# GLUTAMATE RECEPTORS IMPLICATED IN (SELF-)DOMESTICATION REGULATE DOPAMINERGIC SIGNALING IN STRIATAL VOCAL-LEARNING PATHWAYS

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## 1. Introduction: An evolutionary and neural mechanism for the emergence of complex language traits

Comparable morphological changes distinguishing anatomically modern humans (AMH) from their archaic counterparts and domesticates from their wild ancestors (e.g. brain-case shape and size alterations, retraction of the face or muzzle, and decreased tooth size) have been proposed to result from convergent evolutionary pressures (Sánchez-Villagra & Schaik, 2019). The single unifying characteristic of domesticated species, often correlating with the emergence of these physical changes, is tameness, proposed to result from an attenuation in hypothalamic-pituitary-adrenal (HPA) axis signaling, which mediates the stress response (Trut, Oskina, & Kharlamova, 2009; Wilkins, Wrangham, & Fitch, 2014; O'Rourke & Boeckx, 2019). This, in turn, raises the possibility that convergent selection, independently leading to reduced HPA-mediated stress reactivity (including reduced reactive aggression) across domesticated species and in humans, has left signals of positive selection in overlapping regions of these species' respective genomes (Wrangham, 2019; O'Rourke & Boeckx, 2019).

It has been hypothesized that the biological basis for complex language traits could have emerged as a result of a process of self-domestication in our species (Thomas & Kirby, 2018). Here, we present genomic and neurobiological evidence for how one such trait, vocal learning, may have been enhanced in modern human evolution. We present evidence that glutamatergic signaling genes — which show above-chance signals of positive selection in ours and domesticated species — are crucial regulators of the HPA axis and striatal circuits essential for vocal learning. We propose that the actions of kainate and metabotropic glutamate receptors, downregulating net excitation in stress circuits, have had concomitant modulatory effects, increasing plasticity in corticostriatal and thalamostriatal circuits crucial for vocal learning in our species.

## 2. Glutamate receptors in domestication and vocal learning

In a comparison of 488 neurotransmitter receptor genes across fourteen domesticated species and AMH, we have shown that glutamate receptor genes (in particular kainate and metabotropic families) show above-chance signals of positive selection, unparalleled by any other receptor type. These genes are prominently expressed in stress-response and striatal regions, and are implicated in multiple stress and striatum-related disorders, including Tourette's syndrome (O'Rourke & Boeckx, 2019; Singer, 1997; Herman, Tasker, Ziegler, & Cullinan, 2002).

Glutamate receptors are principal regulators of excitatory afferents to striatal dopaminergic circuits implicated in vocal learning. Many of the receptors we have identified function to reduce excitatory signaling acting on dopaminergic output circuits of the striatum, thus decreasing dopaminergic spiking that is often implicated in stress-induced stereotyped behaviors (O'Rourke & Boeckx, 2019; Hoffmann, Saravanan, Wood, He, & Sober, 2016; Moghaddam, 2002; Howes, McCutcheon, & Stone, 2015; Marshall, Xu, & Contractor, 2018; Xu et al., 2017).

Glutamate receptor genes are also implicated in songbird vocal-learning abilities (Wada, Sakaguchi, Jarvis, & Hagiwara, 2004). For example, the domesticated Bengalese finch, which has a reduced stress response and a more variable song repertoire than its wild vocal-learning counterpart, the white-rumped munia (Suzuki, Yamada, Kobayashi, & Okanoya, 2012; Okanoya, 2015, 2017), shows increased expression of *GRM2* in the LMAN song nucleus crucial for song variability (Okanoya, 2014). This gene shows recent signals of selection in our species (O'Rourke & Boeckx, 2019).

Other domestication and modern-human-related glutamate receptor genes (e.g. *GRM8*, *GRIK2*, and *GRIN2B*) are transcriptional targets of *FOXP2*, a gene implicated in striatally dependent vocal-learning abilities of songbirds and humans (Shi et al., 2018; Vargha-Khadem, Gadian, Copp, & Mishkin, 2005). Knockdown of *FoxP2* in the Area X song nucleus interferes with dopaminergic signaling, preventing the switch from a more variable undirected song to restricted directed singing, dependent on LMAN (Murugan, Harward, Scharff, & Mooney, 2013).

The evidence we have compiled suggests that glutamate receptor genes showing signals of positive selection in recent human evolution are implicated in reducing both stress reactivity and stereotyped vocal-learning behaviors. This raises the intriguing possibility that convergent selective pressures of (self-)domestication, attenuating the stress response in our species and domesticated songbirds, had the concomitant result of potentiating striatal-dependent vocal-learning abilities.

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