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Of pride and groom: The gains and limits of studying the neuroanatomy of rodent self-grooming in translational research

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1 Preview Article, Neuron

2 On Xie et al., « A brain-to-spinal premotor circuit for repetitive self-grooming”

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13 **Title**

14 Of Pride and Groom: The gains and limits of studying the neuroanatomy of rodent
15 self-grooming in translational research

16

17 **Abstract**

18 In this issue of Neuron, Xie et al. (2021), characterize a cell-specific premotor circuit,
19 generating rhythmic orofacial forelimb movements. The authors show that neurons of
20 the caudal part of spinal trigeminal nucleus, expressing Cerebellin-2, are necessary
21 and sufficient for triggering forelimb movements, which form a part of rodent self-
22 grooming.

23

24 **Main text**

25 Self-grooming is an evolutionarily conserved behaviour in animals, which is important
26 for physiologically relevant processes including hygiene maintenance. In rodents, self-
27 grooming is organized into a syntactic cephalocaudal sequence of multiple grooming
28 phases, including an initial orofacial grooming phase (Kalueff et al., 2016). This
29 complex sequential patterning of rodent self-grooming makes it an excellent phenotype
30 for studying neural mechanisms of hierarchical motor control in health and disease.
31 Indeed, in recent years, rodent self-grooming has resurfaced and gained in importance
32 as a behavioural readout in animal models of human neuropsychiatric conditions,
33 which are characterized by pathological repetitive behaviours such as e.g. compulsive
34 behaviours. Distortions of the highly stereotyped syntactic chaining of grooming
35 phases, alterations in the number of chain initiations or chain completions need to be

36 finely characterized in order to understand the contribution of various brain areas to
37 the generation of hierarchically structured complex behaviours. The lion's share of
38 studies focuses on cortico-basal ganglia circuits as key players for generating complex
39 syntactic behaviours, in particular the striatum for the execution of sequential patterns
40 of grooming chains (Kalueff et al., 2016).

41 In this issue, Xie and colleagues complement our insights into the neurobiology of
42 rodent self-grooming by shifting the focus into the medulla and investigating orofacial
43 self-grooming at its sensorimotor edges. The authors demonstrate that
44 mechanosensory orofacial stimulation is relayed through neurons that express
45 Cerebellin-2 in the caudal part of the spinal trigeminal nucleus into the cervical
46 segments of the spinal cord that control the forelimbs. Chemogenetic inactivation of
47 these specific neurons blocked orofacial self-grooming; complementarily,
48 chemogenetic activation of these neurons triggered rhythmic forelimb syllables
49 resembling the orofacial episodes of rodent self-grooming. Neuroanatomic input
50 mapping of these neurons revealed robust monosynaptic inputs from the ipsilateral
51 trigeminal ganglion, which perceives sensory information from the face area.
52 Cerebellin-2 neurons in the caudal part of the spinal trigeminal nucleus furthermore
53 receive monosynaptic from several brain areas, including e.g. the primary
54 somatosensory cortex and the paraventricular hypothalamic nucleus. Output mapping
55 corroborates the recently characterized implication of the lateral rostral medulla in
56 forelimb movements and proposes a role of Cerebellin-2 neurons in steering forelimb
57 movements via a strong innervation bias into the cervical segments that control
58 forelimbs. Taken together, Xie et al. refine earlier sensorimotor investigations of the
59 trigeminal nerve and its role in rodent self-grooming by adding molecular and spatial
60 mapping details to the neurobiology of sensorimotor processing of orofacial forelimb

61 movements. Indeed, previous work had investigated the role of somatosensory
62 orofacial trigeminal feedback on forelimb control using trigeminal deafferentation,
63 which specifically removed all orofacial tactile somatosensation and pain while sparing
64 gustatory and trigeminal motor function (Berridge and Fentress, 1986). Interestingly,
65 this work suggested that trigeminal feedback is required for the control of forelimb
66 stroke, but not required for the generation of syntactic rules present in patterned rodent
67 self-grooming. Furthermore, when defining and locating the minimum brain substrate
68 required for syntactic motor chains, descending decerebration studies suggested that
69 at least metencephalic structures were required to maintain syntactic self-grooming
70 chaining (Berridge, 1989). Thus, the gradual deterioration of grooming structure and
71 sequence with descending decerebration point to a distributed and not a single
72 structure steering syntactic grooming. Naturally, Xie et al. highlight the important
73 question of further investigations of the role of Cerebellin-2 neurons beyond isolated
74 orofacial forelimb strokes. Indeed, rodent syntactic self-grooming is more than one
75 isolated grooming phase and more than the sum of its parts. While Xie et al. beautifully
76 demonstrate the implication of Cerebellin-2 expressing neurons of the caudal part of
77 spinal trigeminal nucleus in triggering orofacial forelimb movements, the exact role of
78 this pathway in rodent self-grooming will need to be further characterized.

79 Such study highlights a pending question in the steadily growing literature of rodent
80 self-grooming and its use for translational studies. It furthermore highlights the
81 importance of considering the different levels of description of animal behavior with its
82 precise, comprehensive and contextual characterization. Indeed, this is particularly
83 relevant in modern biological psychiatry where one of the major challenges is to
84 properly assess the phenomenological and brain circuitry homologies between
85 humans and experimental animal models, which are pivotal to uncover shared

86 neurobiological traits and to steer appropriate treatment of neuropsychiatric disorders.
87 More than a decade after the Research Domain Criteria (RDoC) initiative as a new
88 framework to understand and improve accurate treatment of mental illness, most
89 animal models of psychiatric disorders still rely on the conceptual framework of the
90 *Diagnostic and Statistical Manual of Mental Disorders (DSM)/International*
91 *Classification of Diseases (ICD)* system. Consequently, investigators continue
92 focusing on the reproduction of few major symptoms characteristic for the pathology of
93 interest, hereby not only likely missing further important phenomenological features
94 expressed by the model but also ignoring the issue of disease heterogeneity and
95 comorbidity (Benzina et al., 2021). Thus, focusing on a single psychiatric symptom or
96 incorrect labeling of behavioural phenotypes could impede the use of animal models,
97 i.e. this could ultimately mislead the identification of underlying neural substrates and
98 corresponding appropriate treatments. One such example in the context of rodent self-
99 grooming is illustrated by the recent intense research done on one of the showpiece
100 mouse models of current psychiatric research, the Sapap3 knockout mouse (Sapap3^{-/-}).
101 Since its first phenotypical characterization in 2007 (Welch et al., 2007), the Sapap3^{-/-}
102 mouse has exerted strong influence over the understanding of compulsive-like
103 behaviours and their cellular and molecular origins. The flagship-like lesions of this
104 mouse originally described as a consequence of abnormally elevated self-grooming
105 have become nearly synonymous to an expression of compulsivity and, as a
106 consequence, strongly boosted the phenotype of rodent self-grooming in the field of
107 preclinical psychiatric research. However, recent observations of dysfunctional
108 neuronal circuits in this mouse model, which seem to include both associative as well
109 as sensorimotor cortico-striatal loops (Burguière et al., 2013; Corbit et al., 2019), have
110 raised important question marks in the definition of “compulsive-like” self-grooming. In

111 particular, it has been observed that Sapap3^{-/-} mice not only over-expressed full
112 syntactic chain of self-grooming; but also isolated, single-phase, short grooming bouts,
113 which could phenomenologically be related to “tic-like” behaviors (Hadjas et al. 2020).
114 These observations, differentiating the type of self-grooming expression, are in line
115 with the clinical data that report a high comorbidity of tics and compulsions in patients
116 with obsessive-compulsive disorder as well as Tourette syndrome (Worbe et al., 2010).
117 Thus, re-defining the self-grooming phenotype of the Sapap3^{-/-} mouse model alters its
118 face validity and hereby raises its translational value. In this context, it is further
119 remarkable that the neurons relaying sensory information from the orofacial area to the
120 forelimbs, identified by Xie and colleagues in this issue, express Cerebellin-2, which
121 has been identified as a gene associated to Tourette Syndrome and autism spectrum
122 disorder (Clarke et al., 2012). Further research could then investigate whether
123 Cerebellin-2 neurons play a role in the over-expression of isolated orofacial
124 movements resembling tics or stereotypies, rather than of syntactic self-grooming
125 considered as an analog to compulsive behaviors.

126 Taken together, these findings exemplify the importance of a paradigm change from
127 symptom-based classifications to neurobiologically valid model organisms, but they
128 also integrate into the recent neuroscientific call for a reconsideration of fine
129 behavioural evaluation and phenomenological characterization. In their study, Xie et
130 al. used a grooming quantification based on a magnetic induction system which
131 allowed them to finely characterize the dynamics of forelimb movements. By making
132 use of such recent technical advances in tracking, measuring and quantifying
133 naturalistic behaviors combined with machine learning algorithms, large-scale
134 behavioural datasets can be screened for hidden phenotypic information and complex
135 behaviors can be broken down into subcategories. This rapidly growing field of

136 behavioral neuroethology is a unique opportunity to reconsider the phenomenology of
137 animal models and, combined with neural activity monitoring and neuromodulation
138 methods, to better identify the neurophysiological processes implicated in behaviours
139 of interest for neuropsychiatric diseases.

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141 **References**

142 Benzina, N., N'Diaye, K., Pelissolo, A., Mallet, L., and Burguière, E. (2021). A cross-
143 species assessment of behavioral flexibility in compulsive disorders. *Commun Biol* 4,
144 96.

145 Berridge, K.C. (1989). Progressive degradation of serial grooming chains by
146 descending decerebration. *Behav Brain Res* 33, 241–253.

147 Berridge, K., and Fentress, J. (1986). Contextual control of trigeminal sensorimotor
148 function. *J. Neurosci.* 6, 325–330.

149 Burguière, E., Monteiro, P., Feng, G., and Graybiel, A.M. (2013). Optogenetic
150 stimulation of lateral orbitofronto-striatal pathway suppresses compulsive behaviors.
151 *Science* 340, 1243–1246.

152 Clarke, R.A., Lee, S., and Eapen, V. (2012). Pathogenetic model for Tourette
153 syndrome delineates overlap with related neurodevelopmental disorders including
154 Autism. *Transl Psychiatry* 2, e158.

155 Corbit, V.L., Manning, E.E., Gittis, A.H., and Ahmari, S.E. (2019). Strengthened
156 inputs from secondary motor cortex to striatum in a mouse model of compulsive
157 behavior. *J. Neurosci.*

158 Hadjas, L.C., Schartner, M.M., Cand, J., Creed, M.C., Pascoli, V., Lüscher, C., and
159 Simmler, L.D. (2020). Projection-specific deficits in synaptic transmission in adult
160 Sapap3-knockout mice. *Neuropsychopharmacology* 45, 2020–2029.

161 Kalueff, A.V., Stewart, A.M., Song, C., Berridge, K.C., Graybiel, A.M., and Fentress,
162 J.C. (2016). Neurobiology of rodent self-grooming and its value for translational
163 neuroscience. *Nat. Rev. Neurosci.* 17, 45–59.

164 Welch, J.M., Lu, J., Rodriguiz, R.M., Trotta, N.C., Peca, J., Ding, J.-D., Feliciano, C.,
165 Chen, M., Adams, J.P., Luo, J., et al. (2007). Cortico-striatal synaptic defects and
166 OCD-like behaviours in Sapap3-mutant mice. *Nature* 448, 894–900.

167 Worbe, Y., Mallet, L., Golmard, J.-L., Béhar, C., Durif, F., Jalenques, I., Damier, P.,
168 Derkinderen, P., Pollak, P., Anheim, M., et al. (2010). Repetitive behaviours in
169 patients with Gilles de la Tourette syndrome: tics, compulsions, or both? *PLoS ONE*
170 5, e12959.

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