Professor John C. Fentress (1939–2015) passed away suddenly after this manuscript was initially submitted. The remaining authors dedicate this Review to him as a tribute to a brilliant scientist, good friend and a true pioneer of neurobiology research.

Self-grooming in animals is an innate behaviour that is involved in hygiene maintenance and other physiologically important processes, including thermoregulation, social communication and de-arousal[1–6]. It is one of the most frequently observed behaviours in awake rodents and has a patterned, sequential organization with characteristic cephalocaudal progression[7–11] (FIG. 1). Self-grooming is remarkably similar across species in several taxa[1–5]. Humans engage in self-grooming, and this behaviour shows some similarity to that seen in other animals[12,13]. However, human self-grooming behaviour can become pathological, for example, during stressful conditions or in certain neuropsychiatric disorders[7–11,14,15].

The assessment of rodent self-grooming is potentially useful for translational neuroscience research, as aberrant rodent self-grooming can be related to human disorders in which abnormal self-grooming is a symptom. However, it is important to note that animal self-grooming cannot be considered an exact model of any particular human pathology. Rather, the broader value of rodent self-grooming is as a model of complex repetitive, self-di-

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series of individual movements that form functional sequences, including highly stereotyped patterns[9] (FIG. 1a). In the first postnatal days, rodent self-grooming behaviour targets the face and consists of either temporally isolated grooming strokes with the front paws or bouts of strokes with varying amplitude and symmetry. During the following weeks, self-grooming behaviour develops to include symmetrical, double-handed lower amplitude movements and finally matures into the species-typical sequencing of short and long symmetrical and asymmetrical strokes[10]. Thus, in such early stages of development, self-grooming consists of facial grooming alone, but over time comes to include grooming of the entire head, neck and trunk. In addition to displaying the stereotyped grooming that is also present in young animals, adults show more flexible, less stereotyped facial grooming movements[10].

Mature rodent grooming behaviour consists of specific and highly stereotyped patterns of sequential movements, known as a syntactic chain pattern[7], which often occurs during the transition between facial and body grooming (FIG. 1a,b). Syntactic chains of self-grooming have features similar to those of other fixed-action patterns, such as sexual or aggressive behaviours, in that they are highly stereotyped in order, and, once begun, they proceed to completion without requiring sensory feedback[7]. A typical self-grooming syntactic chain in rodents, which is often embedded in other forms of grooming behaviours, serially links 20 or more grooming movements into four distinct, predictable phases that follow the same cephalocaudal (head-to-body) rule[9,29]. The serial structure of such chains is repetitive and consistent in terms of order and time, so that once the first phase begins, the entire remaining sequential pattern reliably continues through all four phases. This syntactic chain pattern accounts for approximately 10–15% of all observed self-grooming behaviours in rodents, the remainder of which follow less predictable sequential patterning rules (FIG. 1; see Supplementary information S1 (movie))[7]. Self-grooming sequencing, chain initiation and chain completion in rodents can be bidirectionally affected by experimental manipulation, including lesions of the dopamine-containing nigrostriatal tract, administration of various dopaminergic drugs, genetic mutations and psychological stress[7]. The syntactic chains are usually interspersed with more flexible 'non-chain' grooming (that is, flexibly ordered mixtures of strokes, licks or scratches that are not components of syntactic chains), which accounts for approximately 85–90% of all grooming behaviours[7] (see Supplementary information S2 (movie)). Ethologically based analyses of grooming behaviours, including both chain and non-chain bouts, are widely used in neurobiological research to assess their global adherence to the cephalocaudal rule[7]. Correct and incorrect cephalocaudal transitions between stages can be studied in this way (FIG. 1c), along with interruptions in grooming bouts (as an index of disturbed self-grooming) and their regional distribution over the body[7,28,30]. Such analyses demonstrate the high sensitivity of grooming sequencing to genetic, pharmacological and psychological challenges[7,27,28,30–33].

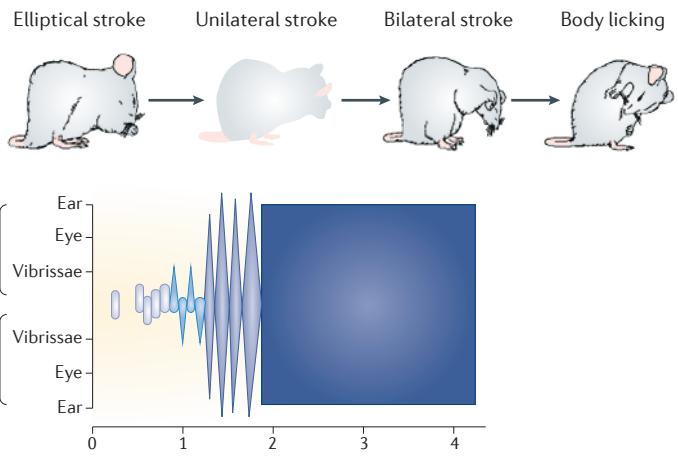
Neural circuitr of self-grooming. Because of its highly patterned nature, grooming is particularly suitable for studying how various neural circuits regulate both the key aspects — motor and sequencing — of this behaviour[34]. Studies of rats decerebrated at successively lower levels of the neuraxis have demonstrated that rats that underwent mesencephalic decerebration, in which the midbrain is intact, have a normal sequential pattern of self-grooming chains, although such animals have difficulty in completing the full pattern[35,36]. By contrast, a gradual degradation of the sequential pattern itself is seen in rats that have been decerebrated at more caudal (that is, metencephalic and myelencephalic) levels, suggesting that the brainstem circuitry is necessary for the execution of fully patterned grooming sequences[35,36] (FIG. 2).

Within the forebrain, circuits that incorporate the basal ganglia and allied nuclei, including the striatum, globus pallidus, substantia nigra, nucleus accumbens and subthalamic nucleus, have been strongly implicated in hierarchical motor control and sequencing of behaviour, including self-grooming. The striatum is the main input region of the basal ganglia. Striatal circuits are involved in learning, motivation and motor sequencing. For example, the basal ganglia[37,38] and, in particular, the striatum, are required for the execution of full sequential patterns of grooming chains and other types of sequential behaviour in mice and rats[18,39,40] (FIG. 2). Lesions of the striatum result in a permanent deficit in the ability to complete sequential syntactic self-grooming chains[34] (FIG. 1b). Extensive work using localized striatal lesions has shown that it is the anterior dorsolateral region of the striatum that is essential for this normal grooming behaviour. Damage to this striatal region impairs the completion of (but not the ability to initiate) syntax patterns of grooming movements[34]. Rats with such striatal lesions completed only ~50% of the syntactic chains, a completion rate that is similar to that of rats with full mesencephalic decerebration (that is, transection above the midbrain)[34], whereas control rats completed ~90% of the chains. Thus, similar deficits of pattern completion are produced by anterior dorsolateral striatal lesions and by decerebration, but both mesencephalic and pontine decerebrates can still produce the basic sequential self-grooming pattern[34].

Fixed-action patterns
Instinctive species-specific behavioural sequences that, once begun, run to their completion.

Basal ganglia
A group of subcortical nuclei involved in motor control, motivation and organizing movements into behavioural sequences.

a


Elliptical stroke
Unilateral stroke
Bilateral stroke
Body licking
Ear
Eye
Vibrissae
Right
Midline
Vibrissae
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1
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3
4

b

c

and the hypothalamus[53,54]. Nuclei of the amygdala, most notably the MeApd (that is implicated in self-grooming[52]), also project to the medial hypothalamus[47]. Finally, the hypothalamic–pituitary system has now been implicated in the modulation of self-grooming, as several hypothalamic and pituitary hormones (including the stress-related peptides corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH)) are known to induce self-grooming[55–58] (see Supplementary information S3 (table)). The effects of these hormones on grooming are partly dependent on the mesolimbic dopaminergic system[59–61] (as we emphasize below). Collectively, this evidence indicates that the hypothalamus (and its connections to the pituitary) is an important brain region that incorporates neural and endocrine regulation of self-grooming[2,62].

Pharmacological modulation of self-grooming. Pharmacological manipulations can potently modulate rodent self-grooming. Dopamine, which is a major modulator in the nigrostriatal and mesolimbic systems, is critical for locomotor function, self-grooming and other complex patterned behaviours[29,34,40,44]. In rodents, systemic administration of dopamine D1 receptor (D1) agonists amplifies complex behavioural super-stereotypy, leading both to excessive production of self-grooming chains, and to more rigid self-grooming chains[8,63,64]. Systemic co-administration of the dopamine D2 receptor (D2) antagonist haloperidol prevents sequential super-stereotypy that is induced by the D1 agonist SKF38393 (REF. 64), and the activation of grooming by SKF83959, a D1 agonist and D2 partial agonist, is eliminated in knockout mice lacking the D1 (but not the D2) gene[65]. Collectively, these results illustrate the importance of a balance between the D1 and the D2 systems of the striatum in the regulation of self-grooming.

Striatal circuits can also be characterized in terms of the compartmental architecture of the striatum. Within the striatum of humans and other mammals, chemically specialized macroscopic zones known as striosomes ('striatal bodies') form a distributed labyrinthine system within the large volume of the striatum that constitutes the extra-striosomal matrix. This architecture is known as the striosome-matrix architecture, which governs the distribution of nearly all neurotransmitters and their receptors as well as the relative distributions of projection neurons and interneurons in the striatum[66]. Studies have shown that, following dopaminergic challenge, striosomes are strongly activated and express early response genes that code for transcription factors, and that this heightened striosomal activation is highly correlated with increased repetitive behaviours, including self-grooming, in both non-human primates and rodents[42,67–70].

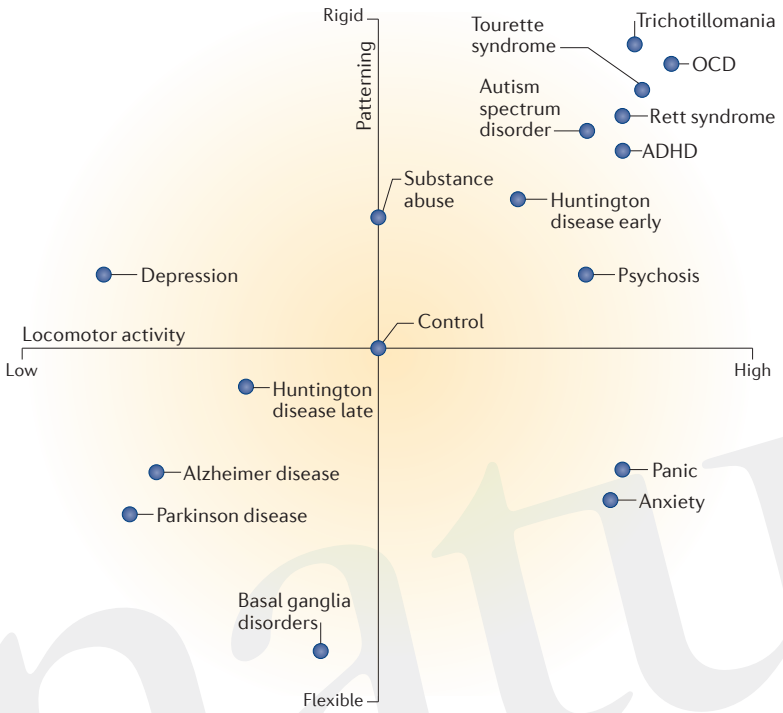
Pharmacological studies have shown that glutamate is also involved in the regulation of self-grooming[71]. For example, the systemic administration of anti-glutamatergic agents, such as an NMDA receptor antagonist phencyclidine (PCP), is a well-established experimental method for inducing grooming in rodents[72]. In addition, PCP induces generalized hyperlocomotion and other stereotypic behaviours in rodents[73–75]. Notably, although PCP increases the duration of experimentally evoked self-grooming, it disrupts the sequencing of self-grooming only when the animals are under stress[72], further indicating that self-grooming activity and its detailed patterning are controlled differently by the CNS.

GABAergic neurotransmission also contributes to the regulation of self-grooming. Drugs that enhance GABAergic tone, such as benzodiazepines and allopregnanolone, generally reduce rodent self-grooming at non-sedative doses[76–78]. By contrast, GABA-inhibiting drugs often increase grooming in rodents and can also reverse the anti-grooming effects that are produced by GABA-enhancing agents[76,77]. The GABAergic system is also a key modulator of stress and anxiety-related behaviours in rodents[32,79]. Drugs that enhance GABAergic tone exert anxiolytic effects and may be useful as augmentation agents for the treatment of obsessive compulsive disorder (OCD)[80]. Thus, these GABA-enhancing drugs and other anxiolytic drugs may suppress stress-induced grooming through attenuating the intensity of the perception of anxiogenic stimuli[81], as anxiety-like states alter rodent self-grooming and its sequencing[28,30,82]. The cephalocaudal patterning of rodent self-grooming is sensitive to GABAergic drugs: drugs that inhibit GABA signalling generally disorganize cephalocaudal patterning and drugs that enhance GABA signalling tend to normalize this response[32,76,83].

Given the ubiquity of GABA and glutamate in the CNS, region-specific manipulations are required to provide further insights into their role in grooming. For example, the injection of the GABA type A receptor ($GABA_A$) agonist zolpidem into the hamster CeA did not affect orexin B-evoked grooming behaviour, whereas co-infusion of an NMDA receptor agonist potentiated the effect of orexin B[49]. Injection of the $GABA_A$ agonist muscimol into the BNST (but not into the BLA) strongly reduced the self-grooming response that is evoked by cat urine exposure[81]

Ventral tegmental area
A midbrain region (implicated in reward, anxiety and aversion) that contains the dopaminergic cell bodies of the mesocorticolimbic system.

Research domain criteria
(RDoC). A strategy in translational mental health research that aims to explore the basic mechanisms of brain deficits to understand symptom sets that are observed across multiple disorders.



Aberrant self-grooming is observed in animal models of several neuropsychiatric disorders, but each disease model is expected to have distinct grooming phenotypes. Shown are the expected rodent self-grooming phenotypes relevant to particular disease models. The x-axis represents the amount of self-grooming activity that can be assessed as ranging from low frequency to high frequency, or from short to long duration, and the y-axis represents the degree of sequential patterning, ranging from rigid and repetitive to more flexible behaviour[7]. The expected behaviour of a wild-type control animal with normal self-grooming behaviour is shown at the centre. In this diagram, a 'rigid' patterning of rodent grooming, based on high adherence to the cephalocaudal progression of grooming sequence (FIG. 1), will be maximal for the stereotyped 'chain' grooming. By contrast, 'flexible' patterning denotes frequent deviations from the cephalocaudal rule, and will be maximal in 'non-chain' grooming. For example, *Sapap3* mice, which display an obsessive compulsive disorder (OCD)-like phenotype, spend more time self-grooming, and their self-grooming behaviour is highly repetitive, compared with wild-type control mice[40]. Rodent models of anxiety (such as stress-exposed rats or mice treated with anxiogenic drugs) also display an increase in the amount of time spent grooming, but patterning of their self-grooming is impaired (see REFS 7,32 for examples). By contrast, animal models of Alzheimer disease and Parkinson disease are likely to show global progressive deficits in their grooming owing to motor impairments (for example, see REF. 160). Note that in animal models of Huntington disease, self-grooming is increased in the early stages of the animal model (see REFS 162,167 for examples), but progressive ataxia and global motor deficits (and thus decreased self-grooming) are likely to be observed at later stages, paralleling the clinical trajectory of Huntington disease. ADHD, attention deficit hyperactivity disorder.

(RDoC)[87,88], we take a dimensional approach and discuss the dysregulation of rodent self-grooming and its value for modelling dimensions of human psychopathology that may cross traditional diagnoses.

Autism spectrum disorder. Autism spectrum disorder (ASD) is a neurodevelopmental disorder with CNS aetiology and complex symptoms, including difficulties with communication, repetitive behaviours and social deficits[89–92]. There is considerable interest in developing experimental animal models of ASD[90,91,93]. Because self-grooming episodes in rodents are thought to recapitulate pathological repetitive behaviours (behavioural perseveration), strains of rodents that exhibit these phenotypes have been investigated, with the goal of identifying neural circuits and genes relevant to ASD[33,90,94]. We discuss rodent self-grooming as a measure of behavioural perseveration rather than as a specific model of an ASD phenotype. Notably, many of the mouse strains discussed here also display other phenotypes that are relevant to ASD (for example, they also show non-grooming behavioural perseverations and/or deficits in other relevant domains, such as social impairments and anxiety).

The inbred BTBR $T^{+}Itpr3^{tf}$/J (BTBR) mouse strain, which exhibits agenesis of the corpus callosum, displays several aberrant behaviours that resemble symptoms of ASD, including social deficits, anxiety and general behavioural inflexibility[19,95,41–43]. Peer rearing with a different ('non-ASD') strain improved social deficits in BTBR mice but did not improve their repetitive self-grooming[96], raising the possibility that different ASD behavioural domains may be regulated by distinct brain mechanisms. However, increased self-grooming in these animals can be corrected pharmacologically. For example, cholinergic agents (which may be useful in correcting postulated cholinergic deficits in ASD[97,98] and/or some of its clinical symptoms[99]) reduce self-grooming[19] and other ASD-like behaviours[100] in BTBR mice. Furthermore, repetitive self-grooming behaviour in BTBR mice is rescued by the inhibition of glutamatergic metabotropic mGluR5 receptors[90,101] and by the stimulation of NMDA receptors by D-cycloserine[102] (which has also been shown to ameliorate some behavioural deficits in individuals with ASD[103,104]). Environmental enrichment reduces the duration, but not the rigid patterning, of abnormal self-grooming in BTBR mice[33]. The ability to modulate the quantity (amount) and the quality (degree of sequencing) of self-grooming in these mice by distinct interventions raises the possibility that there are also distinctions between these different aspects of self-grooming behaviour at the level of circuits and molecular pathways. Consistent with the goal of defining psychiatric diseases as circuit disorders[105,106], this work further emphasizes the value of a nuanced understanding of grooming phenotypes, including self-grooming, in preclinical biological psychiatry research.

The genetic mechanisms underlying ASD have been unclear to date, owing to its highly polygenic nature. Currently, the number of genes associated with ASD is estimated to be ~700, according to the Simons Foundation Autism Research Initiative gene database. Individuals with ASD have heterogeneous behavioural and neuromorphological phenotypes[91,106–109]. Three examples are used here to illustrate how assessing self-grooming in transgenic mice can be useful in investigating the role of particular genes associated with autism. *SHANK1* (SH3 and multiple ankyrin repeat domains 1), *SHANK2* and *SHANK3* encode postsynaptic scaffolding proteins that are crucial for synaptic function in the brain[110], and mutations in these genes are strongly implicated in ASD. In addition to exhibiting ASD-like social

Behavioural perseveration
The repetition of a specific behaviour that becomes inappropriate in the absence of behaviour-evoking stimuli.

Table 1 |

Dat1$^{-/-}$ mice	Increased stereotypy	29
Drd1a mice	Increased frequency and disrupted sequencing	148
Hoxb8 mice	Excessive self-grooming	17,25
Sapap3 mice	Increased frequency and duration*	,40,
Shank1 and *Shank1* mice	Increased duration	21
Shank2 mice	Partially increased in females (lacking exon 7) and in males (lacking exons 6 and 7)	16,112
Shank3 and *Shank3* mice	Mildly increased duration	88,106,107
Syn2 mice	Increased duration	22
Hdc mice	Increased duration	150
Vdr mice	Increased duration and disrupted sequencing	,158
Astrocyte-specific inducible *Glt1* mice	Increased duration	85
Striatum-specific *Gad1* mice	Increased duration	118
MAO-A^{Neo} mice	Increased frequency and duration	192
BTBR mice‡	Increased duration and repetition	19, ,94
RLA rats	Increased duration	159, ,194
LY and HY rats	Different patterning in HY rats compared with LY rats	195,196

Dat1, dopamine transporter; *Drd1a*, dopamine receptor 1A; *Gad1*, glutamic acid decarboxylase 1; *Glt1*, excitatory amino acid transporter 2; *Hdc*, histidine decarboxylase; *Hoxb8*, homeobox protein Hox-b8; HY, selectively bred high-yawning rats; LY, selectively bred low-yawning rats; MAO-A, monoamine oxidase A; RLA, selectively bred Roman low avoidance rats; *Sapap3*, *Shank* *Syn2*, Synapsin II; *Vdr*

*Phenotype can be reversed by genetic deletion of the gene encoding melanocortin 4 receptor, or by optogenetic stimulation

‡Different self-grooming activity is observed across different mouse strains

[27,197,198].

deficits and repetitive behaviours, mice with mutations in different *Shank* genes show aberrant self-grooming phenotypes[111] (TABLE 1). For example, *Shank1*$^{+/-}$ (and, to a lesser extent, *Shank1*$^{-/-}$) mice demonstrate mildly increased self-grooming behaviour as adults, but not as juveniles[21]. Female, but not male, *Shank2*$^{-/-}$ mice lacking exon 7 show increased duration of self-grooming bouts[16], and male *Shank2*$^{-/-}$ mice lacking exons 6 and 7 spend more time engaged in self-grooming during a novel object recognition (but not during the open field) test[112]. Increased duration of self-grooming bouts in *Shank3*$^{-/-}$ mice has also been reported by several groups[89,113,114]. Taken together, these findings establish a link between disruptions in *Shank* genes, aberrant synaptic function in the brain and ASD-related behaviours in mice[88,106,107,111], suggesting the *Shank*-mutant mice, and their self-grooming phenotypes in particular, are good models of ASD.

Ephrin A ligands and ephrin A receptors are strongly implicated in neurodevelopment[115]. Ephrin A ligands are membrane-anchored cellular proteins that bind to ephrin A receptors, members of the receptor tyrosine kinase superfamily. During development, ephrin A-mediated signalling modulates neuronal differentiation and synaptic plasticity[115]. Because ASD is a neurodevelopmental disorder, ephrin A ligands and their receptors may be relevant to ASD and modelling its pathogenesis in animals[115]. For example, mice that lack both the ephrin A2 and the ephrin A3 receptors display robust repetitive self-grooming in addition to motor retardation, increased prepulse inhibition and social deficits (impaired social interaction and preference), thereby paralleling in their phenotypes some of the clinical symptoms of ASD[115]. The search for novel molecular anti-ASD drug targets is a recognized priority[19,93,106,116,117], and the utility of grooming-based analyses for exploring novel candidate pathways of this disorder (for example, ephrin A receptor agonists) continues to emerge.

Another example of rodents with specific mutations displaying an aberrant self-grooming phenotype are mice lacking the GABA-synthesizing enzyme glutamate decarboxylase 1 (GAD1; also known as GAD67) in striatal neurons. These mice display behavioural abnormalities that resemble symptoms of ASD, including stereotypic grooming and impaired spatial learning and social behaviour[118], suggesting that GABAergic output from the striatum might contribute to behavioural deficits in ASD[118].

A deletion on human chromosome 16p11.2, spanning approximately 30 genes, is associated with ASD and other neurodevelopmental disorders[119–121]. Notably, mice heterozygous for a deletion of the syntenic region on chromosome 7F3 (16p11$^{+/-}$ mice) show reduced self-grooming behaviour, but the mice also display hyperactivity and behavioural perseverations, such as increased circling[108]. 16p11$^{+/-}$ mice also have increased numbers of striatal medium spiny neurons expressing the dopamine D2 receptor, fewer cortical neurons expressing

Table 2 |

OCD	Compulsive hand washing	Increased self-grooming	,
Trichotillomania	Compulsive hair pulling	Increased self-grooming	128,199
Body dysmorphic disorder	Obsessive cosmetic grooming	Increased self-grooming	92
Excoriation	Compulsive skin-picking	Increased self-grooming	92
ASD	Behavioural perseveration	Increased self-grooming	16,19–22,
Tourette syndrome	Tics	Increased self-grooming	29
Anxiety disorders and panic disorder	Stress-induced displacement behaviour	Increased self-grooming	7,27, ,158
Schizophrenia	Hyperarousal	Increased self-grooming	92
Trichotillomania	Compulsive hair-pulling	Increased self-barbering*	27,45
ASD	Behavioural perseveration	Grooming patterning rigidity	89–91
Depression	Behavioural perseveration	Grooming patterning rigidity	92
Anxiety disorders and panic disorder	Hyperarousal	Disrupted grooming patterning	27,28,159
Basal ganglia disorders	Impaired action sequencing	Disrupted grooming patterning	64
Depression	Anhedonia and poor hygiene	Reduced grooming activity	92
Neurodegenerative disorders	General decline in motor function	Reduced grooming activity	160

ASD, autism spectrum disorder; OCD, obsessive compulsive disorder. *Self-inflicted hair and whisker loss frequently seen in laboratory rodents in different contexts[126]. This grooming-related behaviour is an important rodent phenotype sensitive to various environmental and genetic manipulations (see Supplementary information S4 (table)).

D1 dopamine receptors, and synaptic defects indicating abnormal basal ganglia circuitry[108]. The behavioural phenotype of these mice is of particular note, because the decreased self-grooming is observed alongside increased non-grooming stereotypies[108], thereby suggesting further distinctions between the activity and patterning aspects of grooming (see TABLE 1 and Supplementary information S4 (table) for more information on genetic models of mouse self-grooming). Finally, studying self-grooming improves the development of animal models of ASD, because when other ASD-like phenotypes are present, the co-occurrence of a self-grooming phenotype as a measure of repetitive behaviour considerably strengthens the validity of the models.

Disorders of the basal ganglia. Excessive self-grooming is a feature of some forms of OCD[24,86] and related illnesses, such as body dysmorphic disorder, excoriation (compulsive skin-picking) and trichotillomania (compulsive hair-pulling)[92]. Studying aberrant self-grooming in rodents may therefore be relevant to modelling such conditions, and may also be useful for modelling the OCD-spectrum disorders that, although they are not associated with abnormal self-grooming, are characterized by excessive repetitiveness of behavioural actions[122,123].

OCD is a common heterogeneous psychiatric disorder that is characterized by obsessions and compulsions[124,125]. Obsessions are intrusive, recurrent and persistent unwanted thoughts, and are often associated with elevated anxiety[124,125]. Compulsions include a range of repetitive behaviours or thoughts. A conventional view is that these are performed to relieve obsessions[124], but this link between obsessions and compulsions is not certain. Compulsions are sometimes focused on aspects of personal hygiene, which can involve self-cleaning or self-grooming behaviours (such as hand-washing), and behaviours to avoid perceived contamination from the individual's surroundings[44,86]. Evidence from studies of individuals with OCD syndromes, including neuroimaging and clinical genetics, and from studies of a wide range of animal models of repetitive behaviour[68], has suggested that basal ganglia-related circuit dysfunction contributes to these syndromes.

A growing number of genetic mutations have been shown to affect self-grooming behaviour in rodents[68] (TABLE 1; see Supplementary information S4 (table)). Some of these may be useful in modelling self-grooming-related symptoms of OCD, including compulsive hand-washing[19,22,25] and obsessive hair-pulling[126–128,129] (TABLE 2). For example, serotonergic drugs that are effective in treating some symptoms of clinical OCD[71] are also successful in reducing aberrant self-grooming phenotypes in some of these mutant mice (TABLE 3). Such findings support the value of rodent self-grooming behaviours in mimicking human OCD. They also raise the possibility that the serotonergic system contributes to the regulation of normal and pathological grooming in both humans and rodents. Although direct support for this notion remains elusive[71], clinical and experimental evidence continues to implicate serotonergic function in various OCD-like symptoms[130–136].

Mutations in *SAPAP3*, which encodes synapse-associated protein 90/postsynaptic density protein 95-associated protein 3, have been implicated, though only weakly,

Stereotypies
Repetitive behaviours involving an abnormal or excessive repetition of a behavioural action in the same way over time.

in OCD and self-grooming disorders, such as pathologic skin picking, nail biting and hair pulling[122,137,138]. SAPAP3 binds to SHANK3, another postsynaptic scaffolding protein that, as discussed above, is linked to ASD[44]. In rodents, SAPAP3 is primarily expressed in neurons in the striatum — a key brain region that is involved in the control of self-grooming. *Sapap3*$^{-/-}$ mice display robust increased self-grooming that is rescued by the re-expression of *Sapap3* in the striatum[40,139]. Because *Sapap3* is expressed in striatal glutamatergic synapses, these findings suggest that excitatory neurotransmission in this region is important for the regulation of normal self-grooming behaviour[139]. Interestingly, although *Sapap3* deletion reduces corticostriatal synaptic transmission, it does not affect thalamostriatal activity[139], providing an excellent opportunity to use the abnormal grooming phenotype of the *Sapap3*$^{-/-}$ mice to dissect the role of thalamostriatal versus corticostriatal circuits in mediating excessive repetitive behaviours in individuals with OCD. The over-grooming phenotype observed in the *Sapap3*$^{-/-}$ mice can be rescued by optogenetic stimulation of the corticostriatal pathway originating in the orbitofrontal cortex[39,68,140,141]. The mechanism underlying this rescue seems to involve striatal high-firing interneurons (that are impaired in this genetic mouse model), directly implicating intrastriatal network activity in the aetiology of the compulsive grooming behaviour. Furthermore, repeated daily stimulation of a nearby part of the orbitofrontal cortex in wild-type mice can evoke a prolonged increase in self-grooming behaviour[15]. These results emphasize the importance of corticostriatal circuits, and potentially intrastriatal microcircuits, in the control of self-grooming in rodents, which may also be relevant to modelling compulsions in individuals with OCD.

Tourette syndrome is another common, highly heritable, childhood-onset neuropsychiatric disorder that is characterized by motor and phonic tics[114,142,127]. This syndrome is frequently comorbid with OCD and attention deficit hyperactivity disorder (ADHD), and can be accompanied by affective disorders, such as anxiety and depression[92,143]. Albeit related to OCD and grooming disorders (such as trichotillomania), Tourette syndrome differs from them genetically and phenotypically[142,144–146]. Owing to its complex repetitive nature, rodent self-grooming behaviour is a logical phenotype to investigate in putative models of Tourette syndrome[29], especially given that the nigrostriatal dopaminergic system has been implicated in sequential stereotypy of behaviour, which manifests itself as inflexible actions or stereotyped 'rigid' thought in individuals with OCD, individuals with Tourette syndrome, or individuals with both OCD and Tourette syndrome. Therefore, rodents with abnormal dopaminergic signalling can be good candidates for modelling aspects of these disorders[29,147].

Dopamine transporter (DAT)-deficient mice, which have elevated levels of dopamine, exhibit more stereotyped and predictable syntactic grooming sequences than their wild-type counterparts, with fewer disruptions of syntactic patterns and a sequential 'super-stereotypy' in the complex fixed-acnt B(h)4(e 4.6(b)12.4(i)AD 19 4.6(9Tc 0 T y

Tics
Sudden, repetitive, involuntary movements or vocalizations with varying intensity and frequency.

weaver (*wv/wv*) mouse possesses a naturally occurring mutation in the *Girk2* gene that encodes a G protein-activated inwardly rectifying potassium ion channel[30,31]. This mutation markedly affects cerebellar and striatal pathways[151–154] (crucial for motor performance), resulting in an aberrant self-grooming phenotype that consists of more frequent, but shorter, grooming bouts with smaller forelimb strokes and less complete sequences[30,31]. Because they display deficits in the two critical CNS circuits, the context- and age-specific neurological defects in *wv/wv* mice provide a useful tool for examining how the two systems control self-grooming during development[155]. For example, although the mutant mice initially spend less time self-grooming, after day 15 they initiate more

Displacement
Behaviour that is seemingly irrelevant to the context, which is displayed during a conflict of motivations or when the animal is unable to perform an activity for which it is motivated.

Krabbe disease
(Also known as globoid cell leukodystrophy). A rare, fatal neurodegenerative disorder that is due to genetic defect causing aberrant brain myelination.

cortex-ventromedial striatum pathway in mice can trigger pathological self-grooming that lasts for weeks, a condition that can be reversed by the chronic administration of the selective serotonin reuptake inhibitor fluoxetine[15]. Stimulating the nearby orbitofrontal cortex (or its intrastriatal terminals) can block compulsive self-grooming in *Sapap3*$^{-/-}$ mice[39]. These findings are important, as they provide strong experimental evidence for circuit-level control of repetitive episodes of grooming. Optogenetic approaches to modulate grooming cannot yet be translated to the clinic, but these studies suggest that future circuit modulation methods may become valuable therapeutic tools in the treatment of disorders that are associated with repetitive behaviour[39].

In-depth analyses of self-grooming behaviour are now an important part of behavioural phenomics (BOX 1). Several automated tools are currently available for both quantity-based and patterning-based studies of grooming phenotypes in laboratory rodents (see also REFS 95,185; Supplementary information S5 (figure)), and their future refinement is expected to contribute to progress in this field.

Given the established role of dopamine-containing neurons in movement initiation and sequencing, the regulation (and dysregulation) of the dopaminergic system in numerous brain disorders will be of particular interest for further study[8,148]. For example, future research may examine larger networks of molecular interactors that are related to dopaminergic genes (genes encoding proteins that directly control dopamine signalling and metabolism, cytoskeletal processes, synaptic release, Ca^{2+}, adenosine, and glutamatergic and GABA signalling), evaluate the role of these genes in rodent self-grooming behaviour, and relate these findings to the genes that have been implicated

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Thi paper de cribe he fir cce f l applica ion of a oma ed beha io r-recogni ion pro ocol o q an if roden elf-grooming beha io r and heir eq en ial micro r c re, and empha i e he al e of grooming anal e in high- hro ghp roden pheno ping.
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Ackno ledgemen
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Compe ing in ere
The authors declare no competing interests.

DATABASES
Simons Foundation Autism Research Initiative gene database

SUPPLEMENTARY INFORMATION
S1 (movie) | S2 (movie) | __ (table) | S4 S5 (figure)

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John C. Fentress (1939–2015) was the Chair Emeritus of the Psychology Department at Dalhousie University, Canada, and the Past President of the Animal Behaviour Society. He dedicated over 50 years of his research career to studying the neurobiology of complex behaviours in both animals and humans. His pioneering work with M. F. Stillwell and K.C.B. from the 1970s onwards described the ontogeny, behavioural complexity and neural regulation of rodent grooming.

Key points

- Self-grooming is an evolutionarily conserved complex innate behaviour that has a role in hygiene maintenance and other physiological functions. Self-grooming is the most frequently occurring awake behaviour in laboratory rodents.
- Self-grooming is an important phenotype to study in translational neuroscience, as it may allow the modelling of human diseases that have symptoms similar to, and/or share pathogenetic mechanisms with, aberrant grooming in rodents.
- Analysing animal self-grooming also has a broader value in the study of neurobiology underlying complex repetitive behaviours, which may be disrupted in certain neurological diseases.
- In this Review, we discuss the neurobiology of grooming, including its underlying circuitry, genetic mechanisms and pharmacological modulation.
- We also highlight studies of rodent self-grooming behaviour in models of neuropsychiatric disorders that suggest that it is valuable asset for clinical and translational neuroscience research, including the identification of neural circuits that control complex patterned behaviours.
- These findings suggest that the study of rodent self-grooming has multiple implications for translational neuroscience, which may extend beyond understanding the self-grooming behaviour itself.

TOC blurb

Allan V. Kalueff, Adam Michael Stewart, Cai Song, Kent C. Berridge, Ann M. Graybiel and John C. Fentress

Rodents spend a large proportion of their waking time engaged in self-grooming behaviour. In this Review, Kalueff and colleagues describe the characteristics and underlying neural circuitry of rodent self-grooming, and discuss its use as a measure of repetitive behaviour in models of psychiatric disease.

Subject categories

Biological sciences / Zoology / Animal behaviour [URI /631/601/18]
Biological sciences / Neuroscience / Diseases of the nervous system / Autism spectrum disorders [URI /631/378/1689/1373]
Biological sciences / Neuroscience / Motor control / Basal ganglia [URI /631/378/2632/1323]

Techniques terms

Life sciences techniques, Experimental organisms [Transgenic mice]
Life sciences techniques, High-throughput screening [Laboratory automation]

Supplementary information

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