways pertaining to grooming behavior from different viewpoints, using a combination of multiple cutting-edge techniques, will undoubtedly provide important insights into how complex behaviors are regulated by the brain under both normal and pathological conditions.

Data availability statement

All data supporting the findings of this study are available within the paper.

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Author contributions

Yiqun YU, Zhenshan WANG, and Yun-Feng ZHANG designed and supervised the project. All authors were involved in collecting related references, drafting subsections individually/cooperatively, and preparing the manuscript. Guanqing LI and Chanyi LU were involved in organizing the manuscript and engaged in the preparation of all subsections. Miaomiao YIN, Peng WANG, Pengbo ZHANG, Jialiang WU, and Wenqiang WANG took charge of subsections 1 and 2. Ding WANG, Mengyue WANG, Jiahan LIU, and Xinghan LIN works on subsections 3 and 4. Jianxu ZHANG works on subsection 5 and cooperated with other authors to modify the table and the figure. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Guanqing LI, Chanyi LU, Miaomiao YIN, Peng WANG, Pengbo ZHANG, Jialiang WU, Wenqiang WANG, Ding WANG, Mengyue WANG, Jiahan LIU, Xinghan LIN, Jian-Xu ZHANG, Zhenshan WANG, Yiqun YU, and Yun-Feng ZHANG declare that they have no conflict of interest.

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