UNIVERSITAT DE BARCELONA

A role for the glutamate system in modern human language and cognition

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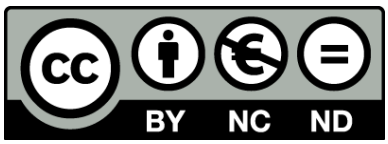

A role for the glutamate system in modern human language and cognition

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Abstract

The human capacity for language is made up of various cognitive subcomponents, the convergence of which allows our species a unique ability to relay our thoughts. Identifying these subcomponents and establishing how they mechanistically interact is a necessary step in approaching any satisfactory explanation for how language evolved. Even given the unique combination of underlying parts that make up the language faculty, comparative research has individuated many language-relevant traits in other species that can serve as useful models to study the biological basis of their human equivalents.

Research into the evolution of language also demands that findings across disparate disciplines in the life and cognitive sciences be connected with each other. The present thesis takes this interdisciplinary comparative approach in seeking to elucidate the biological basis of two component traits of our species' language phenotype: (i) vocal learning, a capacity that underlies our ability to speak, and which has clear but, so far, sparsely observed analogues in the animal kingdom, and (ii) lowered fearful and aggressive reactivity towards other members of our own species. Behavioral measures of these capacities diverge — in kind and degree, respectively — from those of our closest extant ape relatives, suggesting that these traits have made important recent contributions to what makes us human.

Because of the disparity in levels of aggressiveness between modern humans and other extant great ape lineages, Chapter 2 builds on work proposing domesticated species as a more viable comparator for the study of reduced reactive aggression in our species. We investigate genomic signals of convergent evolution between modern humans and domesticated species when compared with their respective archaic and wild counterparts. We find that alterations to glutamatergic signaling genes occur disproportionately in the recent evolution of ours and domesticated species. We review evidence that these genes are broadly expressed across limbic circuits that regulate the hypothalamic-pituitary-adrenal (HPA)-axis stress response cascade. We propose that attenuated glutamatergic excitation of the HPA response has downregulated tendencies towards reactive aggression in our species.

In Chapter 3, we overview evidence that many of the glutamate receptor genes

that have changed in our species' recent evolution — as well as limbic regions implicated in control of the HPA axis — regulate striatal circuits that control the motor output of both stress responses and learned vocalizations. As evidenced by multiple stress and neuropsychiatric disorders in which glutamate receptors are implicated, corticosteroid "stress-hormone" feedback acting prominently on glutamatergic neurons in limbic regions can drive excitation of striatal circuits. We review clinical findings that up- or downregulation of stress-driven excitatory activity can result in differentially modulated midbrain dopamine release to dorsal and ventral striatal regions, promoting diverging tendencies toward stereotyped and exploratory motor behaviors, including vocalization.

We consider the case of the Bengalese finch, a domesticated songbird for which corticosteroid, glutamatergic, and dopaminergic signaling all appear to have been altered in the course of the domestication process. The Bengalese finch also displays reduced aggression, a potentiation of exploratory behaviors, and learns a less stereotyped and more complex song than its wild counterpart, the white-rumped munia. Based primarily on this convergence of paleogenomic, clinical, and songbird data, we propose that corticosteroid-driven modulation of glutamatergic signaling in limbic and striatal circuits may lay the evolutionary basis for the emergence of complex vocal learning abilities in modern humans.

Finally, Chapter 4 considers the role of the limbic system in another important aspect of the human linguistic phenotype: the ability to pick out a unique entity with a proper name. This chapter considers evidence for divergent circuits and mechanistic processes involved in the encoding and retrieval of proper names and the meanings they pick out. We propose that information enabling the subsequent retrieval of proper names is encoded via divergent mechanisms: the first involves the unitization of a name with socio-emotional information, dependent on prominent amygdalar activation. The second, a process of item-item and item-context association, is proposed to subserve the encoding of both proper names and common nouns, involving more prominent hippocampal and posterior medial temporal activations. Subsequent retrieval is also supported by divergent networks, with names encoded in a unitized manner being retrieved via a prefrontal–anterior-temporal network, while those encoded via item-item and item-context associations are later retrieved via more posterior projecting networks.

Resum

La capacitat humana per al llenguatge es constitueix de diversos subcomponents cognitius, la convergència dels quals permet a la nostra espècie una habilitat única per a transmetre els nostres pensaments. Identificar aquests subcomponents i establir com interactuen mecànicament és un pas necessari per a abordar qualsevol explicació satisfactòria de com va evolucionar el llenguatge. Fins i tot donada la combinació única de parts subjacents que componen la facultat del llenguatge, la recerca comparativa ha identificat molts trets pertinents al llenguatge en altres espècies que serveixen com a models útils per a estudiar la base biològica dels seus equivalents humans.

La recerca sobre l'evolució del llenguatge també exigeix que disciplines dispars en les ciències de la vida i cognitives estiguin connectats entre si. La present tesi pren aquest enfocament comparatiu i interdisciplinari en la cerca de dilucidar la base biològica de dos trets components del fenotip del llenguatge: (i) l'aprenentatge vocal, una capacitat que subjeu a la nostra habilitat per a parlar, i que té clars anàlegs en el regne animal (encara que, fins ara, escassament observats), i (ii) la disminuïda reactivitat temorosa i agressiva cap a altres humans. En la nostra espècie, les mesures de comportaments que resulten d'aquestes dues capacitats divergeixen, en tipus i grau, de les dels nostres parents primats més pròxims, la qual cosa suggereix que aquests trets han fet importants contribucions recents al que ens fa humans.

A causa de la disparitat en els nivells d'agressió reactiva entre els humans moderns i altres llinatges de grans simis existents, el Capítol 2 es basa en estudis que proposen les espècies domesticades com un comparador més viable per a l'estudi de l'agressió reactiva reduïda en els humans moderns. Aquí, investiguem les senyals genòmics de l'evolució convergent entre els humans moderns i les espècies domesticades en comparació amb les seves respectives contraparts arcaiques i salvatges.

Trobem que les alteracions en els gens de senyalització glutamatèrgica ocorren de manera desproporcionada en l'evolució recent de la nostra espècie i en la de les espècies domesticades. Revisem l'evidència que aquests gens s'expressen de manera abundant en circuits límbics que regulen la cascada de resposta a l'estrès de l'eix hipotalàmic-pituïtari-adrenal (HPA). Proposem que l'excitació atenuada de l'eix HPA ha regulat negativament les tendències cap a l'agressió reactiva en la nostra espècie.

En el Capítol 3, revisem l'evidència que molts dels gens de receptors de glutamat que han canviat en l'evolució recent de la nostra espècie, així com múltiples regions límbiques implicades en el control de l'eix HPA, regulen els circuits de l'estriat que controlen els moviments motors tant de les respostes a l'estrès com de les vocalitzacions apreses. Com ho demostren els múltiples trastorns neuropsiquiàtrics i d'estrès en els quals estan implicats els receptors de glutamat, la retroalimentació dels corticoesteroides ("hormones de l'estrès") — que actua de manera prominent sobre les neurones glutamatèrgiques a les regions límbiques — pot impulsar l'excitació dels circuits estriatals. L'activitat excitadora impulsada pot resultar en l'alliberament de dopamina del mesencèfal, modulat diferencialment a l'estriat dorsal i ventral, promovent tendències divergents cap a conductes motores estereotipades i exploratòries, incloses de la vocalització.

Considerem el cas del maniquí carpó-blanc domesticat (*Lonchura striata domestica*), un ocell cantaire domesticat per a la qual la senyalització corticoesteroide, glutamatèrgica i dopaminèrgica sembla haver estat alterada en el curs del procés de domesticació. El maniquí carpó-blanc domesticat també mostra una agressió reduïda, una potenciació dels comportaments exploratoris i aprèn una cançó menys estereotipada i més complexa que la seva contrapart salvatge. Basats principalment en aquesta convergència de dades paleogenòmiques, clíniques i d'ocells cantaires, proposem que la modulació de la senyalització glutamatèrgica impulsada per corticoesteroides en els circuits límbics i estriatals pot establir les bases evolutives per al sorgiment d'habilitats complexes d'aprenentatge vocal en els humans moderns.

Finalment, el Capítol 4 considera el paper del sistema límbic en un altre aspecte important del fenotip lingüístic humà: la capacitat de designar una entitat única amb un nom propi. Aquest capítol considera l'evidència que dos circuits i processos mecanicistes diferents estan involucrats en la codificació en la memòria i la subseqüent recuperació dels noms propis i dels significats als quals apunten. Proposem que la informació que permet la recuperació dels noms propis primer es codifica mitjançant mecanismes divergents: el primer implica la unificació d'un nom amb informació socioemocional, dependent d'una activació amigdalar prominent. El segon procés associa (però no unifica) dos elements diferents o un element amb el context en ell que apareix, i afavoreix la codificació tant de noms propis com de substantius comuns. Aquest procés implica activacions més prominents de l'hipocamp i del lòbul temporal mig i posterior. La recuperació subseqüent de la memòria també està facilitada per xarxes divergents: noms propis codificats de manera unitària després es recuperen d'una xarxa prefrontal–temporal anterior, mentre que xarxes de projecció posterior donen suport a la recuperació de noms codificats mitjançant associacions element-element i element-context.

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Full List of Abbreviations

ACTH	adrenocorticotrophin
ADGR	adhesion G protein-coupled receptor
ADHD	Attention Deficit Hyperactivity Disorder
AMH	Anatomically modern human
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ANX	Anxiety Disorder
ASD	Autism Spectrum Disorder
ATL	anterior temporal lobe
BA	Brodmann area
BNST	Bed nucleus of the stria terminalis
BPD	Bipolar Disorder
CNS	central nervous system
CNV	copy number variation
CORT	corticosteroids
CRH	corticotrophin releasing hormone
D1	D_1 dopamine-receptor expressing direct pathway
D2	D_2 dopamine-receptor expressing indirect pathway
DD/ID	Developmental Delay/Intellectual Disability
DG	dentate gyrus
DLPFC	dorsolateral prefrontal cortex
GABA	gamma-Aminobutyric acid
GC	glucocorticoid
GluR	glutamate receptor
GPe	Globus Pallidus externa
GPi	Globus Pallidus interna
GR	glucocorticoid receptor
GWAS	Genome-wide association study
HPA	hypothalamic-pituitary-adrenal
HVC	HVC
IFOF	inferior fronto-occipital fasciculus
iGluR	ionotropic glutamate receptor
ILF	inferior longitudinal fasciculus
KAR	Kainate receptor
KEGG	Kyoto Encyclopedia of Genes and Genomes

LMAN lateral magnocellular nucleus of the nidopallium
LTD Long-term depression
MDD Major Depressive Disorder
mGluR metabotropic glutamate receptor
miRNA microRNA
MITF melanocyte inducing transcription factor
MLF middle longitudinal fasciculus
mPFC medial prefrontal cortex
mRNA messenger RNA
MR mineralocorticoid receptor
MSNs medium spiny neurons
MTL medial temporal lobe
NAc Nucleus accumbens
NBEA Neurobeachin
NCC neural crest cell
NMDA N-Methyl-d-aspartate
OCD Obsessive Compulsive Disorder
OFC orbitofrontal cortex
OMPFC (orbital and medial) prefrontal cortices
OXT Oxytocin
PAG periaqueductal gray
PCP phencyclidine
PD Parkinson's Disease
PET positron emission tomography
PFC prefrontral cortex
PosN postnatal
PPA-S Semantic Variant Primary Progressive Aphasia
PPN Pedunculopontine nucleus
PreN prenatal
PVN paraventricular nucleus of the hypothalamus
RNA ribonucleic acid
SCZ Schizophrenia
SD Semantic Dementia
SNc substantia nigra pars compacta
SNP single nucleotide polymorphism
SNr Substantina nigra pars reticulata
SON Supraoptic nucleus of the hypothalamus
SR/Fear Startle response/Fear response
STN subthalamic nucleus
svPPA Semantic Variant Primary Progressive Aphasia
UF uncinate fasciculus
VMPFC ventromedial prefrontal cortex
VP Ventral Pallidum
VTA ventral tegmental area

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In the time I have known Cedric, my understanding of what it means to take a scientific approach to the study of language has changed drastically and for the better. I have learned a lot from him, not just through the many relevant articles that he has forwarded on or the interesting ideas that he has raised, but through how he approaches problems, and his eagerness to keep an eye out for new directions. Cedric sets an example as someone who is not afraid to reject ideas he once held at the expense of the comfort of feeling right. This makes him a challenging teacher and supervisor, but one that is no less challenging to himself than he is to his students.

Cedric's striving to consider new ideas and his boldness in pursuing them have provided the most important lesson of my time under his supervision. It is now reassuring for me rather than troubling to look back down pathways pursued but ultimately aborted in the study of language, before I happened upon the present path. It is also gratifying to reflect on the work I have been able to do during my PhD and how much I have learned. And yet it is also motivating to consider the many other interesting paths to be pursued in the future. For this I am especially grateful to Cedric.

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Chapter 1

Introduction

The question of how human cognitive capacities evolved poses certain difficulties not faced by most other research in the life sciences. Aside from the intricacies of untangling the polygenic basis of complex traits and restrictions on invasive *in vivo* experimentation in humans, evolutionary studies of human cognition face difficulties in determining, defining and subdividing the very traits under study: for example, research into the biological basis of consciousness is hindered by difficulty in defining the nature of consciousness itself. The truism that cognitive traits do not fossilize further complicates research into their evolutionary basis, as does the related difficulty that such traits are not observable in real time except via behaviors purported to result from them. These obstacles make research into how cognitive traits evolved a necessarily interdisciplinary venture, dependent on methodological advances and theoretical insights from fields across cognitive science, neuroscience, and biology.

The present thesis takes such an interdisciplinary approach to elucidate evolutionary events that have contributed to the human endowment with language. Like that of consciousness, the question of how and why our species gained the capacity for language has long been considered a difficult problem for the life sciences. Both are also questions of keen human interest because the respective endowments are considered among the most fundamental components to what it means to be human. The "hard problem" of consciousness is often considered difficult, not because it is unlikely to have deep evolutionary origins preceding the emergence of *Homo sapiens*, but because its behavioral correlates are not easily discernible beyond subjective reporting (see e.g. Low et al. (2012)). Conversely, the faculty of language has a clear behavioral correlate in speech. Nonetheless, the varied and undbounded nature of linguistic output has been argued to be so qualitatively distinct from any other animal communication system that the study of its fundamental nature falls outside the realm of comparative biology (e.g. Hauser et al. (2002); Berwick and Chomsky (2016)).

The position taken in this thesis is that sufficient progress has been achieved in

picking apart some of the most crucial subcomponents of human cognitive modernity so as to allow for fruitful comparative inquiry into their evolution. Thus, while it may be true that language is uniquely human, I explore evidence that cognitive capacities which contributed to its emergence — namely, a reduction in reactive aggression and the capacity for vocal learning — have analogues elsewhere in the animal kingdom, dependent on shared genetic and neurobiological substrates. These traits have emerged periodically from branches of the phylogenetic tree quite distant from that of primates. Moreover, they are rare enough — and their co-occurrence even moreso — as to warrant the contention that language is indeed a very special or even unique faculty, although not necessarily one that depends on new or unique biological building blocks.

Much of the interest in language as a special communicative system stems not only from the extent of meanings that can be relayed but also their nature. Humans' ability to encode information from the world and relay this to conspecifics provides us with an undeniable advantage in navigating and adapting to occurrences around us. It also allows us to relay to others the inner workings of our minds. An outstanding question for the cognitive sciences is what happens in the mind from the point when information is encoded via the doors of perception to when it is relayed as meaningful speech to another person. The present thesis approaches this question from the point of view of cognitive neuropsychology by looking at the brain networks and cognitive mechanisms involved in the encoding of information that allows for subsequent retrieval of lexical items and the meanings they pick out.

1.1 Building an account of language origins from the bottom up

While the goal of the present thesis is to provide insight into the biological basis of language, I do not take the study of language as a starting point. Rather, I begin by reviewing genotypical and phenotypical changes evidenced to have occurred in the recent evolutionary history of our species and by evaluating likely cognitive correlates of these. In this way, the present collection of papers is highly dependent on recent advances in paleogenomics that point to molecular differences between modern and archaic humans. These studies (e.g. Prüfer et al. (2014); Racimo (2016); Peyrégne et al. (2017)) are a crucial starting point in the interdisciplinary exploration that follows.

An underlying assumption of this approach is that language-relevant changes to human cognition have occurred since the anatomically modern human (AMH) split from Neanderthals and Denisovans. In the past, this assumption may have been readily accepted as pinpointing the most likely window for language origins: human cognitive modernity had been considered to correlate with an explosion of symbolic art

and complex tool making (deemed qualitatively distinct from archaic hominin material culture) at the beginning of the upper paleolithic (Klein, 2000). However, even given difficulties in deriving firm conclusions about linguistic abilities from such findings, recent evidence of Neanderthal symbolic behaviors, and of advanced ornament and tool-making abilities has blurred the line purported to divide modern from archaic cognitive capacities (Douka et al., 2019; Hoffmann et al., 2018). Furthermore, evidence of widespread modern–archaic interbreeding (Racimo et al., 2017) and of shared coding sequences on the language-implicated gene *FOXP2* (subjected to positive selection since the split from non-human primates) (Krause et al., 2007) weighs in favour of archaic humans having had complex language abilities (Dediu and Levinson, 2018).

Nonetheless, other evidence does point to language-relevant changes having occurred in the modern human lineage: this includes signals of positive selection in AMH occurring on multiple regulatory regions implicated in neurodevelopment and neuronal signaling (Racimo, 2016; Peyrégne et al., 2017), and modern–archaic differences disproportionately affecting genes expressed in the striatum, a region highly implicated in language abilities. Neanderthal-introgressed coding sequences on striatally expressed genes show evidence of negative selection in modern humans (Mafessoni et al., 2020). Genomic analyses of archaic genomes suggest differences in social organization, Neanderthals having lived in smaller social groups than ancient modern humans (Castellano et al., 2014). Allied to this, prosocial behaviors in modern humans are associated with genes implicated in the development of the modern human face (Zanella et al., 2019). It is this association between physiological and cognitive phenotypes that marks a point of departure for the present study.

1.2 Self-domestication in *Homo sapiens*

Among primates, extant or extinct, modern humans have a uniquely flattened face and a more globularized brain case, which evolved since the modern–archaic split. This is accompanied by a reduction in tooth size and an overall reduction in body size in our lineage (Theofanopoulou et al., 2017). These gross morphological changes in our species relative to Neanderthals have long been noted (including by Charles Darwin and Franz Boas) to resemble those present in domesticated species with respect to their wild counterparts (Darwin, 1871; Boas, 1938). Domesticated species often display broad phenotypical changes including reductions in tooth, skull, and brain size, retraction of the face or muzzle, depigmentation, the development of floppy ears, and the curling of tails. The coocurrence of these traits has been termed the "domestication syndrome" (Wilkins et al., 2014), the ubiquitous trait of which is tameness (reduced reactive aggression and increased affiliative behaviors) towards humans (Sánchez-Villagra and van Schaik, 2019).

The Russian farm-fox experiment (Belyaev, 1979) has shown that selection against reactive aggression and for tame behaviors can bring about multiple physiological changes typical of the domestication syndrome, including craniofacial remodeling (Trut, 1999). The speed with which these traits emerged (beginning within just five generations of selective breeding) pointed to a crucial role of attenuated hypothalamic-pituitary-adrenal (HPA)-axis stress signaling in the domestication process, a trait common across multiple domesticates (Plyusnina et al., 1991; Naumenko et al., 1989; Turner, 1984; Martin, 1978; Künzl and Sachser, 1999; Ericsson et al., 2014; Suzuki et al., 2014).

Recently, wild urban foxes have been shown to display alterations to snout and skull morphology reminiscent of foxes artificially selected for reduced defensive reactivity to humans (Parsons et al., 2020). These separate artificial and natural experiments highlight aspects of the domestication process and resultant phenotypes that can prove informative as to human evolution: firstly, the farm-fox experiment shows that selective pressures targeting behaviors such as reduced aggressiveness and increased sociability towards humans can have phenotypical effects including craniofacial changes similar to those that have occurred in *Homo sapiens*. Secondly, the craniofacial changes in urban foxes suggest that the onset of phenotypical changes typical of domestication can result independently of human-directed selection.

Ultimately, Darwin considered the idea of *Homo sapiens* as a domesticated species only in passing and rejected it due to humans having lacked a domesticator (Darwin, 1871). However, evidence in line with the evolution of urban foxes points to ancient wild animals — including paleolithic wolves and neolithic wild cats — having self-domesticated many millennia before any semblance of human-directed breeding (Zeder, 2012; Ottoni et al., 2017). The survival advantage of scavenging and hunting around human settlements was gained in lineages of wild animals that evolved a tolerance for close proximity to humans (a behavior likely enabled by stress-response attenuation). This model of domestication — apart from being evidenced by present-day morphometric and neuroendocrine measures, as well as paleogenomic and archaeological studies — requires no conscious direction or breeding on the part of humans. Instead, domestication is considered as a natural evolutionary process driven by selective pressures incurring descent with adaptive modifications to the anthropogenic environment. This, in turn, opens up the very real possibility that modern humans underwent selective pressures convergent with those of domesticated species.

Positive selection on increased tolerance in our species had to be intra- rather than interspecific and has been compared to a similar process in bonobos, which display craniofacial contraction and decreased intraspecific aggression compared to chimpanzees, their closest extant relatives (Hare et al., 2012). Modern humans have been estimated to be about one-hundred times less violent in day-to-day encounters than bonobos (Wrangham, 2019). We also display a marked attenuation of stress signaling compared to most other extant primates measured (Chrousos et al., 1982).

Although we may never definitively know archaic human levels of aggression, the domestication-like phenotypical changes that our lineage has experienced suggest that reduced reactive aggression has come under positive selection in our lineage (Wrangham, 2018).

1.3 An interaction of domestication and vocal learning

The unique explanatory potential of the human self-domestication hypothesis lies in the promise of explaining a crucial recent step in our species' arrival at cognitive modernity. It identifies multiple other species as possible models for having undergone similar evolutionary processes, and in the case of the tamed fox, this process has been experimentally controlled and well documented. This, in turn, may allow for targeted genomic and neurobiological inquiry into the basis of modern human cognition. It is the goal of Chapter 2 to identify such targets.

Although domestication may act as a model for processes crucial to modern human evolution, its relevance to the evolution of language capacities requires some justification: There is evidence (i) that domesticates are better at reading human communicative signals than their wild counterparts (Hare et al., 2002, 2005), (ii) that both domesticates and wild species displaying domestication traits are particularly adept at learning words (Brakke and Savage-Rumbaugh, 1995; Kaminski et al., 2004), (iii) that they have improved social and cooperative learning in general (Schuppli et al., 2017), (iv) that (self-)domestication has altered vocalizations and vocal repertoires across a range of different species (e.g. (Waal, 1988; Bradshaw and Cameron-Beaumont, 2000; Nicastro, 2004; Feddersen-Petersen, 2000; Pongrácz et al., 2005; Monticelli and Ades, 2011; Gogoleva et al., 2011), and (v) that vocalizing abilities and perhaps the ability to learn vocalizations have been potentiated in the marmoset through a process of self-domestication (Ghazanfar et al., 2020).

The case of the Bengalese finch, a songbird domesticated in Japan over the last two and a half centuries, is perhaps the clearest case of an interaction between language-relevant traits and those typical of the domestication syndrome (Okanoya, 2004). Like humans, songbirds have the rare ability to produce vocalizations learned from the world around them (usually from a conspecific tutor) rather than being limited to an innate vocal repertoire.

Despite having been subjected to artificial selection for its white plumage over the last two hundred and fifty years, the Bengalese finch has developed the ability to produce a more complex song than its wild counterpart, the white-rumped munia (Honda and Okanoya, 1999). The domesticated strain also shows behavioral and neuroendocrine correlates reminiscent of the domestication syndrome (Suzuki et al.,

2014). This raises the possibility that the Bengalese finch may act as an informative model for the emergence of complex communicative abilities in modern humans.

1.4 Thesis structure and overview

The above brief synopsis sets out some of the crucial theoretical underpinnings of the chapters that follow. Although I consider that the evidence in favour of the human self-domestication hypothesis is strong, I do not assume its veracity here. Rather, Chapter 2 (published as O'Rourke and Boeckx (2020b)) seeks to explore whether the apparent morphological and behavioral convergence in ours and domesticated species is underpinned by convergence at the level of the genome.

Just as with modern human paleogenomic studies, over the past decade there have been a host of domestication studies pinpointing ancient genomic markers that distinguish domesticated from wild species. These studies allow for direct comparison between genomic targets of recent human evolution and those of domestication. Our research group was the first to carry out such a comparison (Theofanopoulou et al., 2017), finding above-chance intersection between genes targeted in modern human evolution and both cattle and dog domestication, as well as between our species and the combined gene targets of cattle, dog, cat, and horse domestication. No such significant signals of potential convergence were found with any other primate lineage.

Chapter 2 of the present thesis can be considered as a continuance and extension of the Theofanopoulou et al. (2017) study. Both a strength and a limitation of that study was that shared genomic targets of (self-)domestication were identified without any prior hypothesis as to what genes may be involved or their functions. This meant that the intersection identified was less likely to be the result from biases in the curating of data, but it also limited the inferences that could be drawn as to which genes were most likely to have contributed to cognitive/behavioral changes across the different species.

In order to tackle this issue, in Chapter 2, I extend the number of domesticated species subjected to comparison with modern humans (fourteen in total) and limit the genes of potential interest to those involved in neuronal and neuroendocrine signaling. While the extended number of domesticates under comparison certainly provides a more robust measure of potential cross-species convergence, the limitation of genes of interest seeks to target those most likely to be implicated in cognitive/behavioral changes in modern human and domesticated lineages.

The comparison involves 488 neurotransmitter and hormone receptor genes, classified in terms of their endogenous ligands. While we do not argue that receptor genes are the sole or even the most likely neuronal signaling-gene substrates of domesticate behavior, by limiting our analysis to these genes we can carry out like-for-like comparisons and statistical analyses across different signaling systems (for discussion of

broader changes to glutamatergic signaling genes, see Supplementary Information). Each receptor gene family forms a delimited set, which we consider to be partly representative of its neurotransmitter signaling system. In the fifteen species being analysed (fourteen domesticates and anatomically modern humans), we compare signals of selection, adaptive introgression, high-frequency allelic changes, and (in the case of domesticate–wild type comparisons) brain expression differences targeting individual receptor genes and receptor-gene families identified across thirty different studies.

The findings of this chapter point to convergent changes targeting neuronal signaling genes in domestication and recent human evolution. A disproportionate number of those changes fall on glutamate receptor genes, providing the first quantitative evidence that the glutamate excitatory signaling system — the most abundant in the vertebrate brain — is targeted across multiple domesticated species and in recent human evolution. These changes include at least one glutamate receptor gene or a respective regulatory region being detected within a selective sweep region in each of the domesticated species for which such studies had been carried out, as well as multiple such instances being detected in modern humans.

Among the genomic changes identified, a significant preponderance occur on genes that code for glutamate receptors which (i) tend to downregulate glutamatergic signaling, (ii) are highly expressed in limbic and striatal circuits that control how the brain processes and responds to stress, and (iii) are implicated in multiple stress and stress-associated neurodevelopmental and neuropsychiatric disorders, including those with aberrant vocal motor output. Considering this evidence in conjunction with findings that stress responses have been attenuated across multiple domesticated species compared to their wild counterparts and in modern humans compared to other extant primates, we propose that the attenuation of glutamatergic signaling has contributed to the reduction of stress responses in the self-domestication of our species.

In Chapter 3 — under review as O'Rourke et al. (2021) and an extension of a short paper published as O'Rourke and Boeckx (2020a) (see Appendix A) —, we explore evidence that alterations to stress-dependent motor output have played a role in the recent evolution of vocal learning abilities in our species. This is motivated by evidence briefly presented in Chapter 2 that glutamate receptor genes implicated in recent human evolution and the attenuation of stress responses are also highly expressed in basal ganglia substrates for vocal learning.

We briefly overview evidence that alterations to vocalizing abilities are common among domesticates and wild species that exhibit domestication-related traits. In particular, we focus on the Bengalese finch as the clearest case of a domestication event giving rise to complex vocal learning abilities. The Bengalese finch offers the added advantage of being one of a number of songbirds that are, at present, the best developed animal models for the study of vocal learning in our species, including

its neurobiological basis (Lattenkamp and Vernes, 2018). Studies in songbirds have shown vocal learning and complexity to be negatively regulated by developmental stress (e.g. MacDougall-Shackleton and Spencer (2012)), and the Bengalese finch, like many domesticated species, displays attenuated stress-response signaling relative to the wild-type white-rumped munia (Suzuki et al., 2012).

In Chapter 3 we explore the evidence that a stress-dependent neurobiological mechanism played a role in the emergence of the complex vocal learning abilities of our species. In humans, as in songbirds, developmental stress plays a role in driving stereotyped motor output, including vocal tics (Pagliaroli et al., 2016). We review evidence that dopaminergic spiking in songbird Area X and the human dorsal striatum promotes the learning and production of stereotyped vocalizations and other motor behaviors. Dopamine signaling is driven by glutamatergic excitation, which is, in turn, potentiated by corticosteroid stress feedback acting on limbic and prefrontal structures that control striatal activity. Crucially, these excitatory afferents are attenuated by multiple glutamate receptors that have been implicated in the recent evolution of our species (see Chapter 3: Supplementary Information). We review evidence that striatal activity and each of each of the three signaling systems central to our argument (corticosteroid, glutamate, and dopamine) have been altered in the emergence of both modern humans and Bengalese finches.

Attenuated stress and glutamatergic signaling does not simply downregulate but rather modulates striatal dopamineric spiking, attenuating dopamine signaling in dorsolateral areas while promoting this in the ventral striatum via alterations to limbic networks. Ventral striatal activity is prominently implicated in exploratory appetitive behaviors. Compared to other extant primates, modern humans display a "ventral-striatum dominant" neurochemical profile (Raghanti et al., 2018). We explore the potential contibutions of increased ventral-striatal dopamine (and other neurotransmitter) signaling in our mechanistic explanation for how complex exploratory vocalizations emerged in our species.

The final chapter of this thesis (published as O'Rourke and de Diego Balaguer (2020)) focuses on the neural basis of systems underlying our species' lexical encoding and retrieval abilities, with particular focus on proper names. Although we do not delve into the evolutionary steps that may have led to the emergence of lexical encoding and retrieval, the networks described in Chapter 4 may lay the basis for fruitful future inquiry into the evolution of modern-human conceptual–semantic systems. This is especially so when considering evidence, briefly reviewed above and in Chapter 3, that (i) mechanisms for word learning may be potentiated by domestication, (ii) the same limbic structures that modulate HPA and striatal activity are also crucial for the encoding of lexical items, and that (iii) proper names appear to be absent from the calls of other primate species (Hurford, 2007).

Chapter 4 describes the intricate circuitry necessary to encode perceptual infor-

mation from the environment, to associate that information with lexical form, and to imbue the association with meaning, before accessing this at retrieval. We review evidence that diverging lexical encoding processes, dependent on divergent activations of limbic structures — including, for example, the amygdala versus the posterior hippocampal formation — enable subsequent retrieval from similarly divergent anterior versus posterior networks.

A prefrontal–anterior temporal network appears to support only the retrieval of proper names, while a prefrontal–posterior-temporal projecting network supports the retrieval of both proper names and common nouns. We propose that these diverging networks at retrieval result from a duality in earlier memory encoding process, whereby associations considered as a single unit are encoded via the activation more anterior regions, poteniated by socio-emotional processing. Meanwhile more neutral, contextual associations are encoded in a non-unitized manner, and are subsequently retrieved via the activation of more posterior cortical regions. In the concluding section, we explore the potential of our model to inform research into the nature of meaning and how this is relayed in language.

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Chapter 2

Glutamate receptors in domestication and modern human evolution

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Review article

Glutamate receptors in domestication and modern human evolution

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ABSTRACT

There has been a recent resurgence of interest in the hypothesis that anatomically modern humans and domesticated species have followed convergent evolutionary paths. Here, we review results from domestication and modern-human evolutionary studies in order to evaluate evidence for shared changes to neurotransmission across these species. We compare genomic and, where available, brain-expression differences across 488 neurotransmitter receptor genes in 14 domesticated species and modern humans relative to their wild and archaic counterparts. This analysis highlights prevalent changes to glutamate — most notably kainate and metabotropic — receptor genes. We review evidence for these genes' expression and their respective receptor functions in the central nervous system, as well as phenotypes commonly associated with alterations to them. This evidence suggests an important role for kainate and metabotropic receptors in regulating hypothalamic–pituitary–adrenal axis excitation, and we provide a mechanistic account of their actions in attenuating the stress response. We assess the explanatory potential of such actions in contributing to the emergence of the (self-)domesticated phenotype, in particular to reduced reactive aggression.

1. Introduction

It has long been noted that morphological differences between modern and archaic *Homo* resemble those of domesticated species when compared with their wild counterparts (Boas, 1938). Some of these include changes to brain-case shape and size, retraction of the face or muzzle, and decreased tooth size (Sánchez-Villagra and van Schaik, 2019). Experimental observation of domestication unfolding in wild farm-bred silver foxes has unequivocally shown that selection for tameness alone can affect developmental trajectories to bring about a suite of physiological and behavioral traits indicative of the "domestication syndrome" (Dugatkin and Trut, 2017). This raises the possibility that morphological changes in *Homo sapiens* resulted from selective pressures on reduced reactivity to encounters with conspecifics. In turn, this predicts overlapping regions of selection in the genomes, and convergent physiological effects in the brains, of domesticated species and modern humans.

In earlier work, we have shown that prevalent overlapping signals of selection in domesticates (dogs, cats, cattle, and horses) and anatomically modern humans (AMH) occur on glutamatergic signaling genes (Theofanopoulou et al., 2017). Glutamate is the primary excitatory neurotransmitter in the vertebrate central nervous system (CNS), essential for fast synaptic transmission and plasticity, learning, memory, and (in tandem with GABA) modulation of hypothalamic–pituitary–adrenal (HPA) activity (Herman et al., 2004). Glutamate signaling genes are also widely expressed in tissues beyond the CNS, including osteoblasts, osteoclasts, melanocytes, and chondrocytes (Wang et al., 2005; Hoogduijn et al., 2006; Devi et al., 2013; Julio-Pieper et al., 2011; Matta, 2013). Such evidence is suggestive of the potential explanatory power of incorporating alterations to the glutamate system into accounts of domestication and modern-human evolution. To assess this potential, here we extend our comparative analysis to overview changes among 488 neurotransmitter receptor genes across thirty different human and domestication studies and fifteen different species: AMH, dogs, cats, cattle, horses, foxes, sheep, pigs, rabbits, yaks, goats, guinea pigs, chickens, ducks, and rats.

Our goal in carrying out this analysis is threefold: Firstly, we wish to establish whether convergent genomic markers occur on genes implicated in neurotransmission, given its essential role in behavior. Secondly, if such shared markers are present, we aim to investigate the potential functional consequences these changes. The nature of these consequences can be hinted at when gene function is altered, and there is ample evidence of gene function, reviewed here, from genome–phenome association studies among present day populations of both humans and domesticated species (clinical studies being particularly informative and abundant in the case of humans). Thirdly, by inferring

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potential effects on gene function, a central motivation of this paper is to formulate and hone testable hypotheses that can bring research on the genomic markers of domestication and human evolution into the laboratory, a direction we have recently begun to explore for changes related to the neural crest (Zanella et al., 2019).

2. Exploring the prevalence of domestication-associated changes to neuronal signaling systems

In order to delimit our comparison to a clearly-defined gene set within the glutamatergic system, we select the 26 glutamate receptor genes as our cross-species comparator. Glutamate receptors are primarily localized at synaptic nerve terminals in the brain and are divisible into two broad families (ionotropic [iGluR] and metabotropic [mGluR]). There are various widely used names for each receptor and corresponding gene in the literature. For ease of reference, see Supplementary Table S16 (Appendix A: mmc4).

Despite this focus on receptor genes, changes to other glutamatergic signaling genes have also been identified in multiple modern human and domestication studies. These include glutamate transporter, accessory subunit, and related G-protein signaling cascade genes. We detail some of the most noteworthy of these changes in Supplementary Information: Section S1 (Appendix A: mmc1), so as not to distract from the central comparative review of changes to neurotransmitter receptor genes.

To evaluate whether changes to glutamate receptor genes converge in modern human evolution and domestication events at rates significantly higher than those from other neuronal signaling systems, we compare a total of 488 receptor genes from equivalent classes (G-protein coupled receptors and ligand-gated ion channels) and other major receptor superfamilies in the CNS: receptor kinases, given an earlier observation that domestication events may have affected Erb-b2 signaling (Theofanopoulou et al., 2017), and nuclear hormone receptors, given extensive evidence for their effects on stress-hormone levels (see Supplementary Tables S1–S12, Appendix A: mmc3). Within the G-protein coupled receptor family we exclude olfactory, vomeronasal, and taste receptor genes, because of the large cross-species variability in functioning receptors encoded by these, driven, in large part, by species-specific dietary and environmental specializations. We also exclude orphan G-protein coupled receptors from our overview, given that, for the most part, their endogenous ligands and broad functions remain uncharacterized.

2.1. Identifying signals of convergent evolution in domesticates and anatomically modern humans

Whole-genome sequencing and selective sweep studies have been carried out for the majority of the species that we focus on here (see references in Table 1). Studies of ancient selective sweeps in humans and domesticates hold perhaps the greatest potential of identifying genomic signals of convergent evolutionary processes. The presence of a sweep at or near homologous genomic regions in different species provides strong evidence that the relevant allelic variants have increased in frequency at disproportionately high rates across evolutionary time, with favorable functional consequences being preserved for the carriers of those variants, perhaps due to convergent selective pressures.

Selective sweep data are not yet available for the domesticated fox, guinea pig, or rat, although different studies have explored the effects of domestication on gene expression in the brains of each of these species (Wang et al., 2018b; Albert et al., 2012). Gene expression differences may potentially serve as proxies, at the level of biological pathways, for signals of selection. In the case of the fox, perhaps the first and best-documented case of a *de novo* domestication event (Dugatkin and Trut, 2017), recent studies have also highlighted genomic regions with increased divergence, decreased heterozygosity, and significant allele-frequency differences between tame and agressive strains of fox (Kukekova et al., 2018; Wang et al., 2018a).

Given the controlled nature of the farm-fox experiment, at least some of the above genomic responses are likely to result from selection on tame and aggressive behaviors in the respective strains. Nonetheless, it cannot be ruled out that changes may have resulted from founder effects or genetic drift. Similarly, the differential brain expression of genes associated with domestication (or selection for tameness) in the guinea pig, rat, and fox need not have resulted from selective pressures on those genes *per se*, but potentially from pressures affecting other genes in an interacting network, leading to secondary, and not necessarily consequential phenotypical effects in the form of expression changes. In the case of the guinea pig, for which the domestication process was not experimentally controlled, environmental factors may also explain differential expression from its closest wild relative, the cavy. Despite these reservations, when it comes to identifying domestication-related genes with potential functional consequences, brain expression differences, if indeed the result of selection for tameness, have the informative advantage of being a direct neurobiological correlate of behavioral changes that are central to the domestication syndrome.

Finally, signals of adaptive introgression can also serve to shed light on convergent evolutionary events across domesticated species. For example, populations across a range of different species (humans, cattle, horses, chickens, dogs, sheep, goats, and pigs) that have migrated to high altitudes on three different continents show convergent signals of adaptation to these environments either on the same genes or on shared biological pathways; in the case of Andean horses, which have lived at high altitude for less than 500 years, natural selection has targeted the same gene (*EPAS1*) that is regularly introgressed in high altitude populations elsewhere (Witt and Huerta-Sánchez, 2019). Such studies highlight the importance of investigating genomic markers beyond selective sweeps when researching convergent evolution. Signals of adaptive introgression can also result from selection on behavioral traits: hybridization between Mongolian yaks and domesticated cattle, likely driven by artificial selection on the robustness to an unforgiving environment of the former and the high yields derived from the latter — despite the sterility of male hybrids — has left extensive genomic markers of adaptive introgression in the Yak on genes implicated in neural development and neurotransmission, some of which have also been identified as targets of ancient selective sweeps in cattle (Medugorac et al., 2017; Qanbari et al., 2014).

Considering the pros and cons of each of these evolutionary correlates, in our overview we prioritize studies of ancient selective sweeps over allelic frequency, adaptive introgression, or brain expression differences. However, we do not overlook any of these methods, as they utilize complementary measures of convergence (or, in the terms of (Fischer et al., 2019), of "partially shared" evolution of biological mechanisms), whereby the independent emergence of shared phenotypical traits across species may be dependent either on overlapping changes at the genetic level (as highlighted in selective sweep, high-frequency allelic changes, and introgression studies) or on changes to shared biological pathways, perhaps dependent on different genes (as highlighted in expression studies) (Fischer et al., 2019; Sackton and Clark, 2019; Witt and Huerta-Sánchez, 2019)

2.2. Genomic signals of domestication and modern human evolution

At least one glutamate receptor gene shows signals of selection in each of the species for which such studies have been carried out, with the exception of the yak (Table 1: selective sweeps highlighted in red). It should be noted, however that the yak does show signals of adaptive introgression from cattle on multiple glutamate receptor genes, including *GRIK3*, which has been the target of a selective sweep in cattle.

Glutamate receptor genes fall within identified selective-sweep regions at considerably higher rates than any other major receptor type

Table 1
Signals of selection, high-frequency changes, adaptive introgression, and differential expression of glutamate receptor genes in AMH and domesticated species.

	AMH	Dog	Cattle	Cat	Horse	Fox	Yak	Sheep	Goat	Pig	Rabbit	Guinea pig	Chicken	Duck	Total
GRIK1															0(0)
GRIK2		●◆					▲				●			●	3(4)
GRIK3	●	●●●●●	●				▲	●							4(5)
GRIK4	■														0(1)
GRIK5	●● ■														1(1)
GRM1													●		1(1)
GRM2	●● ■														1(1)
GRM3	●●					■									1(2)
GRM4							▲					◆			0(2)
GRM5															0(0)
GRM6	■					■									0(2)
GRM7	■								●	●					2(3)
GRM8	●	●						●		●●					4(4)
GRIN1															0(0)
GRIN2A							▲								0(1)
GRIN2B						■	▲								0(2)
GRIN2C	■														0(1)
GRIN2D	●					◆									1(2)
GRIN3A	●						▲							●	2(3)
GRIN3B															0(0)
GRIA1				●											1(1)
GRIA2	●			●						●					3(3)
GRIA3															0(0)
GRIA4							▲								0(1)
GRID1					●										1(1)
GRID2	●														1(1)
Signals	9(13)	3(3)	1(1)	2(2)	1(1)	0(4)	0(7)	2(2)	1(1)	3(3)	1(1)	0(1)	1(1)	2(2)	26(42)

●: Selective sweep study identifying differences between AMH and archaics or domesticates and their wild ancestors.
■: High frequency changes differentiating AMH and archaics or domesticates and their wild ancestors.
◆: Differential brain expression between domesticated species and wild ancestors.
▲: Adaptive introgression study.
Rightmost column: Total counts across all species per gene. Bottom row: Total counts for each gene per species. Totals outside parentheses denote selective-sweep counts. Totals in parentheses denote all AMH-archaic and domesticate-wild changes. Multiple signals on a given gene in a single species are counted as one; signals of selection are counted in cases where they co-occur with expression differences or high-frequency changes.
Modern–archaic and domesticate–wild comparators: AMH–Denisovan and Neanderthal (Kuhlwilm and Boeckx, 2019; Mallick et al., 2016; Peyrégne et al., 2017; Prüfer et al., 2014; Racimo, 2016; Zhou et al., 2015); Dog–Wolf (Axelsson et al., 2013; Cagan and Blass, 2016; Freedman et al., 2016; Li et al., 2014; Pendleton et al., 2018; Wang et al., 2013); cattle selective sweeps detected by integrated Haplotype Homozygosity Score (iHS) and composite likelihood ratio (CLR) analyses (Qanbari et al., 2014); domesticated cat–European and Eastern wildcat (Montague et al., 2014); domesticated horse–wild Przewalski's horse (Schubert et al., 2014); tame silver fox–aggressive silver fox (Wang et al., 2016), tame red fox–aggressive red fox (Kukekova et al., 2018); domesticated yak–wild yak (Qiu et al., 2015), introgessed segments in domesticated yak determined from consensus genome taken from six bovine species (Medugorac et al., 2017); sheep–Asiatic mouflon (Naval-Sanchez et al., 2018); domesticated goat–wild goat (Alberto et al., 2018; Bertolini et al., 2018; Dong et al., 2015); domesticated pig–wild boar (Leno-Colorado et al., 2017; Moon et al., 2015; Wang et al., 2018); domesticated rabbit–wild rabbit (Carneiro et al., 2014); guinea pig–wild cavy (Albert et al., 2012); chicken–red jungle fowl (Rubin et al., 2010); duck–wild mallard (Zhang et al., 2018).

among the 488 receptor genes studied here (see Supplementary Table S1, Appendix A: mmc3). Where a given gene was detected in a selective sweep region across multiple studies for a single species, this was counted as a one signal, giving a total of 213 signals of selection across all species. Of these, 26 (12.2%) fell on glutamate receptor genes, which make up just 5.3% of the receptor gene total. Averaging across major receptor types, as defined by their endogenous ligands, glutamate receptor genes fall within selective sweep regions at higher rates than receptor genes from any of the other primary neurotransmitter systems in the brain (see Fig. 1a).

We compared the receptor genes as part of 106 distinct multigene families (or 114 when subfamily divisions were included [full list in Table S13, Appendix A: mmc3]). Overlapping signals of selection were most consistently detected on kainate and Group III metabotropic receptor genes across modern human and animal domestication studies, with Group II metabotropic receptors showing prominent signals of selection in human studies. Groups II and III metabotropic receptors share structural and functional similarities, which differentiate them from Group I receptors. Most strikingly, Groups II and III receptor subunits can form functional heterodimers with each other across subfamilies, while they are unable to do so with Group I subunits (Doumazane et al., 2010). Moreover, activation of Groups II and III receptors primarily inhibits adenylyl-cyclase signaling, whereas Group I receptors potentiate this signaling cascade (Niswender and Conn, 2010). The relatively high rates of selective sweeps on metabotropic II/III and kainate receptor gene (sub)families are highlighted in Fig. 1b. We are unaware of any previous observation highlighting the prevalence of selective sweeps on these (sub)families across human and domestication studies.

GRIK3 and *GRM8* were two of only three genes to show signals of selection across four different species (including modern humans), the third being *ADGRB3*. Both the ADGRB3 receptor (BAI3) and kainate receptors are bound postsynaptically by C1ql proteins, regulating synaptogenesis in the case of ADGRB3 binding and postsynaptic recruitment in the case of kainate receptors (Sigoillot et al., 2015; Matsuda et al., 2016; Bolliger et al., 2011; Yuzaki, 2017; Martinelli et al., 2016). *ADGRB3* is implicated in similar neurodevelopmental and stress disorders as kainate and metabotropic glutamate receptors (reviewed further below and in detail in Supplemetary Information: Section S2 [Appendix A: mmc1]) (Lanoue et al., 2013). Of the eight receptor genes that show signals of selection across three or more different species (see Supplementary Table S1, Appendix A: mmc3), four are glutamate receptor genes (*GRIK2*, *GRIK3*, *GRM8*, and *GRIA2*).

In Fig. 1a we consider the proportion of instances where kainate, Group II/III metabotropic, and glutamate receptor genes were detected within a selective sweep region at least once for a species versus instances where they were not (mean cross-species signals per [sub]family divided by number of species studied). We compare this estimated

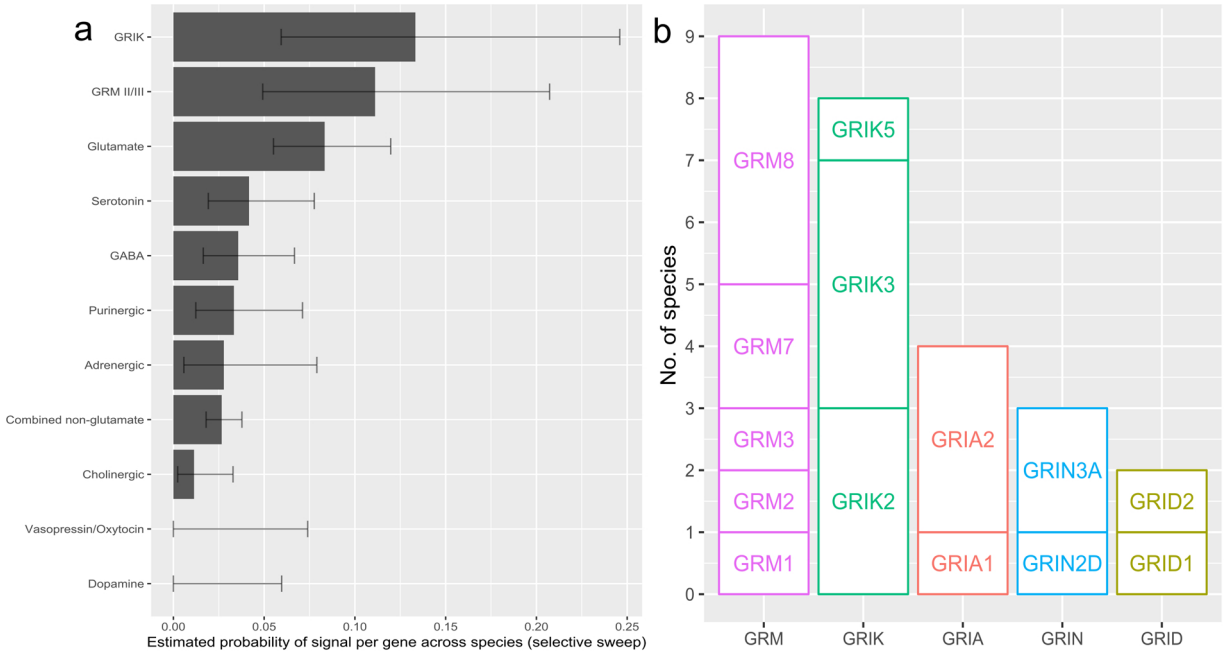

Table1a

	Adrenergic	Cholinergic	Dopamine	GABA	Purinergic	Serotonin	Vasopressin / Oxytocin	Combined non-glutamate
GRIK	0.01781663	**9.51244E-05**	**0.006090056**	0.006909738	0.008335485	0.014972958	0.023861277	**0.000391186**
GRM II/III	0.02834171	**0.000301042**	0.007889382	0.030013347	0.028065267	0.041944083	0.043700911	**0.001294014**
Glutamate	0.049726563	**6.54085E-05**	0.01235728	0.022153936	0.03588914	0.074387625	0.075583555	**3.71282E-05**

Fig. 1. Signals of selection on glutamate and other widely expressed neurotransmitter receptor gene types. For full comparisons of signals of selection on receptor genes, see Supplementary Table S1. (a) Comparison of signals of selection between glutamate receptor genes and seven other receptor gene types: Table 1a shows the results for Fisher's exact test for the proportion of signals detected to non-signals (estimated probability) for each of GRM II/III, kainate, and glutamate receptors as compared with proportions for seven receptor comparators: $p > 0.05$ shaded in grey; $p \leqslant 0.05$ not highlighted (non-formatted text); Bonferroni adjusted p-value ($p \leqslant 0.00625$) **highlighted in bold**. Error bars represent the exact confidence interval for the data summarized in each rectangular bar. (b) Number of species for which signals of selection are detected on a given glutamate receptor gene, organized by receptor families.

rate of occurrence of selective events with respective estimates for seven other neurotransmitter receptor-gene types (defined by their endogenous ligands), as well as with a combined estimate across all seven. For six of these gene types (those encoding for adrenergic, cholinergic, dopamine, GABA, purinergic, and serotonin receptors), our choice is motivated by evidence for their widespread expression and crucial importance for CNS signaling. This is underscored by the high receptor densities from these signaling systems that are exploited in autoradiographic studies to map architectonic structure in the cerebral cortex (Zilles et al., 2002, 2004) (see (Zilles et al., 1991; Abbracchio et al., 2009) for other accounts of relevant receptor distributions). We also compare vasopressin/oxytocin receptor genes, as the oxytocinergic system has been implicated in human prosocial behaviors and has been proposed, alongside serotonin, as a potential substrate for the emergence tame behaviors in domesticated species (Hare, 2017).

Using Fisher's exact test, we took the proportions of signals to non-signals on glutamate receptor genes and compared them with proportions detected on each of the other seven receptor types. The consistently higher signal-to-non-signal ratios on Group II/III and kainate receptor genes were above chance in all two-way comparisons ($p \leqslant 0.05$), as were glutamate receptor gene proportions in all but two comparisons. Both (sub)families, as well as glutamate receptor genes as a whole, fell within selective sweep regions at significantly higher rates than the seven receptor types when they were considered as a single group (the significant difference surviving Bonferroni correction [$p \leqslant 0.00625$], see Table 1a). While these exploratory results are suggestive that glutamate receptor genes are disproportionately implicated in modern-human and domesticate evolution, the small size of certain gene families and the low rates of selective-sweep detection urge caution.

By taking into account other evolutionary 'signals' in these species (allele frequency divergence, adaptive introgression, or brain expression changes), we were able to integrate more species and potential measures of convergence into our comparison. When all such measures are included, a total of 401 putative signals were identified across the 488 genes (a receptor-wide mean of 0.82 signals per gene). As with the analysis taking only selective sweeps into account, glutamate receptor genes, and especially metabotropic II/III and kainate receptor gene (sub)families showed significantly higher proportions of changes when compared with combined major receptor types (see Fig. 2a).

Out of the 32 instances where a functioning ionotropic glutamate receptor gene (NMDA, AMPA, or kainate) was identified in a selective-sweep, high-frequency change, expression, or introgression study, eighteen were detected among the kainate receptor genes, and fourteen of these occurred either on *GRIK2* or *GRIK3*. *GRIK3* exhibits signals of selection in modern humans, dogs, cattle, sheep, and of introgression in yaks, while *GRIK2* shows signals of selection in dogs (as well as increased brain expression as compared with wolves), rabbits, and ducks, and of introgression in yaks. Metabotropic receptor genes are the other major subclass of glutamate receptor genes that consistently display

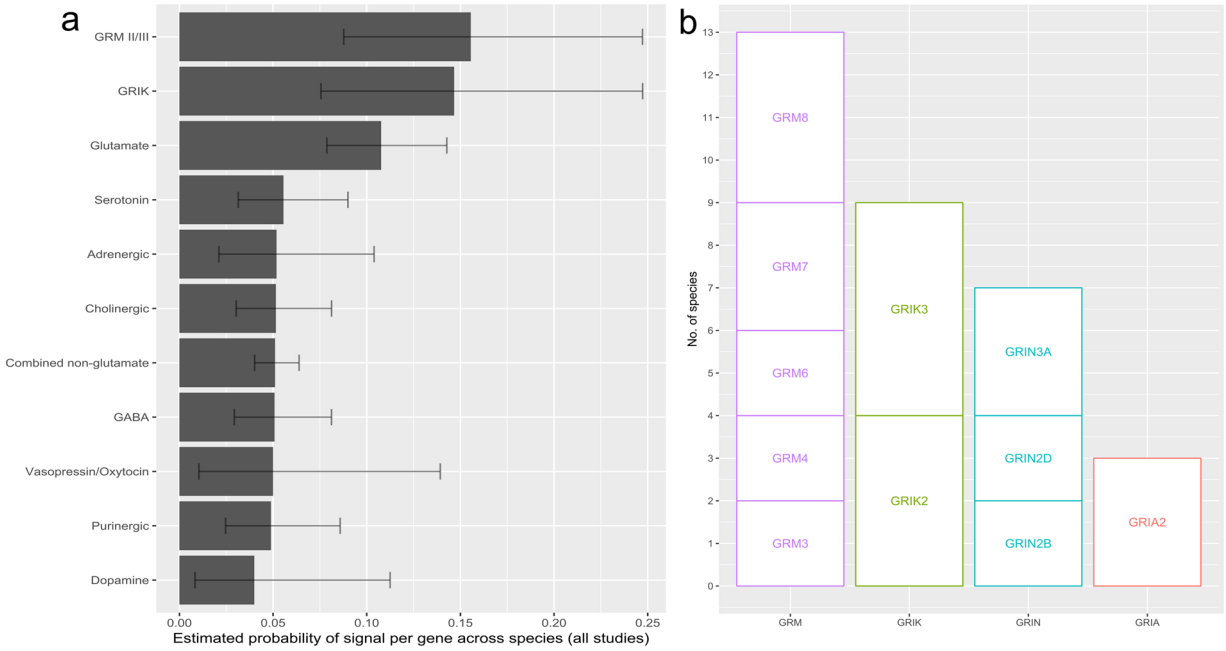

Table 2a

	Adrenergic	Cholinergic	Dopamine	GABA	Purinergic	Serotonin	Vasopressin / Oxytocin	Combined non-glutamate
GRIK	0.036477852	0.008911857	0.046150921	0.008652316	0.008967164	0.012919362	0.121974112	**0.002204602**
GRM II/III	0.017346295	**0.002219419**	0.019340959	**0.002155734**	**0.004326754**	**0.00585167**	0.082737842	**0.000367024**
Glutamate	0.059340109	**0.006299548**	0.086350154	0.008321368	0.011390926	0.023476731	0.24783441	**0.000139093**

Fig. 2. Signals of selection, introgression, high-frequency changes, or expression differences identified on glutamate and other widely expressed neurotransmitter receptor gene types. For full comparisons of receptor genes, see Supplementary Table S2. (a) Comparison of signals of selection, introgression, high-frequency changes, and expression differences detected between glutamate receptor genes and genes encoding seven other receptor types: Table 2a shows the results for Fisher's exact test, taking the proportion of changes to no change (estimated probability of a change occurring) for each of GRM II/III, kainate, and glutamate receptors and comparing these with proportions measured for the seven major receptor types: $p > 0.05$ shaded in grey; $p \leqslant 0.05$ not highlighted (non-formatted text); Bonferroni adjusted p-value ($p \leqslant 0.00625$) **highlighted in bold**. Error bars represent the exact confidence interval for the data summarized in each rectangular bar. (b) Number of species for which domestication/AMH-related changes are detected in at least two species per glutamate receptor gene.

changes that may mark convergent evolutionary processes among domesticated species and modern humans. Out of the 19 instances where selective sweeps, expression differences, allele-frequency changes, or adaptive introgression were detected on metabotropic receptor genes in a given study, 18 occurred in Group II or Group III subfamilies. The only exception to this is the detection of a selective sweep on *GRM1* in the chicken.

Instances of potential convergence on glutamate receptor genes are shown in Fig. 2b, which plots only signals of selection, introgression, high-frequency changes, or expression differences identified on a single gene for at least two species (domesticate or modern human). In terms of potential convergence between domesticated species and modern humans, signals were detected on members of kainate (*GRIK3*), metabotropic Group II (*GRM3*), Group III (*GRM6*, *GRM7*, *GRM8*), NMDA (*GRIN2D*, *GRIN3A*) and AMPA receptor genes (*GRIA2*) in at least one domesticate and one modern-human human study (see Table 1).

Changes on Group III metabotropic receptor genes are identified at a rate higher than those of any other multigene receptor (sub)families (mean of 2.75 signals per gene), including receptor genes for the most widely-expressed neurotransmitters in the brain, such as GABA (mean: 0.76; $GABA_A$ Beta subfamily mean: 1.33; $GABA_B$ family mean: 1.5), serotonin (mean: 0.83; HTR2 family mean: 1.33), (nor)epinephrine (mean: 0.78), acetylcholine (mean: 0.77), or dopamine (mean: 0.6). In general, the association of these receptor gene families with modern human evolution or domestication tended to track the neurotransmitter-wide average of 0.82 (Supplementary Table S2, Appendix A: mmc3).

Of the 114 multigene (sub)families examined, only corticosteroid receptors (mean: 2.5), and adhesion G protein-coupled receptor (ADGR) subfamilies B (mean 2.33) and D (mean 2.5) exhibit domestication or modern-human related changes at higher rates than kainate receptor genes (mean: 2.2). Both the corticosteroid and ADGRD families contain only two receptor genes, meaning that each family had a total of just five signals across the thirty domestication and modern human evolution studies examined here. By contrast, *GRIK3* alone exhibited five signals across these studies, and *GRIK2* four. The small size of the corticosteroid and ADGRD receptor families may well have contributed to the high mean signals highlighted here. To control for the potentially skewed effect of a small number of changes occurring on multigene (sub)families made up of only a few receptor genes, we carried out Monte Carlo random sampling (100,000 simulations) to determine the chance likelihood that receptor (sub)families should show the preponderance of signals that they do, given the amount of genes that they contain.

This analysis showed that the prevalence of signals occurring on Group III metabotropic or kainate receptor (sub)families was unlikely to occur by chance ($p < 0.00001$ and $p = 0.037$, respectively). By contrast, the chance likelihood of signals occurring at the rate they do on receptor families with comparable means (ADGRB, ADGRD, and corticosteroid) was considerably higher ($p = 0.12$, $p = 0.265$, and $p = 0.265$, respectively). Given their ability to form functioning heterodimers, Groups II and III metabotropic receptors could be considered a single functional subfamily. The prevalence of signals occurring on these six genes, when considered as a subsumed subfamily, was unlikely

to have occurred by chance, given the receptor-wide average ($p = 0.003$).

In order to determine if subfamilies with the highest mean signals showed significant divergence from those with lower means, we carried out one-way ANOVA comparisons among all multigene receptor (sub) families identified here. Out of the 22 pairwise comparisons that showed significant differences between means, twenty involved metabotropic subfamily III, while the two other significant comparisons involved the kainate receptor family (see Supplementary Table S14, Appendix A: mmc3). When one considers that alterations to neurotransmission are highlighted in many of the domestication studies analyzed here, these findings suggest that signals on metabotropic III and kainate receptor (sub)families are, at least, significantly higher than background genome-wide signals of selection under domestication.

Averaging across multigene families allows for the identification of potentially convergent signals on distinct genes with similar functional properties. However, this does not allow for analysis of single-gene receptor families, and it may also obscure above-chance convergent signals on individual genes within multigene families. *GRIK3* was one of only two genes exhibiting changes in five species, the other being *ADGRB3* (likelihood according to Monte Carlo simulation: $p = 0.004$). *GRIK2* and *GRM8* were two of only five genes that were identified in four domesticates (including modern humans in the case of *GRM8*) (likelihood according to Monte Carlo simulation: $p = 0.043$). Interestingly, *KIT*, a gene involved in the differentiation of neural crest precursor cells into melanocytes, and important in selection for coat color in domesticated species (Wilkins et al., 2014), was also identified in four different species (showing signals of selection in cattle and sheep, of introgression in the yak, and of brain expression differences in the pig). Given the prevalence of depigmentation in domesticate species, the consistent appearance of *KIT* in our review lends support to the approach of considering multiple correlates of domestication as potential signals of convergent selection.

Three glutamate receptor genes (*GRM7*, *GRIN3A*, and *GRIA2*) were identified among the 10 genes with changes detected in three species. Functional enrichment (Gene Ontology) analyses of the 17 genes with signals in three or more species showed glutamate receptor signaling to be the most highly-enriched pathway in the Biological Process category, with glutamatergic activity being in three of the top five pathways highlighted under Molecular Function. An extended functional analysis of the 92 genes showing signals of selection in two or more species highlighted 'Glutamatergic synapse' as the second most prominent KEGG pathway, behind the more general (and subsuming) category 'Neuroactive ligand-receptor interaction'.

The above analyses are suggestive that glutamatergic signaling has indeed been disproportionately targeted by selective pressures in modern human evolution and domestication. However, despite the fact that combining different measures of domestication allows for a larger number of signals (401) to be identified across all receptor genes, thus increasing the power of statistical inferences, the confound remains that certain of these correlates are not necessarily the result of selective pressures. If the preponderance of signals detected on glutamate receptor genes by measures such as high-frequency allelic divergence or brain expression differences is higher than that for selective sweeps, this may lead to inflated rates of signals on glutamate receptor genes from measures not explicitly associated with selection, thus biasing the statistical analysis.

In order to control for this possibility, we compare the rates of signals occurring on all 488 receptor genes across the 114 (sub)families in the absence of signals determined from brain expression differences, high-frequency allelic divergence, and/or adaptive introgression events (Supplementary Tables S3–S12, Appendix A: mmc3). The studies of high-frequency divergence (human and fox) are qualitatively distinct, in that the fox divergence is explicitly associated with domestication and has resulted from a controlled and documented application of selective pressures. While the human study has the advantage of identifying fixed or near-fixed changes that may therefore be implicated in species-wide human traits of interest to us here, the allelic divergence identified between fox populations is likely more comparable to the selective sweep studies carried out for other domesticates. For this reason, we retain the fox studies in the absence of human high-frequency measures in Tables S3, S5, S7, and S8. Under each of the measures in Tables S3–S12, the rates of signals occurring on glutamate receptor genes (in particular kainate and Group II/III metabotropic) consistently remain higher than those for other receptor types and (sub) families. These results are summarized for major neurotransmitter systems in Supplementary Figs. S3–S12 (Appendix A: mmc2).

To our knowledge, no study to date has sought to explore the extent to which glutamate receptor genes are associated with recent evolutionary events across a large number of domesticates, as well as with the emergence of our own species. More specifically, we are unaware of any previous study that has identified kainate and metabotropic receptor genes among the most prevalent targets of selective sweeps in domestication and recent human evolution. The extent to which these CNS-expressed receptor genes are identified in our review marks them as prime candidates for involvement in the emergence of domesticated and modern human behavioral phenotypes, in particular tameness and the reduction of reactive aggression.

We consider that it is worthwhile to explore the potential functional implications of these changes in domesticates and modern humans. Below we review the expression and actions of Group II/III metabotropic and kainate receptors in the CNS, before examining the phenotypes associated with alterations to these.

3. Association of kainate and metabotropic receptors with stress-related phenotypes

Given their importance for the normal functioning of the organism, synaptic proteins, including glutamate receptors, are rarely subject to extensive structural changes from one species to the next (Bayés et al., 2011; Ryan and Grant, 2009; Goto et al., 2009; Wada et al., 2004). Despite this high structural conservation, there are significant differences between humans and chimpanzees in the cortical expression of glutamate receptor genes (Liu et al., 2012; Muntané et al., 2015), suggesting that changes to regulatory regions may have had important functional consequences for the emergence of the human cognitive phenotype. Similarly, a large proportion of selective sweeps or high-frequency changes on glutamate receptor genes in AMH relative to archaic *Homo* are found in regulatory regions that control gene expression (Peyrégne et al., 2017; Kuhlwilm and Boeckx, 2019). In several of the studies cited in the caption of Table 1, signals of selection on glutamate receptor genes have been suggested as potentially important for behavioral changes during the domestication process (Li et al., 2014; Qanbari et al., 2014; Montague et al., 2014; Schubert et al., 2014; Wang et al., 2018b; Leno-Colorado et al., 2017; Zhang et al., 2018). However, such suggestions often form part of broader discussion on changes to genes related to the CNS under domestication, and no mechanistic details are provided. Furthermore, discussion is usually limited to highlighting the potential importance of glutamatergic-signaling changes in learning, memory, or excitatory transmission in a single domesticated species under study, and tends to focus on cortical regions.

Tameness of domesticates involves a reduction in fearful and aggressive reactions towards carers. Humans exhibit highly reduced reactive aggression among conspecifics compared with other extant primates, and it has recently been proposed that this potentially convergent attenuation of aggressive reactivity came under further positive selection during our recent evolution (Wrangham, 2019). However, any such argument should be able to point to evidence of convergence at the genomic and/or neurobiological level. Having already characterized the extent to which kainate and metabotropic

glutamate receptor genes exhibit overlapping genomic markers in domesticates and modern humans, here below we explore evidence for their participation in regulating the stress response. We articulate the hypothesis that, in ours and domesticated species, glutamate receptors have contributed to the attenuation of the HPA stress response, downregulating net excitatory inputs to the hypothalamus from central and feedforward stress circuits of the limbic system. We review evidence that a reduced stress response in pregnant females can alter developmental trajectories of future offspring *in utero*, and consider the potential of this mechanism to explain the emergence of convergent traits in ancient human and (pre-)domesticated species.

Fear, anxiety, and aggression are stress responses, mediated across vertebrates by the hypothalamic–pituitary–adrenal (HPA) axis (Denver, 2009; Haller, 2014), the hypofunction of which has been proposed as a key mechanism in the development of tame behaviors in domesticates (Trut et al., 2009; Wilkins et al., 2014). Glutamatergic signaling acts as a prominent excitatory driver of HPA activity and has been identified among the top enriched pathways across studies of aggression (Herman et al., 2004; Evanson and Herman, 2015; Takahashi and Miczek, 2013; Zhang-James et al., 2018). Kainate and Group II/III metabotropic receptors have predominantly modulatory or inhibitory, as opposed to purely excitatory, effects on signaling: kainate receptors are both presynaptically and postsynaptically located. At either location, they can have metabotropic (G-protein coupled) actions to suppress or facilitate both glutamate or GABA release (Contractor et al., 2011; Marshall et al., 2018). There is evidence that the extent of glutamate release can determine whether kainate receptors have this suppressive or facilitatory action, with suppression often occurring at high synaptic concentrations (Rodríguez-Moreno and Sihra, 2007). Groups II and III metabotropic receptors are expressed primarily at presynaptic terminals, but also postsynaptically, and, in the case of Group II receptors, on glial cells. They act to inhibit neurotransmitter release — principally glutamate, but also GABA — and, when bound by glutamate, to downregulate excitation of the postsynaptic cell (Niswender and Conn, 2010). The broad range of functions of kainate and Group II/III metabotropic receptors makes them plausible candidates for attenuating excitatory inputs to the HPA and reducing stress responses in humans and (pre-)domesticated species. We further detail these receptor actions in Section 4.

Table 2 summarizes evidence from human, model organism, and animal gene-behavior-correlation studies that kainate and Groups II and III metabotropic receptors highlighted here are implicated in developmental, neuropsychiatric, stress, and mood disorders, as well as divergent tame and agonistic phenotypes in non-human species. Table 2 also highlights associations between members of other glutamate receptor gene families and these disorders (detailed discussion of these gene–disorder association studies can be found in Supplementary Information: Section S2 [Appendix A: mmc1]). Schizophrenia is among the disorders most regularly associated with mutations on metabotropic and kainate receptor genes. In humans, prenatal stress is a prominent risk factor for the development of schizophrenia in adult offspring (van Os and Selten, 1998; Koenig et al., 2002). More broadly, heightened stress experienced during pregnancy can lead to a "persistently hyperactive" HPA axis in offspring, increasing children's propensity to develop Attention Deficit Hyperactivity Disorder (ADHD), as well as adult anxiety and reactivity to stress, while in rats, prenatal stress decreases the propensity to play in juvenile offspring and impairs sociality and extinction of conditioned fear lasting into adulthood (Welberg and Seckl, 2001; Motlagh et al., 2010; Green et al., 2011).

The association of kainate and Group II/III metabotropic receptor genes with multiple stress disorders implicates them in altered HPA-axis activity, and there is evidence for this involvement from early developmental stages. Pharmacological agonists of Group II metabotropic receptors reduce schizophrenia-like phenotypes in adult offspring of prenatally stressed mice (Matrisciano et al., 2012). Furthermore, high glucocorticoid inputs from the adrenal gland to the hippocampus reduce the expression of kainate receptors, and schizophrenics have been found express significantly reduced kainate receptors in this region (Hunter et al., 2009; Benes et al., 2001).

In prenatally stressed cattle, *GRIK3* has recently been identified among genes with the most significant hypomethylation of intronic CpG sites, a process thought to downregulate gene expression (Littlejohn et al., 2018). Similarly, human infants born preterm that exhibit an atypical neurobehavioral profile, including poor attention, self-regulation, and quality of movement, as well as increased arousal, excitability, and systemic signs of prenatal stress, have significantly differential methylation of *GRIK3* when compared with infants showing a more typical neurobehavioral profile (Everson et al., 2019). Thus, not only is there evidence that prenatal stress can contribute to the emergence of the same neurodevelopmental, neuropsychiatric, stress, and mood disorders that are commonly associated with altered expression of metabotropic and kainate receptor genes, but also that these genes may mediate the effects of environmental stressors on the organism.

Selective sweeps on kainate and metabotropic receptor genes in both ancient modern humans and early domesticated species may have resulted from convergent selective pressures on an attenuated stress response. Prenatal suppression of the stress signaling cascade in (pre-) domesticated and archaic human females upon contact with conspecifics, facilitated by these receptor actions, could have provided an important early step in the emergence of tameness and the reduction of stress reactivity. In Section 4, we explore the neurobiological evidence for such a hypothesis by detailing kainate and metabotropic receptor expression at various developmental stages, as well as their actions in regulating the stress-response cascade.

4. Synaptic functions of kainate and metabotropic glutamate receptors in the CNS

Alterations to the HPA axis are considered to be essential for the emergence of tameness in different (indeed competing) theories of domestication (Wilkins et al., 2014; Belyaev, 1979). Below, we detail evidence for the mechanistic actions of kainate and metabotropic receptor (sub)families in distinct structures of the limbic system, suppressing excitatory inputs to the hypothalamus.

Our argument relies on three pieces of evidence: First, that alterations to the HPA axis are common across domesticated species versus their wild counterparts, and in non-reactive versus reactively aggressive humans; second, that the genes highlighted here are extensively expressed across developmental stages in limbic and hypothalamic brain regions crucial for controlling the stress response, where their respective receptors regulate excitatory signaling (in the case of Groups II and III metabotropic receptors inhibiting glutamate release, while kainate receptors provide dual facilitatory and inhibitory functions); and third, evidence that disturbance of this expression alters the stress response. We contend that integrating this neurobiological evidence with current evolutionary theory will add considerable explanatory power to accounts of the emergence of modern humans and domesticated species.

4.1. Alterations to the stress response in domesticated species and modern humans

In response to stress, corticotrophin releasing hormone (CRH) is synthesized in the paraventricular nucleus (PVN) of the hypothalamus. This induces adrenocorticotrophin (ACTH) release from the anterior pituitary gland, which, in turn, stimulates the release of glucocorticoids (GCs: primarily cortisol and corticosterone) from the adrenal gland (Axelrod and Reisine, 1984). GCs are "the principal end-products of the HPA axis", which help to maintain homeostatic balance in the organism (Jankord and Herman, 2008). They also provide feedback directly to neurons in the PVN (Denver, 2009; Herman et al., 2012), or via other brain regions, particularly limbic structures, including the

Table 2
Human and domesticated phenotypes associated with glutamate receptor genes.

Gene	Associated human phenotypes									Tame and aggressive animal phenotypes
	DD/ID	ADHD	ASD	SCZ	BPD	OCD	ANX	MDD	SR/Fear	
GRIK1	◐	●	◐	●	●	●	⇒	●	⇒	
GRIK2	●		●	●	●⇒	●	⇒	●	⇒	Retention of dog-like polymorphisms on *GRIK2* in tame Czechoslovakian wolf–dog hybrid (Caniglia et al., 2018)
GRIK3	◐	◐	◐	●	●	◐	●	●	●	Signals of selection on *GRIK3* differentiating cattle breeds with agonistic and tame behaviors (Eusebi et al., 2018)
GRIK4	◐	●	●⇒	●⇒	●⇒	●	⇒	●⇒	⇒	
GRIK5	◐	◐	●	●	●	◐	◐⇒	●⇒	◐⇒	
GRM1	◐⇒	●	●⇒	●	●	⇒	⇒	●⇒	⇒	
GRM5	●⇒	● ⇒	●⇒	●	●	◐⇒	⇒	●⇒	⇒	
GRM2	◐⇒	◐⇒	◐⇒	●⇒		●⇒	●⇒	●⇒	●⇒	
GRM3	◐⇒	●	●⇒	●	●⇒	●⇒	●⇒	●⇒	●⇒	Missense mutation on *GRM3* differentiating aggressive from tame silver foxes (Wang et al., 2018b)
GRM4	◐	⇒	⇒	●⇒	●	⇒	⇒	●	⇒	
GRM6		◐	◐				⇒	⇒		*GRM6* identified in region of extreme differentiation between tame and aggressive red foxes (Kukekova et al., 2018)
GRM7	◐	●	●	●	●	⇒	⇒	●	⇒	Lower nucleotide variability on *GRM7* in docile Apennine Brown Bear (Benazzo et al., 2017)
GRM8	●	●⇒	●	●		◐	⇒	●	⇒	Lower nucleotide variability on *GRM8* in docile Apennine Brown Bear (Benazzo et al., 2017)
GRIN1	●	⇒	●⇒	●	●	⇒	⇒	●	⇒	
GRIN2A	●	●	●	●	●	⇒	⇒	●⇒	⇒	
GRIN2B	●	●	●⇒	●	●	●⇒	⇒	●	⇒	*GRIN2B* identified in region of extreme differentiation between tame and aggressive red foxes (Kukekova et al., 2018)
GRIN2C		⇒	●⇒	●⇒	●		⇒	●	⇒	
GRIN2D	●	⇒	◐	●	●		⇒	●⇒	⇒	Elevated forebrain expression of *GRIN2D* in tame versus aggressive silver foxes (Wang et al., 2018b)
GRIN3A		⇒		●	●			⇒		
GRIN3B	◐	◐	◐	●	◐		⇒	⇒		
GRIA1	●⇒	⇒	●⇒	●	●	⇒	⇒	●	⇒	
GRIA2	●	⇒	●	●	●	⇒	⇒	●	⇒	
GRIA3	●	⇒	◐	●	●	◐	⇒	●	⇒	
GRIA4	●		●	●		●⇒	⇒	●⇒	⇒	
GRID1	◐		●	●	●		⇒	●⇒	⇒	
GRID2	●	●	●	●	◐	●	⇒	●		

Genes with modern-human or domestication related changes are identified in three or more species are marked in **bold**.
●: Strong evidence for association between receptor gene and disorder from GWAS, human brain expression, and/or multiple case studies.
◐: Inconclusive evidence for gene-disorder association (e.g. single case studies or multi-gene copy-number variants including a given receptor gene).
⇒: Evidence from translational model animal studies for association between a glutamate receptor gene and the relevant disorder.
Detailed discussion of these associations, including references can be found in Supplementary Information: Section S2.
DD/ID – Developmental Delay/Intellectual Disability, ADHD – Attention Deficit Hyperactivity Disorder, ASD – Autism Spectrum Disorder, SCZ – Schizophrenia, BPD – Bipolar Disorder, OCD – Obsessive Compulsive Disorder, ANX – Anxiety Disorder, MDD – Major Depression, SR/Fear – Startle Response/Fear response.

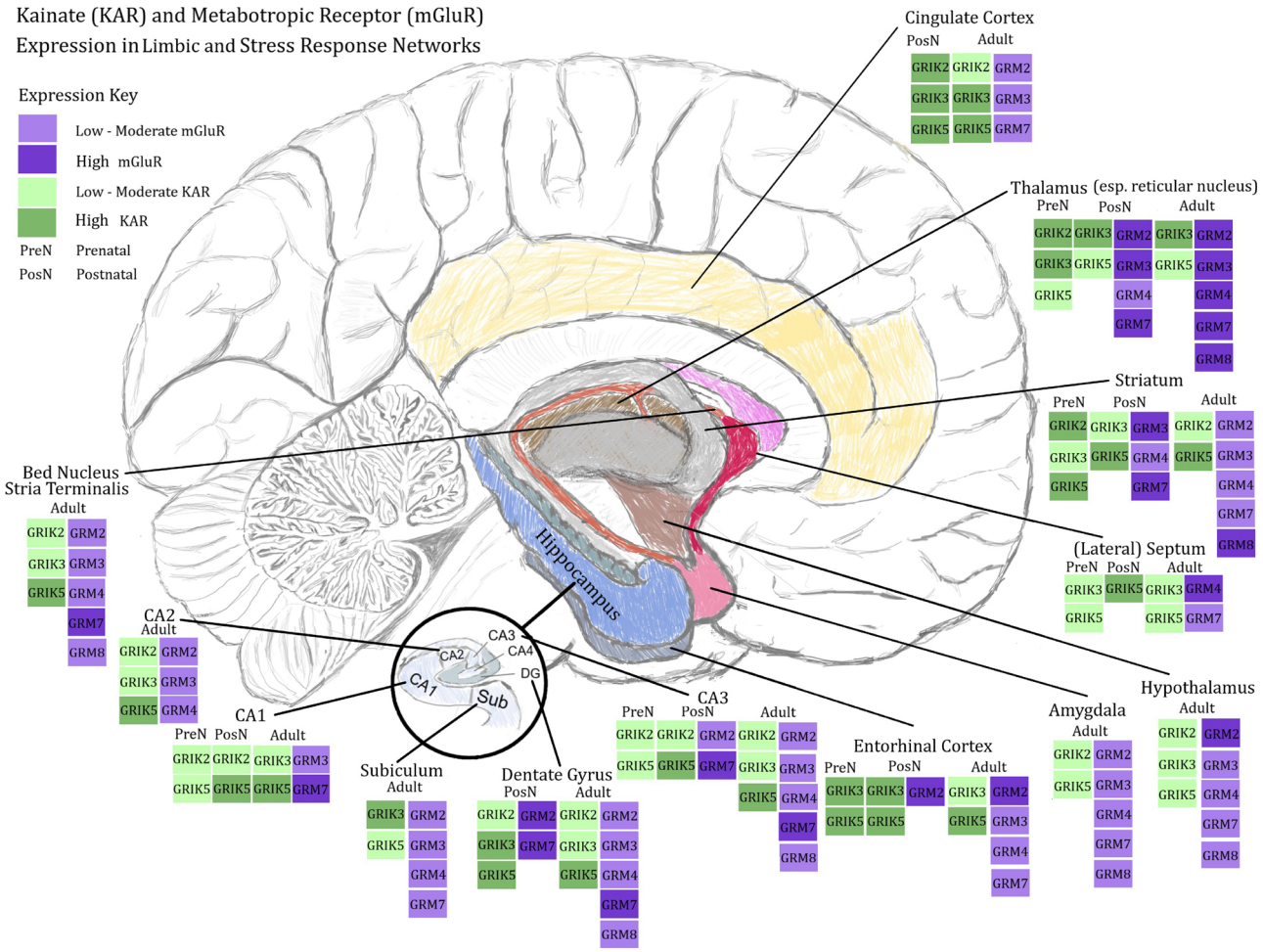

Fig. 3. Expression of kainate and metabotropic receptors implicated in modern-human and domestication studies in brain regions crucial for HPA regulation. Most detailed brain-expression data come from rodent studies. Where available, we have reviewed data from human fetal or postmortem studies. Broadly, there are cross-species parallelisms in the expression of kainate and metabotropic receptors. The expression patterns of these receptors are discussed in detail in Supplementary Information, Section S3: The kainate receptors highlighted here are most prominently expressed in the hippocampal formation (hippocampus and entorhinal cortex) in prenatal and early postnatal periods. Metabotropic receptors are more highly expressed postnatally and in adulthood. Relative to kainate receptors, they show higher expression in the amygdala and hypothalamus. Both the kainate and Group II/III metabotropic receptors are highly expressed in the thalamus and striatum. Again, this expression is predominantly prenatal in the case of kainate receptors, and both postnatal and adult in the case of metabotropic receptors.

hippocampus, thereby promoting or inhibiting further CRH release and the HPA stress response (Herman et al., 2005; Jankord and Herman, 2008). Thus, GC measures can be an accurate indicator of stress response in vertebrates, once basal and stress-response measures can be differentiated (Jacobson and Sapolsky, 1991).

Domesticated foxes, sheep, Bengalese finches, and ducks have lower basal GC levels than their wild ancestors or other closely related wild comparators (Plyusnina et al., 1991; Naumenko et al., 1989; Bassett and Hinks, 1969; Turner, 1984; Suzuki et al., 2014; Martin, 1975, 1978). In the duck and the fox, differences are particularly marked in prenatal and juvenile development, respectively (Martin, 1975, 1978; Plyusnina et al., 1991). Compared to their wild ancestors, Guinea pigs and chickens have a lower spike in GCs in response to stress (Künzl and Sachser, 1999; Ericsson et al., 2014). Although there is no extant ancestral comparator of neuroendocrine function in AMH, our species has considerably lower basal plasma cortisol levels than chimpanzees and most other primates (Chrousos et al., 1982).

Within the human population, variability in GC levels correlate with different individual stress responses, which mirrors findings in laboratory rats. Acute GC increases accompany bouts of reactive aggression, while chronically high basal levels have been found to correlate with increased anxiety and major depression, and may be implicated in reduced aggressive tendencies (Haller, 2014). Chronically low GC levels can correlate with antisocial personality disorder, callous, unemotional tendencies, and externalizing behaviors in children, as well as aggressive delinquency in adults. Proactively aggressive or non-aggressive children tend to have a lower spike in GC levels in response to frustrating tasks than reactively aggressive children (Lopez-Duran et al., 2009). Psychopathic adults (who often exhibit pathological proactive aggression) tend to have no cortisol reactivity to frustrating tasks (Haller, 2014).

The above studies suggest that, from early development into adulthood, lower basal GC levels are shared by domesticates and modern humans relative to closely related extant wild species. Moreover decreased GC spikes in response to stress are common to domesticates and non-aggressive or proactively aggressive modern humans versus reactively aggressive individuals. These findings are consistent with the view that prosocial selective pressures have led to a reduction in reactive over and above proactive aggression in recent human evolution (Wrangham, 2018). It could be considered that proactive aggressors within modern human populations exhibit a pathological version of the non-reactive phenotype that has been under positive selection and is associated with HPA-axis hypofunction under stress.

4.2. Kainate and metabotropic receptor expression in brain regions crucial for HPA regulation

The HPA axis is centrally regulated by the limbic system, primarily through amygdalar processing of perceptual inputs, which are relayed via the bed nucleus of the stria terminalis (BNST) to the paraventricular nucleus (PVN) in the hypothalamus. The limbic system also mediates feedback mechanisms, whereby glucocorticoids and mineralocorticoids act upon receptors in the hippocampus and medial prefrontal cortex, which connect to the PVN via the BNST and lateral septum. Feedback also occurs directly on cells in the PVN to inhibit further HPA reactivity. Feedforward mechanisms, further potentiating the stress response, are relayed from the amygdala to the PVN via the BNST. (Herman and Cullinan, 1997; Herman et al., 2005, 2012).

Glutamatergic and GABAergic signaling are the primary mediators of each of these aspects of HPA (re)activity, and the kainate and metabotropic receptor subfamilies discussed here play prominent roles in regulating the release of both neurotransmitters. These receptors are extensively expressed in limbic regions crucial for central, feedback, and feedforward control of the stress response. Fig. 3 highlights these expression patterns. A detailed overview of kainate and Group II and III metabotropic receptor expression in the developing and adult brain can be found in Supplementary Information: Section S3 (Appendix A: mmc1). In the subsection that follows, we review the mechanistic actions by which metabotropic and kainate receptors regulate and are regulated by HPA activity.

4.3. Control of HPA function by metabotropic and kainate glutamate receptors

The PVN is the crucial hypothalamic mediator of psychogenic stressors that drive HPA activity. Glutamate acting directly on parvocellular neurons of the PVN stimulates CRH release, whereas GABA inhibits this (Herman et al., 2004). This means that suppression of glutamatergic signaling by both kainate and metabotropic glutamate receptors in the PVN may serve to inhibit direct activation of the stress-response cascade.

GRIK2, *GRIK3*, and *GRIK5* are all expressed in the PVN and surrounding regions in adult rats, although *GRIK1* is higher expressed than other kainate receptor subunit mRNA in the PVN proper (Herman et al., 2000). *GRIK5* is extensively expressed on parvocellular neurons (Aubry et al., 1996). Presynaptic activation of GRIK1 (GLuK1, GLUR5) subunits in the PVN has been shown to attenuate HPA activity by inhibiting CRH release from parvocellular neurons (Evanson and Herman, 2015). Similarly, agonism of presynaptic kainate receptors in hypothalamic neurons facilitates inhibitory GABAergic signaling (Liu et al., 1999).

In vitro antagonism of Group II metabotropic receptors in hypothalamic slices has been shown to increase CRH signaling, whereas no other metabotropic receptor agonists or antagonists had this effect. Mice administered with Group II antagonists *in vivo* experienced an increase in corticosterone that mimicked the response to the forced-swim (behavioral despair) test (Scaccianoce et al., 2003). Given their predominant presynaptic and glial inhibitory functions, the above evidence implicates Group II receptors in the attenuation of central glutamatergic inputs to the hypothalamus (likely in the PVN), attenuating the HPA stress response. Group III metabotropic receptors have also been shown to inhibit excitatory inputs to the lateral hypothalamus (Acuna-Goycolea et al., 2004), while Group I metabotropic receptors stimulate both oxytocin and vasopressin release from the SON (Morsette et al., 2001).

Agonism of Group II metabotropic receptors disrupts the fear-potentiated startle response in mice, suggesting that these receptors regulate the learning of fearful experiences (Walker et al., 2002). Knockout of *GRM2* has been shown to correlate with increased stress in social interactions (Morishima et al., 2005). In macaques captured from the wild, six-week chronic intravenous administration of a Group II agonist reduced basal cortisol levels by as much as 50% compared to controls (Coplan et al., 2001). This same agonist has been shown to act on GRM3 (mGluR3) receptors in adrenal gland cells, leading to a reduction in aldosterone and cortisol via inhibition of the adenylyl cyclase/cAMP signaling pathway (Felizola et al., 2014). Yet another Group II agonist attenuates aggressive tendencies, hyperactivity, and deficits in the inhibition of the startle response of mice reared in isolation (Ago et al., 2012).

It has been proposed that Group II metabotropic receptors in the central amygdala dampen the stress response by downregulating the release of glutamate, in turn leading to an increase in GABAergic signaling and overall suppression of excitatory inputs to the PVN. Agonism of these receptors also leads to an increase in activity in the predominantly inhibitory BNST (but also in the PVN) in response to stress, overall suggesting a reduction in HPA activity via suppression of excitatory signaling. At the same time, activation of Group II receptors is downregulated in the hippocampus (Zhao et al., 2006). Excitatory feedback outputs from the hippocampus likely act on inhibitory neurons of the BNST that, in turn, relay to the hypothalamus (Herman and Cullinan, 1997). Thus, decreased Group II suppression of these outputs in response to stress can have the effect of enabling increases of inhibitory signals to dampen the HPA cascade. Within the BNST itself, activation Groups II and III receptors has been shown to suppress excitatory transmission (Grueter and Winder, 2005).

Mice lacking the Group III receptor subunit GRM8 (mGluR8) display increased age- and sex-dependent anxiety-like behaviors and startle response (Duvoisin et al., 2005, 2010). However, in contrast to *GRM2*, knockout of *GRM8* can enhance social interactions, suggesting that this receptor has opposing effects depending on the nature of the stressor. In another contrast with *GRM2* and the Group II subfamily as a whole, ablation of *GRM7* can make mice less fearful and less aggressive (Duvoisin et al., 2011; Masugi et al., 1999; Masugi-Tokita et al., 2016) correlating with a severe reduction in neuronal activity in the BNST. This suggests that activation of the GRM7 (mGluR7) subunit serves to enhance overall excitability of BNST neurons projecting to the PVN (and thus the stress response), perhaps through downregulation of glutamate release innervating GABAergic inhibitory interneurons (Masugi-Tokita et al., 2016). In a recent study of dissocial personality disorder, a rare duplication of *GRM7* was associated with extreme impulsive violence in a male prisoner cohort (Vevera et al., 2019). Activation of GRM4 (mGluR4) reduces anxiety-like behaviors in mice, while *GRM4* knockout enhances fear-conditioning responses and increases anxiety in adult but not juvenile mice (Davis et al., 2012). Such anxiety-related effects are thought to be brought about by alterations to amygdalar function.

Although the above behavioral correlates of Groups II and III receptor (ant-)agonism and ablation are partially contrasting, they indicate that both subfamilies are important for regulating the stress response, including aggressive reactivity. This tendency is clear in Group II metabotropic receptors, while the actions of Group III receptors are more varied according to the specific subunits and brain regions activated. Studies in rodents suggest that GRM8 and GRM7 have broadly opposite effects on anxiety levels, with GRM8 activation tending to be closer to Group II metabotropic receptors in its anxiolytic effects, while GRM7 seems to be more anxiety- (and aggression-)inducing (Swanson et al., 2005). This suggests that the numerous signals of selection on *GRM8* across domesticates and similar signals on Group II receptors in humans may be markers of convergent selection for a decreased stress response. This said, evidence also points more clearly towards activation of Group II receptors in potentiating prosocial behaviors. Future investigation of differences in brain region expression of Groups II and III receptors in domesticated species may help to shed more light on the contributions of each subfamily to the regulation of the stress response.

The kainate receptors we have examined here are expressed in the principal limbic regions that regulate HPA-axis function via glucocorticoid (GC) feedback (in particular the hippocampus and medial

prefrontal cortex, but also more moderately in the amygdala [see Fig. 3]). GCs promote glutamate release in these feedback regions, and the different affinities of mineralocorticoid receptors (MRs; bound by GCs at low concentrations) and glucocorticoid receptors (GRs; bound at higher concentrations) enable the modulation of stress feedback signaling from basal or moderate to acute levels (Jankord and Herman, 2008; Herman et al., 2012).

Glucocorticoids differentially modulate the expression of kainate receptor mRNA in the hippocampus depending on whether MRs or GRs are bound (Joëls et al., 1996; Hunter et al., 2009). Adrenalectomy (lowering corticosteroid levels) leads to increased expression of *GRIK2* in the dentate gyrus (DG) and CA3, and of *GRIK3* in DG (Hunter et al., 2009) (although no change has also been reported for *GRIK2* in CA3 (Joëls et al., 1996)). Single dose treatment with low levels of corticosterone following adrenalectomy — thought to bind MRs — increases *GRIK3* and high affinity subunit (*GRIK4* and *GRIK5*) mRNA in DG, as well as *GRIK5* across the hippocampus (Joëls et al., 1996). MR binding has been reported both to lower and raise *GRIK2* levels in the hippocampus (Hunter et al., 2009; Joëls et al., 1996).

Acute corticosterone treatment in adrenalectomized rats lowers kainate receptor mRNA expression to levels of untreated controls (Joëls et al., 1996). Similarly, chronic treatment leads to lower expression of *GRIK3* and *GRIK4* in hippocampal structures, although no changes were noted for *GRIK2* or *GRIK5* (Hunter et al., 2009). These divergent MR-/GR-mediated patterns of expression can help to elucidate the mechanism by which the genes under selection in domesticates and humans are expressed in a manner that can potentiate or attenuate the stress-induced feedback response.

Kainate receptor activation at CA3–CA1 synapses serves to inhibit glutamate transmission via $G_{i/o}$ signaling, especially when synapses are immature. At mossy fiber synapses connecting DG and CA3 (areas of high kainate receptor expression throughout life), kainate receptors inhibit glutamatergic signaling when glutamate is released at high levels, while facilitating release at lower levels, again via a $G_{i/o}$-coupled mechanism (Negrete-Díaz et al., 2018). Similar two-way modulation has been detected in the neocortex and amygdalae of rodents. Thus, when GCs are circulating at low levels, during basal or low stress, MR binding should lead to higher kainate receptor expression and facilitation of glutamatergic signaling in feedback regions. At higher GC levels (as when under acute stress) GR binding will tend to reduce kainate receptor expression, thus diminishing these receptors' ability to control glutamate release. In contrast, postsynaptic expression of AMPA and NMDA is enhanced under acute stress and corticosterone treatment (Popoli et al., 2011).

Because there are no direct hippocampal, prefrontal, or amygdalar connections to the PVN, feedback from these regions are instead relayed via the BNST, lateral septum, and ventromedial hypothalamus (VMH), which are all predominantly GABAergic (Herman et al., 2002, 2004). For the amygdala, which emits primarily inhibitory outputs to intermediary regions, this results in "GABA-GABA disinhibitory" downstream signals, increasing excitatory inputs to the PVN (Herman et al., 2005). In the case of kainate receptor expression, which is predominant in the hippocampus and medial prefrontal cortex, increased facilitation of glutamate release during basal or low-level stress is likely to primarily innervate GABAergic neurons along pathways relaying to the PVN. Similarly, downregulation of kainate receptor expression by

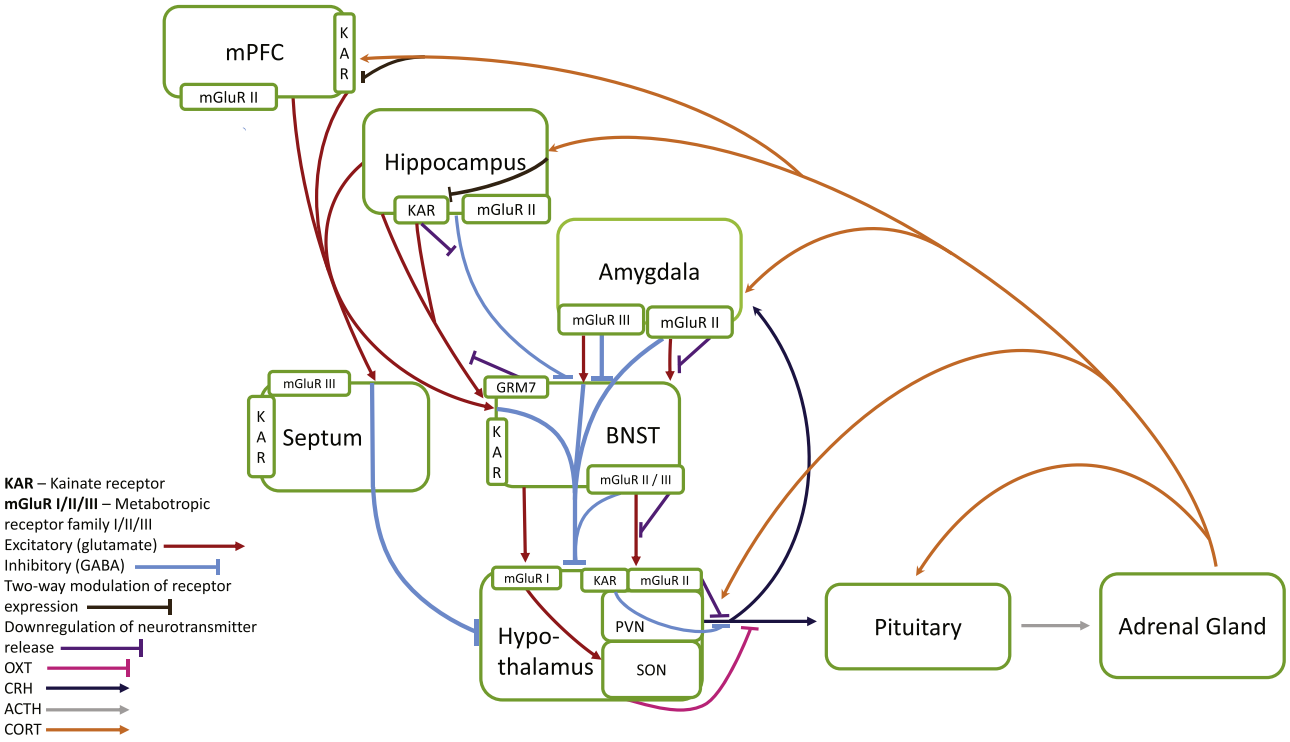

Fig. 4. Actions of Metabotropic and Kainate Receptors in the stress-response cascade. OXT – oxytocin; CRH – corticotrophin releasing hormone; ACTH – adrenocorticotrophin; CORT – corticosteroids; mPFC – medial prefrontal cortex; BNST – bed nucleus of the stria terminalis; PVN – paraventricular nucleus of the hypothalamus; SON – supraoptic nucleus of the hypothalamus. Groups II and III metabotropic receptors limit excitation of central and feedforward stress-response regions of the amygdala and PVN. The reduction in excitatory innervation of amygdalar GABAergic outputs limits GABA-on-GABA disinhibition of the BNST, which supplies the predominant inhibitory inputs to the PVN, the initiator of the hypothalamic–pituitary–adrenal (HPA) signaling cascade. Kainate receptors promote glutamate release during moments of low excitation and inhibit release during high excitation. Kainate-receptor actions in the stress feedback regions of the hippocampus and mPFC are regulated by corticosteroid inputs. During times of low stress, low corticosteroid feedback, and consequently, low stress-driven glutamatergic signaling, kainate-receptor expression is increased, promoting excitatory signaling. During moments of high stress, corticosteroids downregulate kainate-receptor expression, reducing these receptors' abilities to attenuate excitatory signaling. This allows for increased excitatory innervation of the BNST and consequent inhibition of HPA signaling.

GR binding during acute stress serves to diminish the alternate inhibitory effect of kainate receptors during intense glutamatergic release. This, in turn, should allow for NMDA and AMPA receptor signaling to be potentiated, leading to a dampening of the HPA stress response, again via the innervation of inhibitory neurons of the BNST, septum and VMH, which relay to the PVN.

In contrast to prefrontal and hippocampal feedback regions, the effect of glucocorticoids on parvocellular and magnocellular neurons of the hypothalamus is to downregulate glutamatergic signaling via the release of endocannabinoids, in turn promoting the release of GABA (Di et al., 2009). Kainate receptors have been implicated in the mobilization of endocannabinoid signaling in distinct brain regions, as well as in the promotion of GABAergic signaling in the PVN (Evanson and Herman, 2015; Lourenço et al., 2011; Marshall et al., 2018).

Fig. 4 presents a schema of the actions of metabotropic and kainate receptors in central, feedback, and feedforward stress-response regions of the CNS, regulating activity of the HPA signaling cascade.

Increased expression of metabotropic and kainate receptors, attenuating central and feedback stress responses may plausibly have conferred selective advantages in human evolution, not only via the reduction of stress and enabling of prosocial cooperation, but also by enabling subsequent increases in kainate receptor expression: Firstly, Groups II and III metabotropic glutamate receptor attenuation of excitatory inputs to amygdalar fear-processing areas in response to stressors, in combination with kainate and Group II metabotropic receptor inhibition of CRH release in the PVN can lead to a signaling cascade that results in lower glucocorticoid feedback in limbic structures. This, in turn may lead to increased expression of kainate receptors in the hippocampus, prefrontal cortex, and elsewhere, enabling subsequent selection on improvements in plasticity and learning, as well as further resources for attenuation of the stress response in limbic regions.

5. Conclusion

We have argued here that selective pressures, leaving genomic and neurobiological markers of convergence on kainate and Group II/III metabotropic receptor genes in ours and domesticated species, have led to downregulation of net excitatory inputs to the HPA axis and attenuation of the stress response. This may have had the corollary effect of increasing synaptic plasticity in limbic feedback regions that play a crucial role in memory and learning. We have not dealt in detail with G-protein signaling cascades activated by kainate and Group II/III receptors. A more in-depth view of convergence may be gained by exploring the extent to which the same signaling cascades (in particular $G_{i/o}$ signaling) are activated in homologous brain regions across species regardless of the receptor subtype initially bound.

Given the important roles that serotonin and oxytocin play in promoting social and empathetic behaviors across different species, it has been proposed that convergent tameness in domesticates and prosociality in modern humans aredriven by alterations to these systems (Hare, 2017). The present analysis of modern human–archaic and domesticate–wild differences in glutamatergic receptor genes suggests that any such modifications (particularly to oxytocinergic signaling) are more likely to be dependent on upstream changes to glutamatergic signaling. Glutamate mediates the release of oxytocin and vasopressin from the SON and PVN (Busnardo et al., 2012).

Serotonin regulates glutamatergic activity in the brain, often acting to reduce excitatory potentials and to stimulate GABAergic inhibitory signaling (Lesch and Waider, 2012). This regulation from outside the glutamatergic system could potentially produce comparable attenuation of the stress-response to the regulation from within that we propose for metabotropic and kainate receptors. It should be noted, however, that glutamatergic signaling can also control the release of serotonin from the dorsal raphe nucleus (Celada et al., 2001). In studies of genetic differences between tame and aggressive foxes, changes to serotonergic signaling accompany those of the glutamatergic system, along with genetic changes often potentially relevant to both synapses (Wang et al., 2018b; Kukekova et al., 2018). Similarly, domestication of the pig appears to have involved important changes across both systems (Leno-Colorado et al., 2017). Signals of selection associated with serotonergic signaling have also been identified in a tame strain of rat and the domesticated goat (Albert et al., 2011; Dong et al., 2015).

One may reasonably ask whether Groups II and III metabotropic and kainate receptors share functional or structural qualities that have made them more likely to come under selection than NMDA, AMPA, or Group I metabotropic receptor (sub)families in domesticate species and modern humans. These receptors have been implicated in many disorders and phenotypes reviewed here for metabotropic and kainate receptors (see Table 2 and Supplementary Information: Section S2). Even within receptor families, specific subunits (and combinations of them) or splice variants can have diametrically opposing functional properties from others that are nominally similar (Bettler and Mulle, 1995; Perrais et al., 2010).

The shared abilities to downregulate excitatory signaling, overlapping expression patterns, and converging phenotypical associations of those genes that are most consistently detected across domestication and modern human studies has led us to hypothesize an important role for kainate and Groups II and III metabotropic receptors in the regulation of the stress response. However, there is no reason, in principle, why other glutamate receptor families could not have contributed to the emergence of tame behaviors. In fact, genomic markers or expression differences are detected on NMDA receptors in two species for each of *GRIN2B* (fox and yak), *GRIN2D* (AMH and fox), and on three species in the case of *GRIN3A* (AMH, yak, and duck; see Table 1). Each of these genes' respective subunits are highest expressed during embryonic and early postnatal stages, and have been associated with the maintenance of immature dendritic spines during development (Paoletti et al., 2013). If similar patterns of selection should be detected on NMDA receptors across other domesticates, a case could feasibly be made for their contributing to the juvenile cognitive phenotype typically retained by domesticate species into adulthood. On the other hand, the only case of potentially convergent selection on an AMPA receptor gene occurs on *GRIA2* (AMH, cat, and pig), which is a crucial AMPA subunit at mature synapses (Isaac et al., 2007).

The diversity of roles played by kainate receptors in the CNS, including extensive excitatory, inhibitory, ionotropic, and metabotropic activities (Contractor et al., 2011), provides a wide range of possible functions upon which natural selection can act. Selective pressures seem to have honed varied specializations for kainate receptors in different brain regions. Groups II and III metabotropic receptor subunits can have opposing actions within a single brain region that can vary according to the stressful stimuli being processed. This suggests that these subunits often have complementary functions within their subfamilies. Nonetheless, there are considerable overlaps of function, and these subunits primarily inhibit adenylyl-cyclase signaling and postsynaptic excitation. Each receptor subfamily acts, broadly, to dampen stress responses. These overlaps in function very plausibly contribute to numerous signals of selection being spread across different metabotropic receptor genes in distinct species.

In the future, it may be worthwhile to examine the extent to which the glutamatergic changes discussed here could have impacted the vocal abilities of the relevant species, including ours. Although the extent of archaic humans' vocal-learning abilities is not known, this capacity is highly striatum-dependent, as can be seen in the neurology of Tourette's syndrome. Glutamatergic signaling alterations in the striatum have been implicated in Tourette's syndrome, including genes with AMH-specific changes (Singer et al., 2010). Vocal learning deficits in humans who carry a mutation on the *FOXP2* gene are thought to arise, in part, from abnormalities in the striatum (Vargha-Khadem et al., 2005). Knock-in experiments of the humanized *FOXP2* allele in mice have shown the principal structural changes to take place in the

striatum, where MSN dendrites are longer and respond to stimulation with increased long term depression (Reimers-Kipping et al., 2011). *FOXP2* is also expressed in glutamatergic projection neurons of the motor cortex and is highly expressed during the development of corticostriatal and olivocerebellar circuits, important for motor control (Reimers-Kipping et al., 2011; Lai et al., 2003).

Several glutamate receptor genes discussed above, such as *GRIK2* and *GRM8*, have been identified as a transcriptional target of FOXP2 in the developing songbird brain (Shi et al., 2018). Significant changes to glutamatergic expression have also been found in the song nuclei of vocal-learning birds, and in the domesticated Bengalese finch compared to its wild ancestor the white-rumped munia (Wada et al., 2004; Okanoya, 2015, 2017). These changes are thought to play a role in the more complex singing capabilities of the Bengalese finch. Glutamate receptor genes form part of the most highly co-expressed module in the periaqueductal gray of bats, a mammalian species that displays strong evidence of vocal-learning capabilities (Rodenas-Cuadrado et al., 2015).

Finally, an important question arising from the evidence presented here is how glutamatergic involvement in the regulation of the stress response relates to the hypofunction of the neural crest, proposed to account for the suite of phenotypic changes that make up the domestication syndrome (Wilkins et al., 2014). At this point, the evidence from selective sweep studies strongly points to the involvement of glutamatergic signaling in domestication. Our comparison of different receptor types does not allow for evaluation of arguments that a "mild neurocristopathy" drives the emergence of the domesticated phenotype. The neural-crest-related gene (*KIT*) was detected in studies of cattle, sheep, pigs, and yaks. This gene is involved in melanocyte differentiation, and evidence points to its importance in selection for coat color: Signals occurring on *KIT* in Clydesdale horses and Birman cats have been implicated in their breed-specific coat patterns (Schubert et al., 2014; Montague et al., 2014). As such, selection on *KIT* is unlikely to be related to the unifying domesticated trait of tameness, as proposed here for the attenuation of glutamatergic signaling in stress-response regions of the brain. Whether this extends to other neural-crest related genes, in line with arguments against the universality of the effects predicted by the neural crest hypothesis (see (Sánchez-Villagra et al., 2016)) remains to be determined.

There are various possible explanations for how glutamatergic signaling may interact with, or even bypass, the neural crest to bring about the broader phenotypical features of the domestication syndrome, two of which we briefly evaluate here. Under one account, the reduction in neural crest cell (NCC) proliferation may occur subsequent to changes in glutamatergic transmission. Thus, overall net reduction of glutamatergic inputs to the hypothalamus would attenuate HPA-axis signaling, and ultimately glucocorticoid output, from the adrenal cortex in (pre-) domesticated females during pregnancy. Modified hormonal concentrations would then affect embryonic development, altering neural crest cell inputs to different tissues prenatally. In cell cultures, glucocorticoids are essential for NCC survival and differentiation (Doupe et al., 1985). An increase in corticosteroid concentrations has been shown to increase NCC numbers and alter cell fates, for example converting small intensely fluorescent cells, which are normally dopaminergic, into epinephrine-synthesizing cells. Removal of corticosteroids and replacement with nerve growth factor converts small intensely fluorescent cells and chromaffin cells into sympathetic neurons (Doupe et al., 1985a, 1985b). Mice embryos lacking the glucocorticoid receptor cannot survive outside the womb due to widespread defects, including severe reductions in chromaffin cells from early development. Those cells that remain lose their ability to synthesize epinephrine (Cole et al., 1995).

The above studies suggest that lowered stress hormone levels in the womb, resulting from HPA hypofunction in the mother can have the knock-on effect of bringing about neural crest hypofunction and cell-differentiation changes in embryonic development. Under our hypothesis, mild reductions in NCC inputs could be driven by down-regulation of excitatory input to the stress-response cascade during pregnancy, resulting from selection for tameness. Corticosterone treatment during embryonic development of domesticated ducks can bring about mallard-like behaviors in neonates (Martin, 1975, 1978), and glucocorticoid levels are lower during gestation in both tame rats and foxes compared with aggressive strains (Oskina et al., 2010). Suppression of glucocorticoid levels in pregnant aggressive females between days 12 and 14 of gestation leads to a concomitant reduction in embryonic glucocorticoids by day 20. This, in turn, leads to significant increases in depigmentation in neonate rats (Oskina et al., 2010). In both the rat and duck studies, the effects of glucocorticoids on embryonic development take place long after neurulation and migration of neural crest cells away from the neural tube. This suggests that at least some of the most important phenotypical features of domestication need not depend on genetic changes to NCC development or migration, but, rather, on postmigratory regulation of expression at different tissue sites by glucocorticoids.

An alternative possibility is that alterations to glutamate receptor signaling can directly account for both behavioral and physical changes in domestication. Some evidence for this derives from the fact that glutamate receptor, transporter, and other signaling genes identified in different domestication studies are expressed in melanocytes, osteoblasts, osteoclasts, chondrocytes, and other tissues beyond the CNS (Wang et al., 2005; Hoogduijn et al., 2006; Devi et al., 2013; Julio-Pieper et al., 2011; Matta, 2013). Thus, traits such as floppy ears, shortened snouts, or depigmentation could feasibly result from alterations to glutamatergic receptor expression in these tissues. Bone is innervated by glutamatergic fibers and glutamate receptors are thought to play a role in osteoblastic differentiation and proliferation (Jones et al., 2004; Xie et al., 2016). *GRIK5*, *GRM4*, and *GRM8* along with NMDA and AMPA receptor genes are expressed *in vitro* in developing rat calvarial osteoblasts (Hinoi et al., 2001, 2002). Group II and III metabotropic receptors have been shown to prevent mineralization of chondrocytes, implicating them in cartilage development (Wang et al., 2005; Matta, 2013). NMDA receptors have been implicated in the maturation and differentiation of chondrocytes (Takahata et al., 2008). Glutamate receptor genes (among them *GRIK3*) are expressed on melanocytes, and inhibition of AMPA-mediated excitatory transmission has been found to decrease the expression of *MITF* (melanocyte inducing transcription factor) (Hoogduijn et al., 2006).

On considering these two alternative accounts of glutamatergic signaling in the emergence of the domestication syndrome (NCC-interacting versus NCC-independent), we prefer to be cautious about attributing too many functional consequences to the domestication-related signals highlighted here. We consider that a mild neurocristopathy will almost certainly explain some physical trait changes in domesticate species, and that this may serve to entrench earlier selection for tameness via reduced inputs to stress-hormone cells in the adrenal glands, in line with the proposal of (Wilkins, 2019). Future investigations may help to determine whether these reductions result from upstream attenuation of glutamatergic inputs to the hypothalamus. In some species, changes to glutamatergic signaling, driven by selection, may also have acted to directly alter the development of physical traits, independently of genetic or epigenetic alterations to the neural crest.

Authors' contribution

Data collection and analysis: TOR, CB; proposed mechanism: TOR; draft preparation: TOR, with input and revisions from CB; project supervision: CB.

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Conflict of interest

The authors have no competing interests to declare.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neubiorev.2019.10.004.

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Note on Supplementary Information

Besides the supplementary information that follows, an Excel file is also available here: Supplementary Tables S1-S15.

Supplementary Information: Glutamate receptors in domestication and modern human evolution

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S1. Broad changes to glutamatergic signaling under domestication

Signals of selection have been detected in AMH and Yaks on *NETO2* [1, 2], which encodes an accessory subunit that modulates the desensitization of kainate receptors, and interacts with the GRIP scaffolding protein to increase receptor abundance at synapses [3, 4]. In mouse hippocampal cultures, NETO2 and GRIK2 proteins interact to increase recycling of the co-transporter SLC12A5 to the surface membrane [5] (signals of selection occur on the corresponding gene in AMH [6]). Increased SLC12A5 at hippocampal dendritic spines suppresses AMPA mediated excitatory transmission by preventing the transmembrane diffusion of GRIA1 proteins [7], and NETO2-SLC12A5 interactions during development promote increases in GABAergic inhibitory signaling in the hippocampus [8]. Altered prefrontal expression of different *SLC12A5* transcripts have been associated with schizophrenia and affective disorders [9], and this gene has also been associated with autism spectrum disorder (ASD), epilepsy and developmental delay [10, 11, 12]. The signals of selection on *NETO2* and *SLC12A5*, their postsynaptic interactions with kainate receptors, regulation of excitatory and inhibitory transmission, and associations with affective and developmental disorders make them candidate interactors for the modulation of the stress response in both domesticate species and modern humans.

In a recent study of convergent signals of selection on domesticated goats and sheep, Neurobeachin (*NBEA*), a gene that regulates glutamate and GABA receptor expression at synapses, was highlighted as being one of the most likely genes to be implicated in behavioral changes under domestication [13].

In the case of rats selected for tame behaviors, expression differences are also prominent in glutamatergic signaling genes implicated in the stress response. Most notably, *SLC17A7*, which encodes for a vesicular glutamate transporter, is detected at twice the levels in the brains of tame rats as in those of the aggressive strain. Underexpression of *SLC17A7* has been implicated in increased anxiety in mice [14].

The postsynaptic scaffolding proteins DLGAP1 and DLGAP3, have both been implicated in obsessive compulsive disorder (OCD) and Tourette's Syndrome [6, 1, 15, 16, 17]. *DLGAP1* and *GRIK2* have been identified in a genome-wide association study as high-confidence interactors in the etiology of OCD [18]. Signals of selection have been identified on *DLGAP1* in a horse domestication study [19]. Stereotyped and compulsive behaviors are common in horses, as well as many other domesticated animals [20, 21]. Indeed, pharmacological targeting of glutamatergic signaling is successful in treating both Canine Compulsive Disorder and human OCD, suggesting a shared etiology for these conditions [22]. Both *DLGAP1* and *DLGAP3* (signals of selection in AMH [1, 6]) have been implicated in Tourette's syndrome and OCD, as well as schizophrenia and major depression. At the postsynaptic density, DLGAP proteins interact with DLG membrane-associated proteins, and associate with kainate receptors. Signals of selection have been detected on *DLG4* in yaks [2]. When cotransfected in cell cultures, GRIK2 subunits associate with DLGAP3 only when accompanied by DLG4 [23]. GRIK2/GRIK5 heteromeric receptors desensitize more slowly to glutamate when they associate with DLG4 [24].

DLGAP1 knockout mice exhibit marked social deficits, correlating with loss of associations between postsynaptic scaffolding complexes and the DLG membrane-associated proteins [25]. *DLGAP3* knockout mice exhibit OCD like behaviors, and have increased NMDA and reduced AMPA transmission at corticostriatal synapses [26]. Knockout of all five kainate receptor genes (*GRIK1-5*) results in comparable preservative behaviors, yet also leads to reduced NMDA:AMPA ratios at corticostriatal synapses [23]. The same effects were not found in CA3 of the hippocampus, suggesting that kainate receptors are not essential for NMDA mobilization in this region. Postsy-

naptically localized GRIK2 receptors inhibit glutamate signaling in striatal direct pathway medium spiny neurons by activating presynaptic cannabinoid CB_1 (G-protein-coupled) receptors, thus regulating plasticity in basal ganglia circuits [27]. The interactions of kainate receptors with DLG and DLGAP proteins, their roles in the regulation of striatal plasticity, and their involvement overlapping stress-related phenotypes make them plausible candidates for having come under convergent selection in domestication and modern human evolution.

Many glutamate signaling genes have been identified in a recent study of genomic regions associated with tame behaviors in the domesticated fox [28]. These include *SORCS1*, whose encoded protein is involved in trafficking and maintaining AMPA receptors at the cell membrane, increasing synaptic transmission [29]. This gene was detected alongside other glutamatergic signaling genes, including *SORCS2*, *SORCS3* (identified in the fox study), and the AMPA receptor gene *GRIA1* in a draft human selective sweep study [30]. However, in a revised version of the same paper, only signals on *SORCS2* remained [6]. The SORCS2 protein is highly enriched on post-synaptic densities in the striatum and hippocampus, where it regulates NMDA-dependent synaptic plasticity and spatial learning [31]. *SORCS2* knockout mice display manic-depressive symptoms, and polymorphisms in the human population have been associated with bipolar disorder, schizophrenia, and attention deficit hyperactivity disorder (ADHD) [32]. *SORCS3* knockout mice have fear-extinction and spatial-memory deficits [33]. Each of the above SORCS proteins interact with DLG4 [29, 31, 33].

PLCB1 and *PLCB4* display signals of selection in red foxes, pigs, and yaks [28, 34, 2]. PLCB4 acts downstream of GRM1 synaptic signaling to mobilize endocannabinoids, which suppress glutamate release [35]. In humans, this gene has been implicated in syndromic malformations of the ear and jaw [36]. PLCB1 also modulates GRM signaling and has been implicated in schizophrenia [37, 38]. Signals on *KCNJ3* have been identified in foxes and multiple human selective sweep studies [1, 30, 15, 28]. This gene is expressed in the adrenal gland, and its encoded protein has been implicated in cell guidance and localization during CNS development, associates with postsynaptic glutamatergic proteins, and has been implicated in schizophrenia [39, 40, 41].

CACNA1C, which encodes for a voltage-dependent calcium channel subunit, has been detected in a cattle domestication study, and distinct allelic variants are associated with tame and aggressive breeds of foxes [42, 28]. In humans, this gene has been associated with bipolar disorder, schizophre-

nia, and major depression [43]. A single polymorphism on *CACNA1C* in schizophrenics is associated with increased expression and higher activity in the hippocampus in response to emotional stimuli [44], as well as higher left amygdala activity in bipolar disorder [45]. *CACNA1D* has been detected in human and horse selective sweep studies [1, 19]. Both *CACNA1C* and *CACNA1D* are intensely expressed in striatal medium spiny neurons (MSNs) [46]. CACNA1D subunits bind to glutamatergic scaffolding proteins of striatopallidal MSNs, where they inhibit glutamate transmission by allowing Ca^{2+} influx, thus downregulating dendritic spine densities. MSNs are targeted by dopaminergic afferents which drive glutamatergic transmission and inhibit CACNA1D channel opening. When dopaminergic signaling is abolished, spine densities are decreased via the opening of CACNA1D channels in a process thought to be critical in the motor deficits experienced by Parkinson's disease patients [47]. *CACNA1D* is also expressed in the adrenal gland [48].

The striatal expression of kainate and other glutamatergic signaling genes, their interactions at synapses, overlapping involvement in cognitive and stress disorders, including OCD, and associations with tame behaviors in the fox, suggest that convergent selection on striatal-mediated behaviors may have accompanied modulation of the HPA stress response. In the case of humans, it has recently been argued that increases in prosociality following our divergence from other extant primate lineages was driven by neurochemical changes in the striatum, particularly altering dopaminergic signaling [49]. We propose that such selective pressures on prosociality have continued following our split from Neanderthals, and that potentially convergent signals of selection with domesticates across the glutamatergic system may be indicative of this.

SLITRK1, which encodes for a transmembrane protein at excitatory synapses, has a high-frequency missense change in modern humans and shows signals of positive selection in our lineage [50, 6, 51]. This gene has also been implicated in OCD and Tourette's syndrome [52]. Beyond the receptor genes highlighted in the present study, OCD is associated with a number of genes related to glutamatergic signaling that show signals of selection in AMH. These include *SLC1A1*, which encodes for a neuronal glutamate transporter, is expressed prominently on hippocampal dendrites, and is most consistently associated with OCD among glutamatergic signaling genes [6, 53, 54, 55].

4

S2. Glutamate receptor genes in human and domesticated behavioral phenotypes

There is extensive evidence from human and translational studies for the involvement of glutamate receptor genes in neurodevelopmental and neuropsychiatric disorders, the etiologies of which include alterations to the stress system during early development (see main text: Section 3; Table 2). Furthermore, distinct markers on these genes — evidenced to result from natural or artificial selection in the case of non-human species — have been associated with divergent measures of aggressiveness across multiple species. These include differences between domesticated breeds, distinct wild (sub)species, domesticate–wild crosses and their wild counterparts, as well as between aggressive and non-aggressive humans (see e.g. [56, 57, 58, 59]. For each of the twenty-six glutamate receptor genes, here below we review evidence from human genotype-phenotype associations and model-animal studies of neurodevelopmental, stress, mood, and neuropsychiatric disorders.

S2.1. Kainate receptor genes in human and domesticated behavioral phenotypes

Single Nucleotide Polymorphisms (SNPs) on *GRIK1* have been identified as significant susceptibility loci in genome-wide association studies (GWAS) of ADHD and OCD patients [60, 16, 61]. A chromosomal deletion that included sixteen of *GRIK1*'s seventeen exons has also been highlighted (among other deletions) in a single-case study of a young autistic male with prominent speech delay [62]. This gene may also contribute to learning deficits identified in a partial-trisomy mouse model of Down's Syndrome [63]. A case-control and family-based association study has implicated *GRIK1* in schizophrenia, while postmortem gene-expression studies have found decreased expression of this gene in the brains of schizophrenic, bipolar disorder, and major depressive disorder (MDD) patients [64, 65, 66]. Multiple model-organism studies have implicated *GRIK1* in anxiety and fear-related behaviors, including startle response [67, 68, 69, 70].

Brain expression and genomic markers on *GRIK2* have been associated with schizophrenia [71, 72, 66] and bipolar disorder [65, 73]. Evidence from knockout mice points to a role in manic behaviors, including hyperactivity, fearlessness, decreased anxiety, and increased aggressiveness (traits absent from *GRIK1* knockouts) [74, 75]. Among humans, aggression and antisocial personality disorder are significantly higher in bipolar and schizophrenic

patients than in the wider population [76, 77, 78, 79].

Association studies have found *GRIK2* SNPs to be implicated in autism spectrum disorder [80, 81, 82]. Potentially relevant to our account of the maternal influence on the emergence of domesticated phenotypical traits are findings that *GRIK2* variants associated with schizophrenia and ASD are significantly more likely to be maternally transmitted [72, 81]. *GRIK2* has also been associated with major depressive disorder, including significantly higher expression in depressed females [83, 84]. Multiple studies have also found associations with the stress disorder OCD [85, 86]. Mice that have all five kainate receptors knocked out exhibit increased preservative and diminished exploratory behaviors, a tendency typical in OCD, although these abnormalities are absent in *GRIK2* knockout mice [23].

Deletions and loss-of-function mutations on *GRIK2* can cause intellectual disability and social impairments, including autistic behaviors [87, 88, 89]. A gain-of-function mutation on *GRIK2* in humans has been shown to bring about syndromic changes during development that include slight microcephaly, intellectual disability, happy demeanor, short attention span, increased drooling, stereotyped behavior, and increased aversion to loud noises [90]. Some of these symptoms are comparable to behaviors and phenotypes often observable in domestic dogs.

The Czechoslovakian Wolfdog, a tame hybrid resulting from a recent wolf-dog crossing experiment, has accumulated a significantly higher number of dog-like polymorphisms on *GRIK2* [58], making this gene a strong candidate gene in enabling the retention of tame behaviors. Domestic rabbits — which have signals of selection on *GRIK2* — exhibit gross brain changes in regions known to mediate fear response [91].

GRIK3 has been implicated in behavioral differences between modern domesticated cattle breeds: Lidia cattle (Spanish Fighting Bulls), which have been artificially selected for agonistic behaviors, display differential signals of selection on *GRIK3* when compared to tame breeds [56]. These allelic differences, in turn, implicate ancient signals of selection detected on *GRIK3* in the emergence of the domestic phenotype in cattle [42], resulting from selection for tameness.

Similar functional implications are likely for yaks, for which signals on *GRIK3* have been detected from cattle introgression. *GRIK3* has also been identified in various dog domestication studies (see Table 2). As in cattle, *GRIK3* is a strong candidate for having been subject to changes in the initial stages of dog domestication [92].

In humans, a microdeletion including *GRIK3* has been reported in a case of severe developmental delay affecting language, motor, social, and attentional skills [93]. Duplication including several genes in the same chromosomal region has also been associated with autism spectrum disorder [93, 94]. *GRIK3* has been implicated in schizophrenia [95], bipolar disorder [96], major depression [97] [84]), high anxiety comorbid with depression [98], increased startle response [99], and personality traits such as decreased cooperativeness and compassion, and increased shyness and harm avoidance [100]. A recent epigenomic analysis, relevant to ADHD, found differential methylation at sites on *GRIK3* in preterm infants exhibiting an abnormal neurobehavioral profile that included lowest scores in attention, self-regulation, and quality of movement, with highest levels of excitability, arousal, and stress [101]. Despite negative results in association studies of *GRIK3* variants with OCD [85, 102], differential expression of this gene has been identified in the caudate nucleus of patients [102]. An integrated gene-expression and pathway enrichment analysis has also recently implicated *GRIK3* in OCD [103].

GRIK2 and *GRIK3* code for low-affinity kainate receptor subunits which share many brain-region and synaptic localizations, and which can coassemble with each other or with high-affinity kainate receptor subunits [104, 105, 106]. These similarities likely explain why *GRIK2* and *GRIK3* are implicated in many of the same clinical disorders, and suggests that changes to these genes may have played similar roles in domestication and recent human evolution.

In one cohort study, *GRIK4* was listed among genes with copy number changes most likely to be associated with intellectual disability [40]. This gene has also been identified in a case study of a patient with comorbid intellectual disability and schizophrenia [107] (see also [108]). Duplications of *GRIK4* have been associated with ASD [109, 110] and overexpression of this gene in mice brings about autism-like features including social impairment [111].

GWAS analyses have implicated *GRIK4* in ADHD [112], OCD [16], and schizophrenia [113, 114]. Distinct variants of *GRIK4* have been shown to be protective against or to increase susceptibility to bipolar disorder, with protection being associated with increased brain expression [115, 116]. Conversely, knockout of *GRIK4* in mice can have anxiolytic and anti-depressant effects [117], and SNPs in humans have been associated with MDD [118]. *GRIK4* ablation in mice diminishes the startle response, impairs prepulse inhibition (as in schizophenic patients), and increases hyperactivity in a man-

ner reminiscent of bipolar disorder [119].

GRIK5 has been identified within single genome linkage intervals shared by patients with intellectual disability in consanguineous families [120]. Multiple rare missense mutations on *GRIK5* have been associated with autism spectrum disorder [121]. A rare missense change, absent in non-pathological family members, has been identified in a father/daughter proband pair with comorbid ASD and ADHD. However a microdeletion in a different chromosomal region was considered a stronger candidate in the etiology of the condition [122]. A separate integrative analysis of GWAS, expression quantitative trait loci (eQTL), and postmortem expression studies has highlighted a *GRIK5* subnetwork among the most prominent causal pathways in ADHD [123]. Although we did not find direct evidence of *GRIK5* involvement in OCD, this gene has been identified as being differentially associated with comorbid ASD and Tourette's syndrome patients when compared with non-comorbid ASD patients. Tourette's syndrome is also often comorbid with OCD [124].

Significantly lower expression of *GRIK5* has been reported in the hippocampus, prefrontal cortex, and various thalamic nuclei of schizophrenia patients, [71, 125, 126]. A SNP on this gene was shown to have above-chance association with panic-disorder and, especially, bipolar-disorder patients [127]. A separate pathway enrichment analysis, using data compiled from candidate genes and expression studies of bipolar disorder, highlighted *GRIK5* among top-ranked genes [103]. Increased hippocmpal expression of both *GRIK4* and *GRIK5* has recently been observed in maternally separated rats, which are often used as a model for MDD and show increased anxiety but a blunted stress response [128, 129]. Differential expression of *GRIK5* in patients versus controls has also been associated with major depressive events [130], and this gene has also been identified as significantly associated with MDD in a GWAS meta-analysis of over 135,000 patients and some 345,000 controls [131].

S2.2. Group I Metabotropic receptor genes in human and domesticated behavioral phenotypes

There is ample evidence that metabotropic glutamate receptors are implicated in the emergence of tame and prosocial behaviors, in modulating the stress response, and in many of the same neurodevelopmental and neuropsychiatric disorders as kainate receptors.

Altered *GRM1* expression and synaptic signaling has been identified in the cerebellum of Fragile X syndrome mouse models [132]. A leading theory of the etiology of this developmental disorder highlights dysregulation of Group I metabotropic receptor signaling, but particularly GRM5 (mGluR5), for which there is also ample evidence of altered brain expression in mouse models, as well as from postmortem human samples [133, 132]. Alongside intellectual disability, Fragile X patients typically display autistic traits and are often hypersensitive to sensory stimuli [132].

Mouse models of non-syndromic ASD have also identified altered expression and signaling of *GRM1*, and reversal of autistic phenotypes in mice can be brought about via antagonism of either GRM1 or GRM5 receptors [132, 134]. Rare, potentially deleterious mutations have been identified in autistic patients on both *GRM1* and *GRM5*, as well as in multiple genes coding for proteins in the Group I metabotropic signaling pathway [135].

In a GWAS of ADHD, duplications of *GRM1* and deletions of *GRM5* have been shown to be significantly overrepresented among patients as compared with controls [61]. An intronic SNP in *GRM5* has been highlighted in a separate GWAS as a top candidate for association with ADHD [112, 136]. *GRM1* has been found to harbor a disproportionate amount of potentially deleterious non-synonymous SNPs in schizophrenic patients compared to controls [137], while distinct common variants of *GRM5* in schizophrenia have been found to correlate with lower hippocampal volume and impaired cognitive performance [138]. A significant reduction in GRM5-mediated signaling was also found in postmortem samples taken from the prefrontal cortex of schizophrenic patients versus controls [139].

A study of schizophrenic and bipolar patients found an above chance clustering of non-synonymous SNPs on *GRM1* compared to controls [140], while an integrative study including gene-expression and genomic data has also highlighted this gene among top candidates for association with bipolar disorder [141]. Further evidence of *GRM1*'s association with bipolar disorder comes from a postmortem study, which found significantly decreased expression in the prefrontal cortices of patients versus controls [142]. *GRM5* is expressed at significantly higher levels in the cerebella of bipolar and major-depressive patients compared to controls [143].

In a mouse model of OCD, ablation of EAAC1 — a glutamate transporter encoded by *SLC1A1* (signals of selection in AMH [6]) — has been shown to lead to increased activation of the Group I metabotropic receptor cascade, in turn affecting striatal dopamine signaling and leading to increased

anxiety and preservative behaviors[144]. Antagonism of both metabotropic Group I receptors or of GRM5 alone has been shown to rescue OCD-like behaviors[144, 145]. A human positron emission tomography (PET) tracer study has shown that increased GRM5 receptor binding across multiple brain regions correlates with higher scores in measures of obsessions, but not compulsive behaviors [146]. There is certainly stronger evidence for *GRM5* contributing the etiology of OCD, although *GRM1* may play a role.

Both GRM1 (mGluR1) and GRM5 antagonists have anxiolytic effects in mice and rats [147, 148]. Polymorphisms on *GRM1* have been associated with depression [149], and *GRM5* was highlighted in the same GWAS meta-analysis that pointed to the implication of *GRIK5* in MDD. Selective antagonism of both GRM1 and GRM5 have antidepressant effects in mice and rats [150, 151]. Antagonism of either receptor also attenuates the fear-potentiated startle response, [152], while *GRM5* knockout mice show a marked increase in startle magnitude [153]. Intrahippocampal injection of a non-selective Group I agonist was found to decrease fear-conditioned freezing responses in rats, while a selective GRM5 agonist had no effect. Selective antagonism GRM1 but not GRM5 increased fear-conditioned responses [154].

S2.3. Group II Metabotropic receptor genes in human and domesticated behavioral phenotypes

A fixed missense mutation on *GRM3* differentiates aggressive farm-bred foxes from their tame counterparts and is thought to be one of the most important signals of the behavioral differences between the two groups [155]. Group II metabotropic receptors are implicated in multiple stress, mood, and developmental disorders [156, 157, 158, 159].

A deletion including *GRM2* and one other brain-expressed gene (*DOCK3*) has been associated with syndromic moderate intellectual disability, although *DOCK3* was highlighted as being most likely implicated in the disorder [160] It has been suggested that a deletion of *GRM3* may contribute to intellectual disability in a case where *CACNA2D1*, encoding a voltage-gated calcium channel, was considered the primary cause of the syndromic traits [161]. A recent meta-analysis of GWAS data has identified an association between *GRM3* and human intelligence [162]

Antagonism of Group II metabotropic receptors has been reported to rescue abnormally enhanced long-term depression (LTD) in the *FMR1*-knockout mouse model of Fragile X syndrome, while in wild-type mice the antagonist induces LTD [163]. Rats reared in an impoverished environment show

working-memory deficits that correlate with decreased expression of Group II receptors in the ventral PFC, with decreases for Group I receptors reported in the dorsal PFC [164]. Conversely, agonism of Group II receptors has been shown to impair cognitive performance, an effect likely mediated by the GRM2 (mGluR2)-receptor inhibition of hippocampal synaptic transmission. This effect was reversed by antagonism of Group II receptors, although the antagonist did not improve performance in control animals [165]

In a rat model of ASD, developed using prenatal exposure to valporate, the rescue of social deficits by N-acetylcysteine treatment was reversed by Group II-receptor antagonism. Both *GRM2* expression and Group II protein levels were shown to be significantly reduced in the valporate-exposed animals [166]. *GRM2* has been identified as part of multigene segments of high homozygosity shared among ASD subjects [167]. ASD-associated variants and regions of high homozygosity specifically within *GRM3* have been identified in GWAS and patient cohort–control studies [167, 110]. Moreover, a duplication of *GRM3* has been implicated in autistic traits that often co-occur with 22q11.2 deletion (DiGeorge) syndrome, where wider mGluR network dysregulation has been proposed to result in ASD symptoms [168]. Similarly, an ASD patient cohort–control comparison of CNVs highlighted the metabotropic glutamate-receptor gene interacting network among the most prominently affected in the disorder, despite non-significant findings for individual receptor genes. Nonetheless, CNVs in *GRM3* along with members of receptor families I and III were identified in the study [169].

A single case of a *GRM2* deletion has been identified in a GWAS of ADHD [61]. In a combined case-control, GWAS, and pathway analysis, SNPs in regulatory regions of *GRM3* were highlighted as being among the most significant of interacting genes implicated in ADHD [170]. Agonism of Group II receptors serves to attenuate attention deficits and impulsivity brought about by overactivation of the 5HT2A serotonin receptor in a rodent model of the disorder [171].

In a patient–control study, hypermethylation of the *GRM2* promoter region has been reported as protective against schizophrenia, and patients had significantly increased expression of this gene compared to controls [172]. Expression of *GRM2* was found to be significantly decreased in both the striatum and PFC in a putative rat model of schizophrenia [173]. On the other hand, postmortem human studies have found increased expression of *GRM2* and Group II receptors in the PFC of human schizophrenia patients. However, as in many postmortem expression studies of psychiatric disorders,

the possibility that receptor levels were affected by antipsychotic treatment could not be ruled out [174, 175].

Multiple studies have found associations between SNPs on *GRM3* and schizophrenia (see [176] for a review and [177] for a meta-analysis of GWAS data). Reduced levels of dimeric GRM3 (mGluR3) in the prefrontal cortex of schizophrenic patients has been reported [178]. A schizophrenia-implicated SNP on *GRM3* has been associated with increased expression of a receptor splice variant in the dorsolateral prefrontal cortex (DLPFC) irrespective of previous neuroleptic treatment [179]. This splice variant has subsequently been shown *in vitro* to reduce ligand binding of GRM3 receptors [180].

A GWAS of bipolar disorder has identified a *GRM3* variant as potentially being associated with the disease [181]. Another SNP has been associated with BPD in two separate case–control studies, while a third study highlighted another locus associated with the disorder [182, 183, 184]. Lithium, which is used in the treatment of bipolar disorder, has been found to alter expression of *GRM3* in mice [185].

In one study, antagonism of Group II receptors significantly attenuated anxiety-driven repetitive marble-burying behaviors, proposed as a model of OCD [186]. In rats, antagonism of these receptors also has anxiolytic and antidepressant effects [187], and in mice reared in isolation, increased depressive and anxiety-like behaviors correlated with increased Group II receptor densities in the prefrontal cortex and hippocampus, whereas antagonism had anti-depressant effects [188]. However, a separate study of marble-burying behaviors found that a group II *agonist* has potent anxiolytic effects [189], consistent with various studies showing anxiolytic effects of Group II agonism [190, 191, 192]. Also in line with this, in a trial study, agonism of Group II receptors proved effective in reducing anxiety symptoms of patients with generalized anxiety disorder [193]. Multiple clinical trials and case studies have reported improvements in OCD patients' symptoms under N-Acetylcysteine treatment, the efficacy of which is dependent on Group II mGluR activation [194, 195].

In MDD postmortem brains, increased expression of *GRM2* in the DLPFC has been significantly associated with cases of suicide [84], while *GRM3* expression has been reported to be upregulated in suicide cases, with or without overt accompanying MDD symptoms [196]. Increased postmortem levels of Group II receptor proteins — shown to be unlikely to result from treatment with serotonin reuptake inhibitors — have also been reported in the lateral PFC of MDD patients [197]. Conversely, decreased Group II receptor binding

has been reported in the anterior cingulate cortex [198]. Group II antagonism rescues behavioral despair following selective binding of GRM3 in the dorsal striatum, thus particularly implicating this subunit in the depressive behaviors observed [199]. Prenatal chronic mild stress has been shown to give rise to depression-like behaviors in rats correlating with decreased expression of Group II receptors in the hippoampus and PFC [200].

Finally, there is experimental evidence that GRM3 activation in the medial prefrontal cortex is necessary for fear extinction via long-term depression of synaptic connections in mice [201], and agonism of Group II metabotropic receptors inhibits the expression of the fear potentiated startle response in rats [202]. Similarly, in a human trial, startle magnitude was reduced and anxiolytic effects reported under Group II agonist administration [203].

S2.4. Group III Metabotropic receptor genes in human and domesticated phenotypes

The Group III metabotropic receptor gene *GRM8* is detected in more domesticate or human selective sweep studies than any other metabotropic receptor gene. In one natural experiment, very much relevant to domestication but not encompassed by these selective sweep studies, the endangered and highly inbred Apennine brown bear, known for its docility towards humans, was shown to have significantly lower nucleotide variability on *GRM7* and *GRM8* than the genome-wide average. Similar patterns were detected on other genes related to tameness in domesticated species. The authors of the study postulated that these changes were the result of selection on reduced aggressiveness in the Apennine bear population [57].

Both a duplication and a deletion including *GRM4* and surrounding genes have been associated with developmental delay [204, 205]. Activation of GRM4 (mGluR4) can relieve autism-like symptoms and reduce anxiety-like behaviors in mice [206]. In rats, potentiation of GRM4 receptors reduces certain measures of impulsivity, while increasing others and impairing visual attention (ADHD-like phenotype) [207].

In a population association study, SNPs on *GRM4* have been significantly associated with both schizophrenia and bipolar disorder [208]. A microRNA (miRNA) associated with bipolar disorder has been shown to regulate *GRM4* expression [209]. In a putative model of schizophrenia, orthosteric agonism of the GRM4 receptor has been reported to attenuate pharmacologically induced symptoms of psychosis in mice [210].

Positive allosteric modulation of GRM4 has also been reported to reduce repetitive marble burying in a commonly used mouse model of OCD and anxiety-related behaviors. The same study reported a reduction in indices of behavioral despair in mice subjected to the forced-swim test, which is used to induce depressive behaviors [211]. However, a selective orthosteric agonist of GRM4 has also been shown to increase behavioral despair in forced-swim and tail-suspension tests [212]. *GRM4* knockout enhances cued fear-conditioning responses and increases anxiety in adult mice [213].

Increased expression of *GRM4* has been reported in the postmortem DLPFC in female MDD patients relative to controls [84]. The expression of mir-1202, another miRNA that regulates the expression of *GRM4*, has been shown to have increased postmortem expression in the locus coeruleus of MDD patients, but decreased expression in the postmortem PFC compared to controls or patients on antidepressants [214, 215]. Mir-335, which can also target *GRM4*, has been shown to be downregulated in MDD patients [216], and a SNP at an miRNA binding site on *GRM4*, potentially disruptive to mir-1202 attachment, has also been found at significantly higher frequency in MDD patients [217].

In the CNS, *GRM6* is predominantly expressed in the ON-bipolar cells of the retina. Unsurprisingly, it has been associated with fewer stress-related or neurodevelopmental disorders than any other glutamate receptor gene. Nonetheless, a single case of a *GRM6* deletion has been identified in a GWAS as being associated with ADHD [61], and a case of a duplication including *GRM6* has been implicated in ASD [218]. It has been suggested that abnormal retinal signaling in certain individuals with ASD may result from altered mGluR interactions, predominantly involving receptors expressed in the brain, but potentially including GRM6 (mGluR6) [219]. Intrahippocampal injection of a GRM6 agonist has been shown to have anxiolytic effects at dosages between sixteen and thirty-three times higher than those required for a non-selective Group III agonist, reflecting the very low expression of this receptor in the hippocampus [220, 221]. Despite this, there is evidence that hippocampal *GRM6* may be responsive to stress, with increases reported (alongside upregulation of many other glutamate receptor genes) in aldosterone-treated rats that display depression-like behaviors [222].

In individual case studies and a small patient–control study, CNVs including *GRM7* as well as SNPs within this gene have been implicated in developmental delay with comorbid ASD [223, 224]. *GRM8* has been highlighted as a leading candidate gene in a case of microdeletion causing severe

intellectual disability [225]. Microdeletion within *GRM8* accompanied by a microduplication elsewhere in the genome, as well as microdeletions affecting only *GRM8*, have also been implicated in developmental delay [226, 227, 228].

Both *GRM7* and *GRM8* have been implicated in multiple studies of autism spectrum disorder [229], including single-gene hemizygous deletions on each [230, 231]. A partial duplication of *GRM8* has also been implicated in ASD [232]. A missense variant and a deletion in *GRM7* have been associated with both ASD [233] and comorbid hyperactivity and ASD, respectively [224]. Hemizygous deletion of *GRM7* has been implicated in ADHD [234], and this gene has been highlighted among the most significantly associated genes with the disorder in a case-control analysis of SNPs and interacting gene networks [170]. A separate case-control study has also found a polymorphism on *GRM7* to be associated with ADHD [235]. Multiple cases of deletions of both *GRM7* and *GRM8* have been identified in a separate GWAS of ADHD [61], and a case-control study has identified both a deletion and a duplication of *GRM8* as being implicated in the disorder [236]. *GRM8* knockout mice have been reported to display hyperactivity in a novel environment[237]

Polymorphisms on *GRM7* and *GRM8* have been implicated in schizophrenia in separate targeted screens of each gene individually and in an analysis of both genes together [238, 239, 240, 241, 242]. A genome-wide scan of patients and controls also found a deletion affecting *GRM7* to be associated with schizophrenia [243].

Deletions and SNPs on *GRM7* have been associated with bipolar disorder in case–control studies, and this gene is regularly highlighted among top-ranked candidates in GWAS [244] [245] [246]. In bipolar patients, variants on *GRM7* are associated with personality traits such as high anxiety and neuroticism. Lithium and valporic acid treatments of bipolar disorder, have been shown to increase *GRM7* expression, most likely via downregulation of miR-34a [247, 248].

Evidence from the marble-burying test and pharmacologically-induced compulsive behaviors in mice suggests that knockout, negative allosteric modulation, and antagonism of GRM7 (mGluR7) receptors serve to alleviate OCD-like symptoms [249, 250, 251]. A small duplication including only *GRM8* has been associated with early-onset OCD [252].

Higher expression of *GRM7* has been detected in the postmortem DLPFC in females with major depressive disorder [84]. An analysis of case–control cohorts found variants on *GRM7* to have a top-ranked association with MDD

of selected candidate genes [253]. SNPs on both *GRM7* and *GRM8* have been significantly associated with MDD in a patient-cohort study, including the identification of MDD-related loci implicated in interactions between these two genes [242]. Distinct meta-analyses of MDD GWAS data have found *GRM7* to have a top-ranked association with the disorder [254, 255]. *GRM8* was also listed as having a significant association with MDD in multiple meta-analyses [256, 255].

Studies in rodents broadly seem to support the view that activation of GRM8 (mGluR8) serves primarily to reduce anxiety, whereas GRM7 activation has the opposite effect [156, 257]. *GRM7* knockout broadly decreases anxiety in mice [258] and can cause fear-response and fear-memory deficits [259]. Agonism of GRM8 receptors in the amygdala inhibits acquisition and expression of fear as measured by startle response [260]. *GRM8* knockout has been shown to increase levels of anxiety, although some measures are age- and sex-dependent (including startle response), and social anxiety is attenuated by knockout [261, 262]. Conversely, other studies have shown *GRM8* knockout mice to have attenuated acoustic startle response as well as deficits in conditioned fear learning and extinction [237, 263].

S2.5. NMDA receptor genes in human and domesticated behavioral phenotypes

Multiple missense polymorphisms on *GRIN1* have been implicated in intellectual disability [264, 265]. GRIN1 (NR1, GluN1) protein levels were found to be increased in postmortem brain samples from autistic patients, and increased expression of *GRIN1* was found in a mouse model with heritable autism-like traits [266, 267]. Distinct studies have detected altered brain expression of *GRIN1* in a prominent rat model of ADHD [268, 269]. Multiple studies have found associations between polymorphisms on *GRIN1* and schizophrenia and abnormal expression in the thalamus has been determined in some postmortem studies of the disease [176, 270]. Multiple postmortem expression studies have also found decreased brain expression of *GRIN1* in bipolar disorder [65, 271, 272]. Mice displaying OCD-like behaviors have been shown to have significantly reduced expression of *GRIN1* in the subthalamic nucleus compared with those for which these behaviors were attenuated by environmental enrichment [273]. A separate study has found *GRIN1* increases in corticostriatal circuitry [26]. The offspring of prenatally stressed rats, which display anxiety-like behaviors, have significantly decreased expression of *GRIN1* in the hippocampus, while mice carrying a

missense mutation on this gene display abnormal anxiety, with significantly decreased startle response and impaired fear-conditioned memory [274, 275]. Finally, *GRIN1* has also been listed in a GWAS among genes prominently associated with major depressive disorder [276].

GRIN2A was detected as the only affected gene shared in three cases of intellectual disability with chromosomal deletions [277]. Mutations on this gene have also been associated with ASD [278, 279] and ADHD [280, 281]. Polymorphisms and decreased expression of *GRIN2A* have been implicated in schizophrenia [282, 283], while decreased expression has been detected in the hippocampus in bipolar disorder [271]. Decreased levels of the GRIN2A (NR2A, GluN2A) protein were detected in mice with OCD-like behaviors [284], while prenatally stressed rats with anxiety-like behaviors show reduced gene expression in the hippocampus, prefrontal cortex, and striatum [274]. Conversely, truncation of the intracellular domain of the GRIN2A receptor has been shown to produce anxiolytic effects [285] and knockout can produce anxiolytic and anti-depressant-like effects in mice [286]. Reduced expression of *GRIN2A* has been reported in postmortem studies of the perirhinal and prefrontal cortices of MDD patients [65, 287]. Antagonism of GRIN2A-containing receptors in the amygdala of rats disrupts both fear conditioning and startle response [288].

Multiple studies have found deletions and mutations on *GRIN2B* to be associated with intellectual disability [289, 290, 291], while mutations and copy number variations have been regularly associated with ASD [278, 109, 292], ADHD [293, 281], and schizophrenia [294] (see [291] for a review of associations between variants of *GRIN2B* and these disorders). A mouse model of ASD was also found to show increased expression of *GRIN2B* in frontal cortical tissues [267], while abnormal expression has been found in the postmortem brains of schizophrenics across multiple studies [270]. *GRIN2B* has also been shown to have decreased postmortem expression in the medial temporal lobe of bipolar and major depressive disorder patients [65], and distinct variants have also been associated with treatment-resistant MDD [295]. Decreased expression of *GRIN2B* has been found in a mouse model of OCD, and human variants have been associated with the disorder, including decreased glutamate concentration in the anterior cigulate cortex [284, 296, 297, 298]. Replacement of *GRIN2C* expression in mutant mice with that of *GRIN2B* produced increased anxiety-like behaviors and increased fear-induced freezing [299]. Antagonism of amygdalar GRIN2B- (NR2B-, GluN2B-)containing receptors impaired fear conditioning [288], while a separate study found that

reduced receptor levels in *GRIN2B* mutant mice correlated with an increased startle response [300].

Significantly increased expression of *GRIN2C* and decreased expression of *GRIN2D* have been detected in different brain regions of a rat model of ADHD [268]. *GRIN2C* has also been listed among genes with copy-number variants significantly associated with ASD, while in a mouse model of the disease, *GRIN2C* was found to be significantly underexpressed in the cortex [231, 301]. For its part, *GRIN2D* has been detected among genes hypomethylated in ASD patients versus controls [302], and rare missense mutations have been associated with intellectual disability [303]. In the postmortem brains of schizophrenic patients, *GRIN2C* prefrontal expression has been found to be significantly decreased, while *GRIN2D* expression is significantly reduced in thalamocortical projecting neurons [304, 305]. *GRIN2D* SNPs have also been associated with schizophrenia [306]. SNPs on both genes have been identified as risk factors for bipolar disorder [307, 308]. Decreased prefrontal expression of *GRIN2C* has been identified in postmortem brains of bipolar patients, while the same study detected increased expression of *GRIN2D* in MDD patients [309]. Significantly elevated expression of *GRIN2C* has been detected in the postmortem locus coeruleus of MDD patients [310, 214].

Mice with increased stereotyped behaviors show higher expression of *GRIN2D* in the subthalamic nucleus [273]. Knockout of *GRIN2D* can lead to the development of major-depression-like traits, as well as social-recognition deficits and increased social stress [311]. In a separate study, knockout of *GRIN2D* has been shown to induce other anxiety-like behaviors while both *GRIN2C* and *GRIN2D* knockout result in increased startle response and depression-like behaviors. The reduced behavioral response of *GRIN2C* knockout mice to phencyclidine was also proposed to suggest schizophrenia-like behaviors [312]. As mentioned above, decreased *GRIN2C* expression in mice with overexpressed *GRIN2B* can also induce anxiety-like behaviors [299]. *GRIN2C* knockouts show deficits in fear-conditioned memory, while selective positive allosteric modulation of GRIN2C/GRIN2D (NR2C, GluN2C / NR2D, GluN2D) receptors in the amygdala potentiates fear-conditioned responses as well as subsequent fear extinction [313, 314].

GRIN3A and *GRIN3B* are the least studied of the NMDA receptor genes, and fewer associations with stress-related and neurodevelopmental disorders have been found. Investigation of potential associations with intellectual disability found that rare mutations on *GRIN3A* and *GRIN3B* were present in both patients and unaffected family members [315]. A single case study

has identified associations between *GRIN3B* and intellectual disability [316]. A model animal study of ADHD has associated decreased expression of *GRIN3A* in the PFC with the inattention behaviors that form part of the disorder [317]. Our review found a single case of a missense mutation on *GRIN3B* associated with ASD [318]. In schizophrenic patients, *GRIN3A* shows increased expression in the postmortem prefrontal cortex, while an uncommon variant on this gene has also been associated with the disease [319, 320]. A null-variant of *GRIN3B* acrosss multiple patients has also been implicated in schizophrenia [321]. *GRIN3A* shows decreased postmortem expression in the prefrontal cortex of bipolar patients [319]. Our review found only a single study noting differential association between a small sample of *GRIN3B* variants and bipolar patients who had previously attempted suicide [322]. We did not find any direct association between anxiety and *GRIN3A* in model-animal or human studies, and a mouse knockout study has shown no change in anxiety-related behaviors [323]. A pathway analysis has suggested this gene to be implicated in anxiety-related phenotypes associated with early-life stressors [69]. On the other hand, *GRIN3B* knockout increases anxiety levels, but also sociability in mice [324]. Induced depression-like phenotypes in rats have been associated with decreased expression of both *GRIN3A* and *GRIN3B* in the hippocampus [222]. Although both knockout of *GRIN3A* and a common human variant of *GRIN3B* have been associated with altered prepulse inhibition of the startle response (consistent with these genes' implication in schizophrenia), we did not find any evidence for their association with measures of startle magnitude [325, 326, 321].

S2.6. AMPA receptor genes in human and domesticated behavioral phenotypes

Knockout of *FMR1* brings about reduced cortical expression of *GRIA1*, which has been proposed to contribute to the intellectual disability present in Fragile X syndrome [327, 328]. Mutations associated with nonsyndromic intellectual disability in genes encoding for synaptic proteins that interact with glutamate receptors have been shown in cell cultures to lead to reduced binding of the GRIA1 (GLUA1, GLUR1) receptor, in turn dysregulating AMPA receptor trafficking [264]. Significantly increased protein expression of GRIA1 has been reported in the postmortem cerebellum in ASD [266], and similar increases have been found in the frontal cortex in a mouse model of the disorder [267]. Rats used to model ADHD have decreased expression of *GRIA1* in the nucleus accumbens [269]. *GRIA1* ablation is also used as

a model of ADHD [329]. There is evidence of decreased *GRIA1* expression in the medial temporal lobe and thalamus of the postmortem schizophrenic brain [330, 126, 270]. Similarly, *GRIA1* expression is significantly lower in the postmortem perirhinal cortex of bipolar and MDD patients compared to controls [65]. Decreased expression of GRIA1 proteins has also been reported in the corticostriatal tract in a mouse model of OCD [284]. Loss of GRIA1 subunits in serotonergic neurons has been shown to bring about anxiety-like behaviors in mice [331], a finding paralleled in *GRIA1* knockout mice [332]. Reduction or ablation of *GRIA1* expression impairs fear learning in mice [333, 334].

Like GRIA1, the dysregulation of binding of GRIA2 (GLUA2, GLUR2) by interacting proteins has been reported in intellectual disability [264]. A hemizygous deletion including *GRIA2* has been reported in a case of ASD with developmental delay [335]. Copy number variants of *GRIA2* have been reported in autism, including a confirmed rare *de novo* duplication associated with the disorder [336]. *GRIA2* shows significantly increased expression in a rat model of ADHD [268], while decreased expression has been found in the postmortem hippocampus of schizophrenic patients [337]. Similar decreases in the prefrontal cortex have been found to be associated with schizophrenia, bipolar disorder, and major depression, as well as in the entorhinal cortex in bipolar disorder [338, 65].

In a mouse model of OCD, GRIA2 subunits, like GRIA1, were found to be significantly depleted in the corticostriatal pathway [284]. *GRIA2* knockout has been shown to reduce behavioral manifestations of anxiety in mice [332]. *GRIA2* was also identified among differentially hydroxymethylated regions in an early-life-stress mouse model of anxiety [69]. Increased GRIA2 subunits in the mouse hippocampus have been associated with fear consolidation and retrieval [339], while endocytosis of GRIA2-containing receptors has been associated with fear extinction [340].

Deletions of *GRIA3*, leading to a near 80% reduction in subunit levels, have been identified in multiple subjects with moderate cognitive impairment [341]. Meanwhile, a partial duplication of this gene has also been implicated in intellectual disability [342], and a separate duplication has been identified in a case study of Autism Spectrum Disorder [343]. In contrast to the increased expression of *GRIA2* in a rat model of ADHD, decreased levels of *GRIA3* have been reported [268]. Decreased expression of *GRIA3* has been reported in the thalamus of schizophrenic patients [126, 270], while in both bipolar disorder and major depression, decreases have been found in the

perirhinal cortex. These are accompanied by decreases in the entorhinal cortex in bipolar disorder, with reductions in the prefrontal cortex reported in major depression [65, 338]. *GRIA3* has also been associated with treatment-emergent suicidal ideation in major depression [83]. In a small patient cohort study, a SNP on *GRIA3* was identified as a possible genetic marker of comorbid OCD and anorexia nervosa [344]

GRIA3-deficient mice show higher levels of sociability but are also more aggressive [345]. In contrast, in mice used to model anxiety-like behaviors, increased GRIA3 (GLUA3, GLUR3) protein levels have been reported [346]. Overactivation of GLUR3-containing receptors by specifc antibodies increases anxiety measures in mice [347]. Rats exposed to chronic corticosterone treatment show decreased GRIA2 and GRIA3 subunit expression in the ventromedial prefrontal cortex, correlating with deficits in fear extinction [348].

Mutations in *GRIA4* have been associated with intellectual disability across multiple patients [349]. In a postmortem study of ASD, differential editing of *GRIA4* RNA has been identified in the cerebella of patients compared to controls [350]. Increased GRIA4 (GLUA4, GLUR4) subunits have been identified in a postmortem study of the schizophrenic prefrontal cortex [351], and a significant association between SNPs on *GRIA4* and schizophrenia has been reported in a patient population study [352]. *GRIA4* has been identified in a GWAS of OCD [18] and mice displaying stereotyped behaviors show decreased expression of *GRIA4* in the STN relative to controls in which these behaviors had been attenuated [273].

A GWAS of major depression with comorbid nicotine addiction detected a SNP on *GRIA4* as the top-ranked significant association [353], and *GRIA4* expression is significantly increased in postmortem prefrontal cortex samples from female MDD patients [84]. Rats with depression-like symptoms show decreased expression of *GRIA4* in the hippocampus [222].

In mice with enhanced excitation in the central amygdala, displaying abnormal anxiety, modification of GRIA4 (GLUR4) subunits, weakening the excitatory current, rescued the abnormal behaviors [354]. *GRIA4* knockout mice show minimal deviation in anxiety-like behaviors from wild-type mice [355]. Experiments in rats have shown the GRIA4 subunit to be essential for long-term fear consolidation [356].

S2.7. Delta glutamate receptor genes in human and domesticated behavioral phenotypes

GRID1 has been highlighted as a candidate gene in the etiology of developmental delay in multiple patients with deletions on chromosome 10. However, it has also been suggested that *GRID1* may be implicated in heart defects that are often part of the syndromic symptoms that appear [357] (see also [358]). Deletions in *GRID2* have been implicated in multiple cases of cerebellar ataxia, including developmental delay [359]. Typically, intragenic deletions, but also duplications and missense mutations on *GRID1* and *GRID2* have been implicated in autism spectrum disorder [109, 360, 361, 362, 363]. A GWAS has highlighted *GRID2* among top ranked genes associated with ADHD [364]. SNPs on *GRID1* have been associated with schizophrenia and GRID1 (GluD1) receptor subunits have been shown to control dopaminergic burst firing, strongly implicated in the disease [365, 366, 367]. A GWAS has also highlighted intronic SNPs on *GRID2* as three of the top five ranked variants associated with schizophrenia in the sample [368] (see also [114]). *GRID1* has been highlighted in two association studies of bipolar disorder [208, 369]. We found a single study of a small cohort highlighting a possible association between *de novo* variants on *GRID2* and bipolar disorder [73]. One study of OCD has highlighted female-specific associations with variants of *GRID2*, while a meta-analysis of GWAS studies highlighted this gene among the highest ranked genes associated with the disease [370, 371].

Knockout of *GRID1* has been shown to lower anxiety-like behaviors in mice [372], while reduced GRID2 (GluD2) protein levels have been found in mice displaying increased anxiety [373]. *GRID1* knockouts have deficits in fear conditioning [374]. Among the papers we have reviewed, *GRID1* was highlighted in two genome-wide association studies of major depressive disorder [253, 375] and shows decreased frontal expression in a rat model of the disorder [376]. *GRID2* has also been highlighted in genome-wide meta-analyses of associations with depressive symptoms and MDD [377, 255].

S3. Kainate and Group II/III metabotropic glutamate receptors in the CNS

S3.1. Kainate receptor expression

Although kainate receptors are structurally similar to AMPA receptors, "they fulfill a more varied range of synaptic and extrasynaptic roles" than

their ionotropic counterparts [27]. Apart from ligand gating, kainate receptors regulate glutamate release and activate second-messenger signaling cascades to a greater extent than AMPA or NMDA receptors [378, 379, 380]. Kainate receptors may serve to facilitate or inhibit glutamate or GABA release, regulate dendritic outgrowth during development, potentiate AMPA-dependent excitatory synaptic transmission, or activate distinct non-ionotropic signaling mechanisms, including $G_{i/o}$ proteins, the principal second-messenger targets of Groups II and III metabotropic receptors [381, 382, 383, 380]. Thus, depending on the primary roles played by kainate receptor subunits in a given brain region, their expression may have distinct functional implications far beyond excitatory synaptic transmission [380].

Here, we focus on the regional expression of the low affinity receptor genes, *GRIK2* (because of signals of potential convergence among domesticates) and *GRIK3* (because of parallel signals among domesticates and humans), as well as the high-affinity receptor gene *GRIK5* (given signals of selection detected in AMH). Because signals of convergence with domesticates have yet to be identified for *GRIK5*, this receptor gene received little attention in the cross-species comparisons of selective sweep studies. However, *GRIK5* has been identified in both selective-sweep studies of modern human populations and among high-frequency differences distinguishing archaic from modern human populations [6, 384]. For these reasons we include it in our review of expression data.

GRIK2 mRNA is highly expressed in cerebellar granule cells and is also found in the caudate putamen and hippocampus, while *GRIK3* is strongest expressed in deep layers of the cerebral cortex, the cingulate cortex, the subiculum, the caudate-putamen, thalamic reticular nucleus, and stellate/basket cells of the cerebellum [385, 106]. *GRIK5* is the most universally expressed of all kainate receptor genes and can be detected across most brain regions, although the encoded subunit must coassemble with low-affinity kainate receptor subunits (GRIK1-GRIK3) in order to form functional ligand-gated ion channels [386, 385, 106]. In general, kainate receptor gene expression is highest in the hippocampus and the cerebellum [106]. Kainate receptor mRNA is detectable in the amygdala, although *GRIK1* is considerably higher expressed than other receptor genes that have been detected, with *GRIK2* having moderate and *GRIK5* low expression [387].

Expression levels of kainate receptor genes are developmentally regulated, peaking in the rat brain in the late embryonic and early postnatal period [385]. As early as embryonic day 10, four kainate receptor genes (*GRIK2*-

GRIK5) are expressed in the rat neural tube. This expression is higher than that of AMPA receptors and is present in both progenitor cells and differentiated neurons, with GRIK2 and GRIK5 subunits being upregulated during neural cell differentiation [388]. During later embryonic periods, brain expression is highest in the cerebellum and striatum, later extending to the cortex, septum, hippocampus, and thalamus. Expression levels drop markedly in the thalamus from the late postnatal period onwards [385]. *GRIK5* is highest expressed in the cortical plate in the late embryonic period. In general, *GRIK2* is not highly expressed in the cortex, although expression is higher in the cingulate cortex, peaking during early postnatal development. *GRIK3* is more broadly expressed in the surrounding cortex than *GRIK2*, but autoradiograph images nonetheless show increased expression in the cingulate cortex during the immediate postnatal period, and moderate to high expression into adulthood [386, 385]. Highest expression levels for *GRIK3* during postnatal development are detected in the entorhinal cortex [385].

In the rat hippocampus, expression of kainate receptor genes peaks in the late embryonic and early postnatal period. This is particularly transient in CA1 but remains high in CA3 into adulthood. Expression of kainate receptor genes in the dentate gyrus (DG) also remains high from the postnatal period into adulthood. Similarly, immunolabeling of GRIK2, GRIK3, and GRIK5 subunits in adult rats is strongest in the pyramidal layer of CA3 and in neurons in DG, being present in both cell bodies and apical dendrites [104]. *GRIK3* and *GRIK5* are moderately expressed in the septum from embryonic development, with these levels remaining unchanged in the lateral septum into adulthood [385, 386]. *GRIK2*, *GRIK3*, and *GRIK5* are the only kainate receptor genes consistently detected in the striatum during embryonic development, with *GRIK5* remaining highly expressed into adulthood [385]. These genes are moderate to intensely expressed in the thalamus at different stages of prenatal development, while *GRIK3* expression remains strong in the reticular nucleus into adulthood. Finally, in the cerebellum, *GRIK2* and *GRIK5* are the predominant kainate receptor genes expressed in granule cells throughout life, while *GRIK3* is the only kainate receptor gene expressed in stellate/basket cells [386, 385].

In a study of the human fetal cortex, *GRIK3* and *GRIK5* mRNA were detectable at higher levels than those of other kainate receptors throughout the different developmental stages measured (between gestation week 8 and week 20) [389]. This broadly matches with data from the prenatal rat brain, in which *GRIK2*, *GRIK3*, and *GRIK5* are the most widely expressed sub-

units [385]. Moreover, both the expression of receptor mRNA and receptor binding — indicating full translation into functional subunits — was found to be greater for kainate receptors during fetal development than for any other ionotropic glutamate receptors, especially during the later gestational periods measured [389]. The expression of kainate receptor transcripts is highly synchronized with that of NMDA receptors at each of the different stages measured. It is likely that these subunits are involved in regulating different processes of neurogenesis during ontogeny, including neuronal migration [389].

Somewhat contrary to these findings, AMPA receptor binding from gestational week 16.5 to week 26 has been found to be considerably denser in the hippocampus, entorhinal cortex, temporal cortex, cingulate cortex, putamen, and thalamus than for than for the other ionotropic receptors [390]. NMDA receptor densities were also greater than those of kainate receptors, although these were broadly comparable across most regions and time points, perhaps due to the same synchrony observed in other studies [390, 389]. These discrepancies between mRNA measures and receptor binding densities may be down to delays of the translation into full kainate and NMDA receptor subunits in the regions studied [389].

Some evidence for this delayed development of receptor subunits comes from comparisons of receptor binding in the hippocampi of second trimester fetuses with postmortem measures of full-term infants, three-month-olds, and adults: NMDA receptors made up around half of total glutamate receptors in the infant hippocampi measured, as compared to around a third during the second trimester of gestation or in adults. This was especially the case in the stratum lucidum (CA3) and the molecular layer of the fascia dentata (DG). Moreover, the percentage of the remaining glutamate receptors that bound quisqualate was minimal throughout development [391]. Given that quisqualate binds AMPA receptors with much higher affinity than kainate receptors, a considerable percentage of the remaining glutamate receptors may be expected to be kainate preferring [392, 393, 391]. A separate study of kainate binding in the newborn hippocampus confirms this, with a marked increase relative to prenatal or adult levels in the stratum lucidum and the molecular layer of the fascia dentata, again suggesting synchrony between kainate and NMDA receptor expression during development [394]. Given the relative intensity of *GRIK3* and *GRIK5* expression during earlier stages of human fetal development, it is not implausible that these receptor genes also drive the increase in postnatal expression.

Postmortem mRNA measures taken from adult human brains confirm *GRIK2*, *GRIK3*, and *GRIK5* as the highest expressed kainate receptor genes. However, lower relative expression patterns have been detected for *GRIK3* in adult humans compared to adult rat or fetal human brains. Overall, the dentate gyrus and CA3 remain regions of highest expression, with *GRIK2* and *GRIK5* predominant [71]. It should be noted that studies of adult mRNA expression and receptor binding generally find decreased densities in the human hippocampus relative to rodents and monkeys [395, 396]. However, contrary to the findings of the human study mentioned above [71], it has been posited that these decreases are primarily due to lower expression of *GRIK2* and *GRIK4*, rather than *GRIK3* and *GRIK5* [395]. Moreover, during the postnatal peak of kainate binding in CA3 and DG, human densities of kainate receptors are comparable to or even exceed those of the rat [394]. Possibly, then, selective pressures in our lineage may have driven the increased ontogenetic expression of *GRIK3* and *GRIK5*.

Non-selective immunolabeling of GRIK1-GRIK3 in the monkey hippocampus suggest more qualitative differences in localization as compared with both human and rat data. These low-affinity subunits were found to be densest in CA1 and the subiculum rather than DG or CA3 [397]. The authors of this study suggest that discrepancies identified between the monkey and the rat may be down to species differences. By comparison, a similar postmortem study in humans found strongest labeling of these subunits in CA2 and CA3 pyramidal neurons (particularly CA2) [398]. Again, it cannot be ruled out that human-monkey differences in low-affinity kainate receptor expression are driven in part by the regulatory changes on *GRIK3* that came under selection in our lineage.

In histological studies of the rat hypothalamus, GRIK2, GRIK3, and GRIK5 receptor proteins have been detected at moderate levels in the supraoptic nucleus (SON), arcuate nucleus, and the junction of the median eminence and infundibulum. Light to moderate staining was detected in the retrochiasmatic region of the SON and the medial mammillary nucleus [104]. Another study found that non-NMDA (mainly kainate) receptors were bound most predominantly in the SON, anterior hypothalamic area, and paraventricular nucleus (PVN) [399]. Both *GRIK2* and *GRIK5* subunit mRNAs are expressed in the anterior parvocellular region of the PVN, while *GRIK5* is highest expressed in the medial parvocellular nucleus and is expressed on CRH-releasing neurons [400]. *GRIK2* and *GRIK3* are most highly expressed in the the subparaventricular zone and perinuclear region surrounding the

PVN [401]. Studies *in vitro* confirm that kainate receptors are extensively expressed in the hypothalamus during embryonic development [402], although we are unaware of any study detailing specific subunit abundances or localizations during ontogeny.

These expression data underscore the particular importance of kainate receptor genes that most often show signals of selection in domesticates and modern humans. Evidence that *GRIK3* and *GRIK5* are the kainate receptor subunits with highest expression levels in the developing human brain is suggestive that they are important for neurogenesis and differentiation. Although no easy comparisons can be made between the brain-expression data for embryonic or perinatal rats and a human fetuses, *GRIK3* and *GRIK5* expression levels are high in each species, suggesting that similar developmental processes are regulated by these subunits. The comparatively higher expression of *GRIK2* as compared with *GRIK3* in the rat suggests there may be a more prominent role for the former in CNS development in mammals other than humans. If this is so, human *GRIK3* may occupy homologous ontogenetic functions to *GRIK2*, perhaps helping to explain the tendency for both *GRIK2* and *GRIK3* to show signals of selection in domesticated species, whereas this is only the case for *GRIK3* in AMH.

The relatively high expression of kainate receptor genes in limbic structures (e.g. hippocampus, entorhinal cortex, cingulate cortex, and, to a lesser extent, the lateral septum and hypothalamus) points to the importance of these genes in the primary functions of these structures, including control of emotions, memory, learning, and neuroendocrine regulation. This is especially the case during the postnatal period, when kainate receptor genes are highest expressed. The cingulate cortex and hippocampus, which prominently modulate HPA-feedback activity, retain moderate to high expression of these genes into adulthood. As detailed above, in the DG and CA3, *GRIK2* and *GRIK5* are expressed most strongly in the adult rat brain, while *GRIK3* and *GRIK5* are stronger expressed in DG during early postnatal development.

S3.2. Metabotropic glutamate receptor expression

Group II and Group III metabotropic glutamate receptor genes are expressed throughout the central nervous system and are often highly expressed in limbic structures, including the hippocampal formation, as well as in sensory pathways, such as the olfactory and visual systems [106]. The Group II receptor genes, *GRM2* and *GRM3* are moderate to intensely expressed in

various regions of the limbic cortex, Golgi cells of the cerebellum, the dentate gyrus, and in distinct amygdaloid nuclei [403, 404]. Of the Group III receptor genes, *GRM4*, *GRM7*, and *GRM8* are distributed widely across the brain, *GRM7* most expansively and densely, followed by *GRM4*, and *GRM8*, which is widely distributed, but expressed in lower quantities [405, 406]. *GRM6* expression is limited to the ON-bipolar cells of the retina. Groups II and III receptors play a more prominent role than Group I in the presynaptic modulation of glutamatergic signaling [106, 406].

In the rat brain, *GRM2* is most intensely expressed in the in Golgi cells of the cerebellum, accessory olfactory bulb, and anterior olfactory nucleus, followed by the entorhinal and parasubicular cortices, granule cells of the dentate gyrus, basolateral and basomedial amygdala, various thalamic nuclei, the medial mammillary nucleus of the hypothalamus, and the cingulate and retrosplenial cortices [403]. Human *GRM2* mRNA is most prominently detected in the cerebellum, hypothalamus, and thalamus, with lighter expression in the hippocampus [407].

In the rat, *GRM3* expression is strongest in the thalamic reticular nucleus, followed by the lateral and basolateral amygdala, Golgi cells of the cerebellum, the cingulate, retrosplenial, perirhinal, entorhinal, and parasubicular cortices, distinct subparts of the brain stem, and the supraoptic nucleus of the hypothalamus, with lighter expression in the paraventricular and lateral areas of the hypothalamus, as well as granule cells of the dentate gyrus, and stellate/basket cells of the cerebellum [404]. In humans, *GRM3* mRNA has been shown to be similarly expressed in the dentate gyrus, cerebellum, and thalamic reticular nucleus, although there is also evidence of more extensive expression across thalamic nuclei and cerebellar cell types. Strong GRM3 receptor immunoreactivity signals have been detected in the human prefrontal cortex, and low to moderate levels in the hippocampus, amygdala, and thalamus [408].

Non-selective labeling of Group II receptors in the human hippocampus identified dense staining in the dentate gyrus, CA2-CA4, and granule cells of CA3, with lighter staining in CA1 and the subicular cortex [409]. Elsewhere in the brain, Group II immunoreactivity is present in the prefrontal cortex and striatum [408].

GRM4 is highest expressed in the rat sensory ganglia and in granule cells of the cerebellum. In general, it is more extensively expressed than both Group II receptors in the olfactory system and septum, but less so in the limbic cortices. Expression in the amygdala is limited to the rostral portion

of the intercalated nuclei. Like *GRM2*, expression of *GRM4* within the rat hypothalamus is mostly limited to the medial mammillary nucleus. Moderate expression within the hippocampus is mostly limited to the rat dentate gyrus, with similar levels detected in the entorhinal cortex [405]. However, immunocytochemical localization has detected more intense labeling of GRM4 proteins on cell bodies and apical dendrites in CA1 and CA3, and on the bodies of granule cells in DG [410]. In humans, *GRM4* mRNA is strongest detected in the cerebellum, and more moderately in the hippocampus, hypothalamus, and thalamus [407]. In a postmortem human immunohistochemical study of the hippocampus, a specific GRM4 isoform showed moderate labeling on CA3 mossy fibres, with weaker labeling in CA2. Labeling was also detected on the hippocampal efferents of the alveus, parts of which contribute to inputs of the lateral septal nuclei [409, 411]. These data largely parallel with data from the rat, although there is evidence of higher *GRM4* mRNA levels in the human caudate nucleus and putamen, which form part of the dorsal striatum [412].

GRM7 is expressed in almost all brain regions in the rat, generally at moderate levels. This includes all limbic, amygdalar, hippocampal, and thalamic regions, and practically all hypothalamic subdivisions. Like GRM4, intense immunocytochemical staining can be detected for GRM7 subunits in all regions of the hippocampus, although this is most apparent in neuropil rather than on cell bodies [410]. Highest gene expression is detected in the sensory ganglia, the locus coeruleus within the brainstem, the main olfactory bulb, and the medial septal nucleus [405]. In accordance with studies of the rat, human *GRM7* mRNA levels are also widely distributed at moderate levels in various regions of the human brain, being highest in the neocortex, cerebellum, and regions DG and CA3 of the hippocampus, followed by CA1 [221, 413]. Expression was also detected in the thalamus, with lower levels in the caudate-putamen, in contrast to studies of the rat and the inverse of species expression differences for *GRM4* [413].

In the rat, *GRM8* is highest expressed in the olfactory bulb, pontine nuclei of the brainstem, piriform cortex, and reticular nucleus of the thalamus, with lower expression in the the neocortex, hippocampus, basolateral amygdala, and mammillary body of the hypothalamus [414, 415, 221]. In humans, distinct *GRM8* isoforms are differentially but widely expressed, with the most broadly found variant showing highest expression in the thalamus, subthalamic nucleus, caudate nucleus, and amygdala, with a second variant being expressed in the visual cortex, caudate-putamen, and cerebellum [416].

Among all glutamate receptor subtypes, metabotropic glutamate receptor binding densities in the rat hypothalamus are second only to NMDA receptors (particularly in dorsomedial, ventromedial, and paraventricular regions) [399]. Given the mRNA expression levels reviewed above and relatively low Group I metabotropic receptor expression in the adult rat hypothalamus, a considerable percentage of these metabotropic receptors may be expected to comprise multiple Group II and Group III subtypes, most prominently in the medial mammillary nucleus [417, 403, 404, 405]. GRM2 and GRM3 receptor proteins have been detected in the mouse and rat hypothalami and have been shown to inhibit HPA activity [418].

Unlike kainate receptors, developmental regulation of Groups II and III metabotropic receptors in the rat hypothalamus may tend towards increased expression in adulthood. Such increases have been identified in both arcuate and suprachiasmatic nuclei for Groups II and III subunits [419]. On the other hand, across brain regions, most metabotropic receptors show similar patterns to kainate receptors, peaking in the early postnatal period. *GRM2* shows a progressive increase in expression during postnatal development in the rat, but remains high in the entorhinal cortex, DG, and various nuclei of the thalamus into adulthood. Low expression levels were found in CA1 and CA3 (in contrast to the human postmortem study described above [409]), and none was detected in the striatum [420]. In the human fetal brain, *GRM2* expression is higher than in that of adults, although no regional-specific prenatal expression has been described [407]. *GRM3* generally has highest postnatal expression just after birth, especially in the striatum and cerebellum, decreasing progressively throughout development, but remaining high in the thalamic reticular nucleus into adulthood [420, 421].

Expression levels for *GRM4* were found to be low throughout development in one study of the rat, with little change into adulthood, except in granule cells of the cerebellum, where they rise considerably [420]. Other studies have found a similar rise in *GRM4* expression on cell bodies in all major regions of the hippocampus in adulthood [421]. GRM7 proteins show increased postnatal staining in the rat relative to adult levels across almost all regions studied, including the pons, cerebellum, thalamus, hippocampus, olfactory cortex, and striatum, although expression remains relatively high in the hippocampus, bed nucleus of stria terminalis (BNST), medial mammillary body of the hypothalamus, and various thalamic nuclei into adulthood [422]. In humans, *GRM8* shows increased expression in the fetal brain relative to that of adults [416].

Kainate and Groups II and III metabotropic receptors have broadly overlapping localizations and timings of expression, with predominant postnatal expression in limbic cortices, the hippocampus (especially DG and CA3), cerebellum, thalamus (particularly the reticular nucleus), and hypothalamus (most notably the medial mammillary nucleus, although perhaps asynchronously). Differences include higher metabotropic expression in sensory pathways, as well as the amygdala, thalamus, distinct hippocampal regions, and in the adult hypothalamus more generally. Kainate receptor expression seems to be more predominant in the cingulate cortex and striatum, particularly during ontogeny. Both receptor subtypes can have metabotropic functions to suppress the release of glutamate, and both are part of G-protein coupled signaling cascades. Together, these receptor subtypes are extensively expressed in regions crucial for the modualtion of how an organism deals with stress, from the moment sensory inputs for a stressor are received, right through to regulation of feedback mechanisms that inform best responses.

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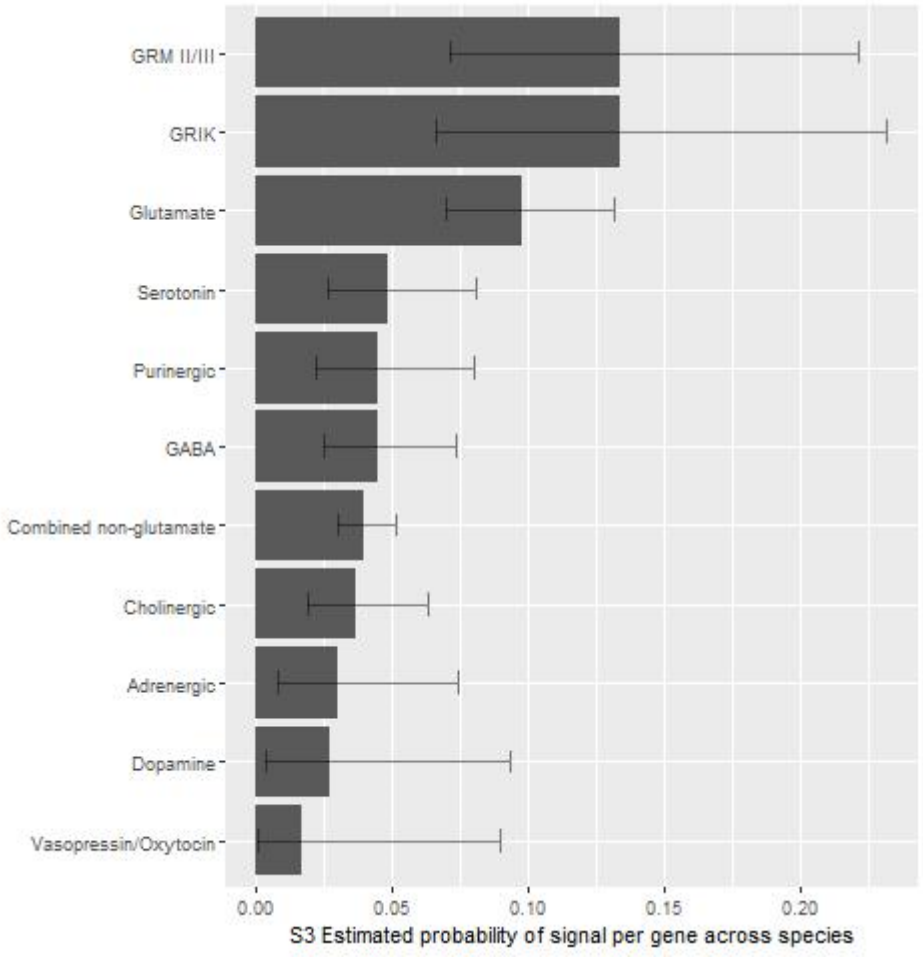

Figure S3 – Comparison of proportions of domesticate or modern-human related signals across major receptor gene types from selective sweep, adaptive introgression, brain expression, and fox high-frequency allelic divergence studies (excludes human high-frequency allelic divergence studies). Error bars represent the exact confidence interval for the data summarized in each rectangular bar.

	Adrenergic	Cholinergic	Dopamine	GABA	Purinergic	Serotonin	Vasopressin / Oxytocin	Combined non-glutamate
GRIK	0.0071146	**0.0026016**	0.0312465	0.0125421	0.0136717	0.0159243	0.03190657	**0.001253002**
GRM II/III	**0.0061705**	**0.0013274**	0.0219698	**0.0055826**	0.011987	0.0140695	0.028390725	**0.00046857**
Glutamate	0.00985	**0.0011575**	0.0437946	0.0086471	0.0190142	0.0253252	0.068193657	**2.63759E-05**

Table S3a: Results from Fisher's exact test comparing kainite, group II/III metabotropic, and glutamate receptor-gene (sub)families with other major receptor-gene types for data summarized in Figure S3: $p > 0.05$ shaded in grey; for $p \leq 0.05$, text is not highlighted; Bonferroni adjusted p-value ($p \leq 0.00625$) **highlighted in bold**.

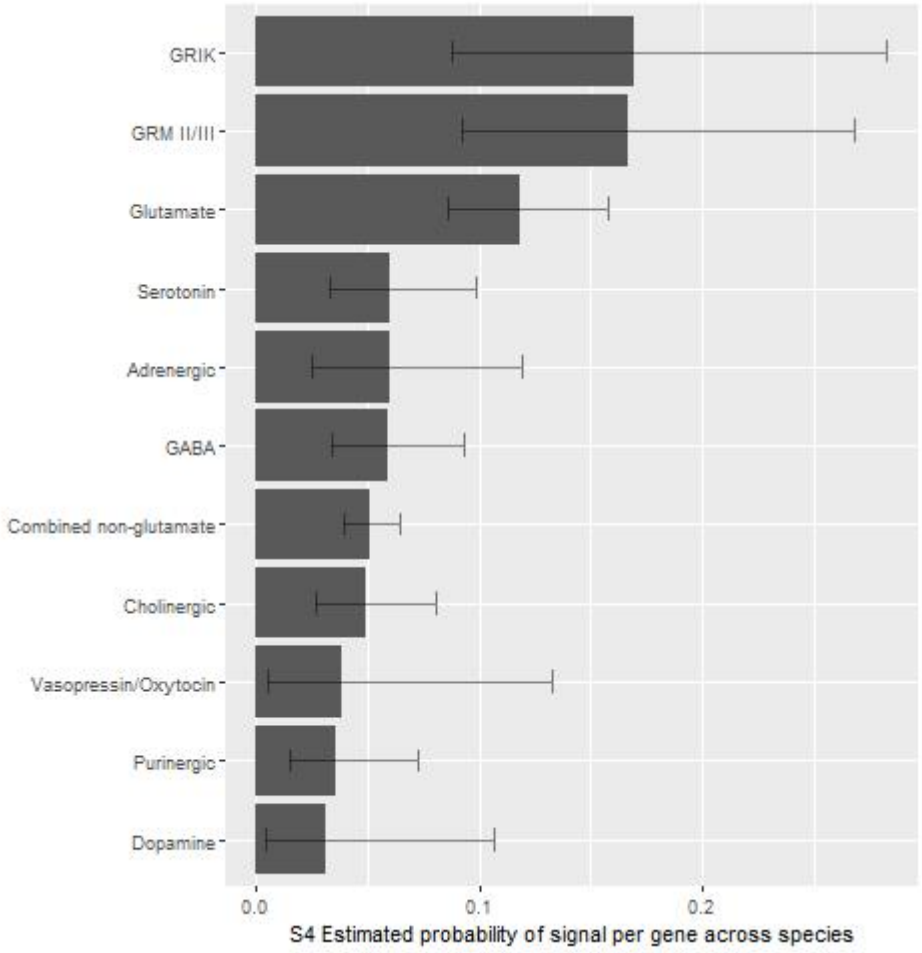

Figure S4 – Comparison of proportions of domesticate or modern-human related signals across major receptor gene types from selective sweep, adaptive introgression, and high-frequency allelic divergence studies (excludes brain-expression studies). Error bars represent the exact confidence interval for the data summarized in each rectangular bar.

	Adrenergic	Cholinergic	Dopamine	GABA	Purinergic	Serotonin	Vasopressin / Oxytocin	Combined non-glutamate
GRIK	0.0351592	**0.00202652**	0.016361	0.008275	**0.000806**	0.009414	0.05232006	**0.0006901**
GRM II/III	0.0278591	**0.00120467**	0.011647	**0.004416**	**0.000473**	0.00864	0.0498464	**0.0002979**
Glutamate	0.0794228	**0.00244998**	0.043052	0.011175	**0.000815**	0.019869	0.13631622	**3.067E-05**

Table S4a: Results from Fisher's exact test comparing kainite, group II/III metabotropic, and glutamate receptor-gene (sub)families with other major receptor-gene types for data summarized in Figure S4: $p > 0.05$ shaded in grey; for $p \leq 0.05$, text is not highlighted; Bonferroni adjusted p-value ($p \leq 0.00625$) **highlighted in bold**.

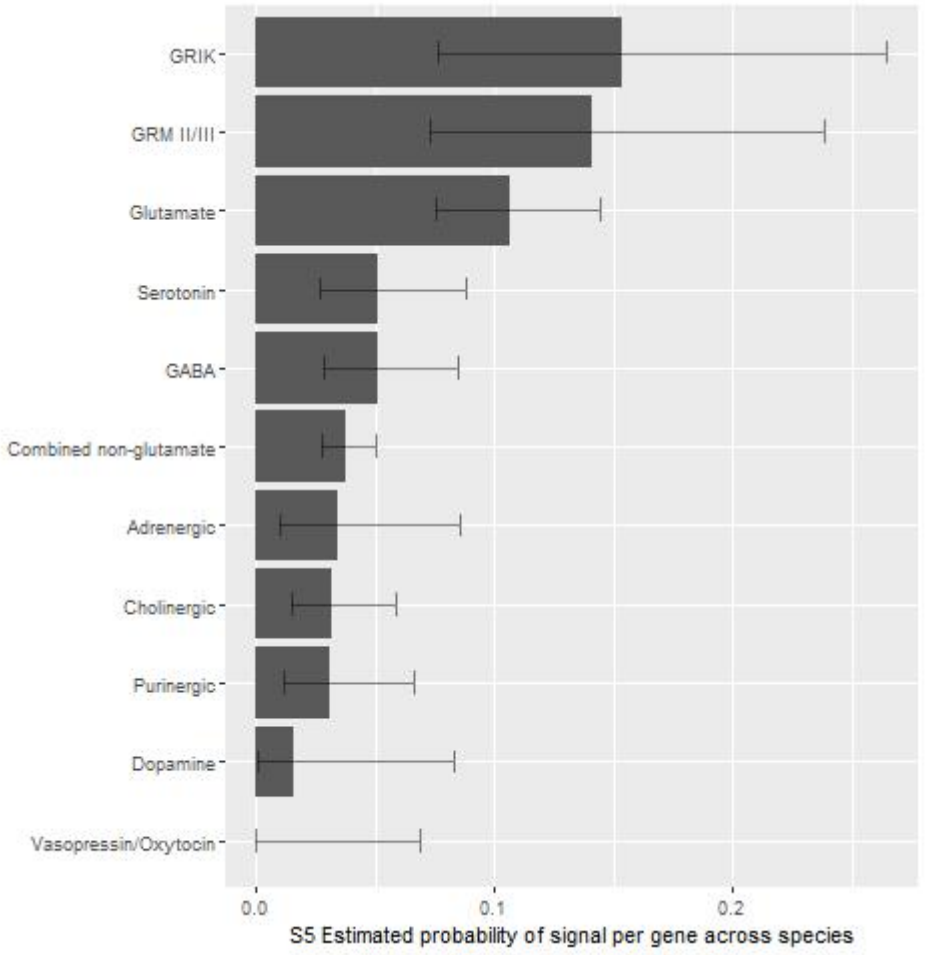

Figure S5 – Comparison of proportions of domesticate or modern-human related signals across major receptor gene types from selective sweep, adaptive introgression, and fox high-frequency allelic divergence studies (excludes brain expression and human high-frequency allelic divergence studies). Error bars represent the exact confidence interval for the data summarized in each rectangular bar.

	Adrenergic	Cholinergic	Dopamine	GABA	Purinergic	Serotonin	Vasopressin / Oxytocin	Combined non-glutamate
GRIK	0.006819	**0.000574**	0.008624	0.012108	**0.001145**	0.012254	0.008667	**0.000302**
GRM II/III	0.01111	**0.000726**	0.006558	0.011275	**0.001504**	0.012719	0.012115	**0.000347**
Glutamate	0.021393	**0.000278**	0.017185	0.01686	**0.001344**	0.021115	0.026908	**3.28E-06**

Table S5a: Results from Fisher's exact test comparing kainite, group II/III metabotropic, and glutamate receptor-gene (sub)families with other major receptor-gene types for data summarized in Figure S5: $p > 0.05$ shaded in grey; for $p \leq 0.05$, text is not highlighted; Bonferroni adjusted p-value ($p \leq 0.00625$) **highlighted in bold**.

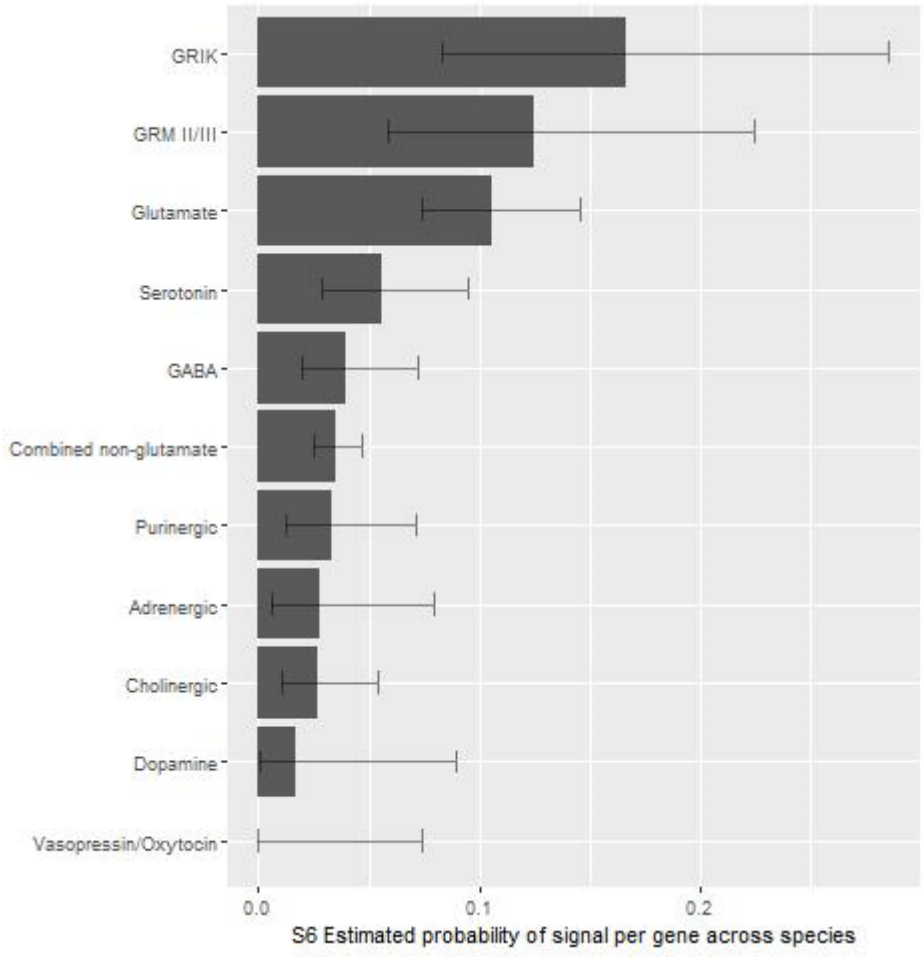

Figure S6 – Comparison of proportions of domesticate or modern-human related signals across major receptor gene types from selective sweep and adaptive introgression studies (excludes expression and high-frequency allelic divergence studies). Error bars represent the exact confidence interval for the data summarized in each rectangular bar.

	Adrenergic	Cholinergic	Dopamine	GABA	Purinergic	Serotonin	Vasopressin / Oxytocin	Combined non-glutamate
GRIK	**0.002069**	**0.00016**	0.008385	**0.001295**	**0.001108**	0.011972	0.008409	**8.88E-05**
GRM II/III	0.014217	**0.001898**	0.021736	0.01832	0.014235	0.065399	0.028298	**0.001533**
Glutamate	0.009603	**0.000208**	0.026195	**0.003693**	**0.004919**	0.056126	0.036126	**2.62E-06**

Table S6a: Results from Fisher's exact test comparing kainite, group II/III metabotropic, and glutamate receptor-gene (sub)families with other major receptor-gene types for data summarized in Figure S6: $p > 0.05$ shaded in grey; for $p \leq 0.05$, text is not highlighted; Bonferroni adjusted p-value ($p \leq 0.00625$) **highlighted in bold**.

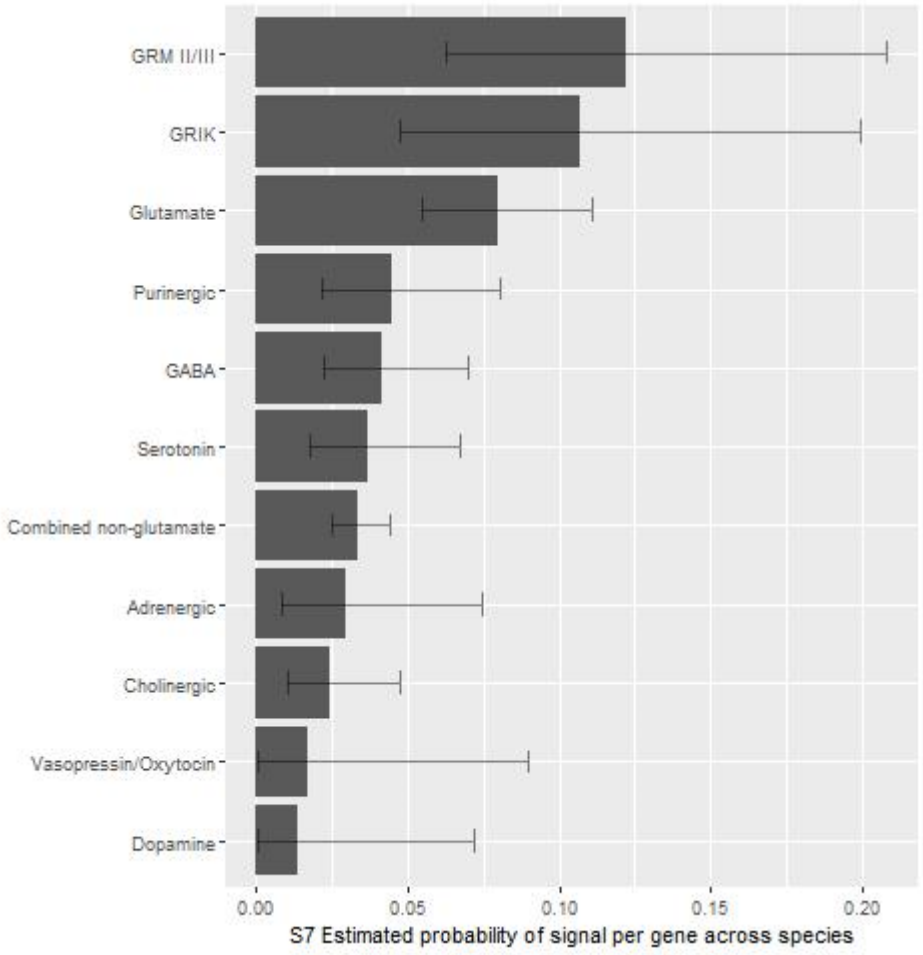

Figure S7 – Comparison of proportions of domesticate or modern-human related signals across major receptor gene types from selective sweep, expression, and fox high-frequency allelic divergence studies (excludes introgression and human high-frequency allelic divergence studies). Error bars represent the exact confidence interval for the data summarized in each rectangular bar.

	Adrenergic	Cholinergic	Dopamine	GABA	Purinergic	Serotonin	Vasopressin / Oxytocin	Combined non-glutamate
GRIK	0.0294233	**0.0035354**	0.0335376	0.040731	0.08669049	0.033786	0.08257927	**0.005156669**
GRM II/III	0.0115423	**0.0004185**	0.0068415	0.008953	0.02167438	0.006984	0.04262899	**0.00043042**
Glutamate	0.0461984	**0.001384**	0.0431191	0.041739	0.1298292	0.032124	0.13548692	**0.000207903**

Table S7a: Results from Fisher's exact test comparing kainite, group II/III metabotropic, and glutamate receptor-gene (sub)families with other major receptor-gene types for data summarized in Figure S7: $p > 0.05$ shaded in grey; for $p \leq 0.05$, text is not highlighted; Bonferroni adjusted p-value ($p \leq 0.00625$) **highlighted in bold**.

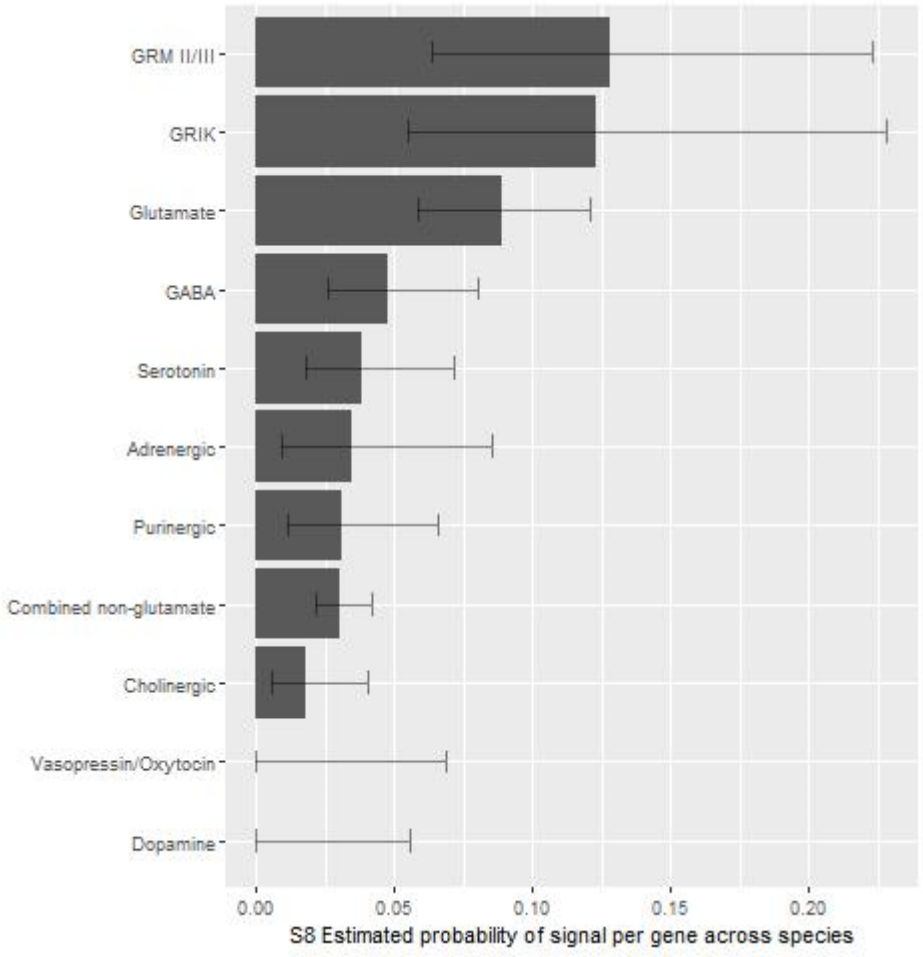

Figure S8 – Comparison of proportions of domesticate or modern-human related signals across major receptor gene types from selective sweep and fox high-frequency allelic divergence studies (excludes expression, adaptive introgression and human high-frequency allelic divergence studies). Error bars represent the exact confidence interval for the data summarized in each rectangular bar.

	Adrenergic	Cholinergic	Dopamine	GABA	Purinergic	Serotonin	Vasopressin / Oxytocin	Combined non-glutamate
GRIK	0.0287453	**0.0005537**	**0.0062153**	0.039904	0.008482	0.015206	0.02429476	**0.0013303**
GRM II/III	0.0207452	**0.0001455**	**0.0020126**	0.017911	**0.003753**	0.01056	0.0186983	**0.0002863**
Glutamate	0.065519	**0.0001332**	0.0076382	0.076618	0.017043	0.026662	0.05593465	**4.235E-05**

Table S8: Results from Fisher's exact test comparing kainite, group II/III metabotropic, and glutamate receptor-gene (sub)families with other major receptor-gene types for data summarized in Figure S8: $p > 0.05$ shaded in grey; for $p \leq 0.05$, text is not highlighted; Bonferroni adjusted p-value ($p \leq 0.00625$) **highlighted in bold**.

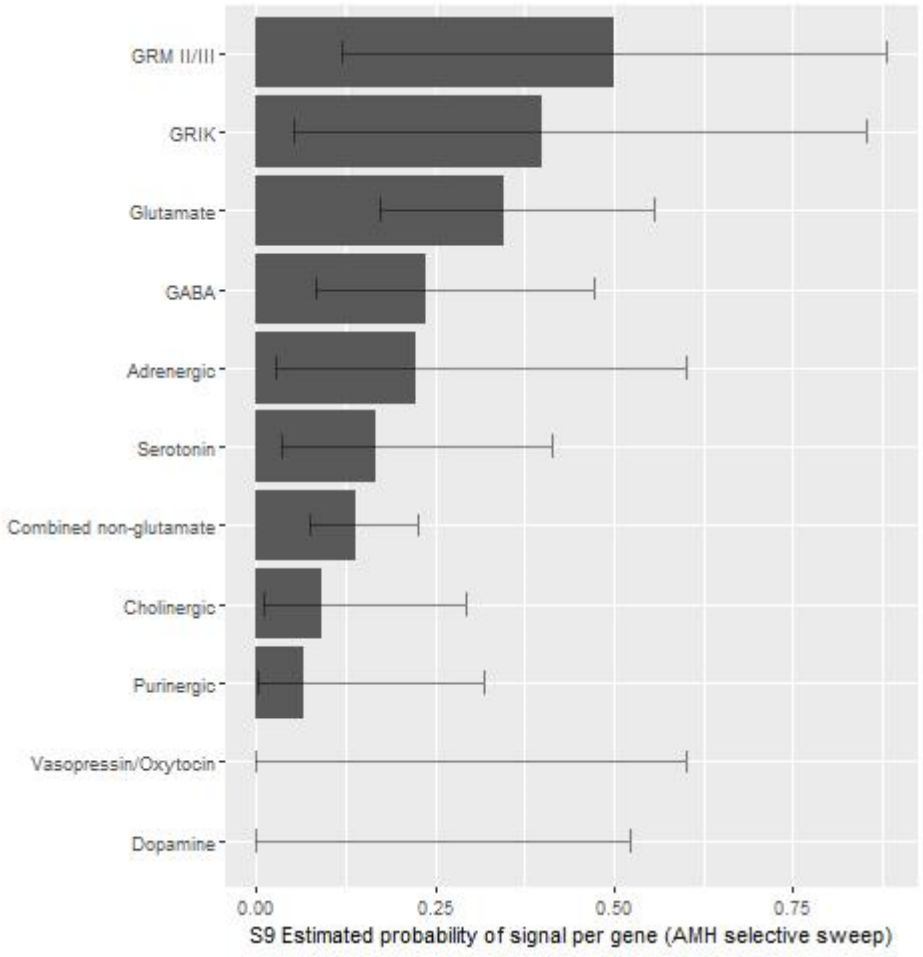

Figure S9 – Comparison of proportions of signals across major receptor gene types from human selective sweep studies only (excludes human high-frequency allelic divergence and all domestication studies). Error bars represent the exact confidence interval for the data summarized in each rectangular bar.

	Adrenergic	Cholinergic	Dopamine	GABA	Purinergic	Serotonin	Vasopressin / Oxytocin	Combined non-glutamate
GRIK	0.5804196	0.14444444	0.444444	0.5875	0.1403509	0.290677	0.5303348	0.1637038
GRM II/III	0.3286713	0.05042735	0.181818	0.3191	0.0526316	0.139113	0.32412659	0.0503992
Glutamate	0.6854675	0.0453873	0.286244	0.528	0.0634515	0.303456	0.4119809	0.0224305

Table S9a: Results from Fisher's exact test comparing kainite, group II/III metabotropic, and glutamate receptor-gene (sub)families with other major receptor-gene types for data summarized in Figure S9: $p > 0.05$ shaded in grey; for $p \leq 0.05$, text is not highlighted; Bonferroni adjusted p-value ($p \leq 0.00625$) **highlighted in bold**.

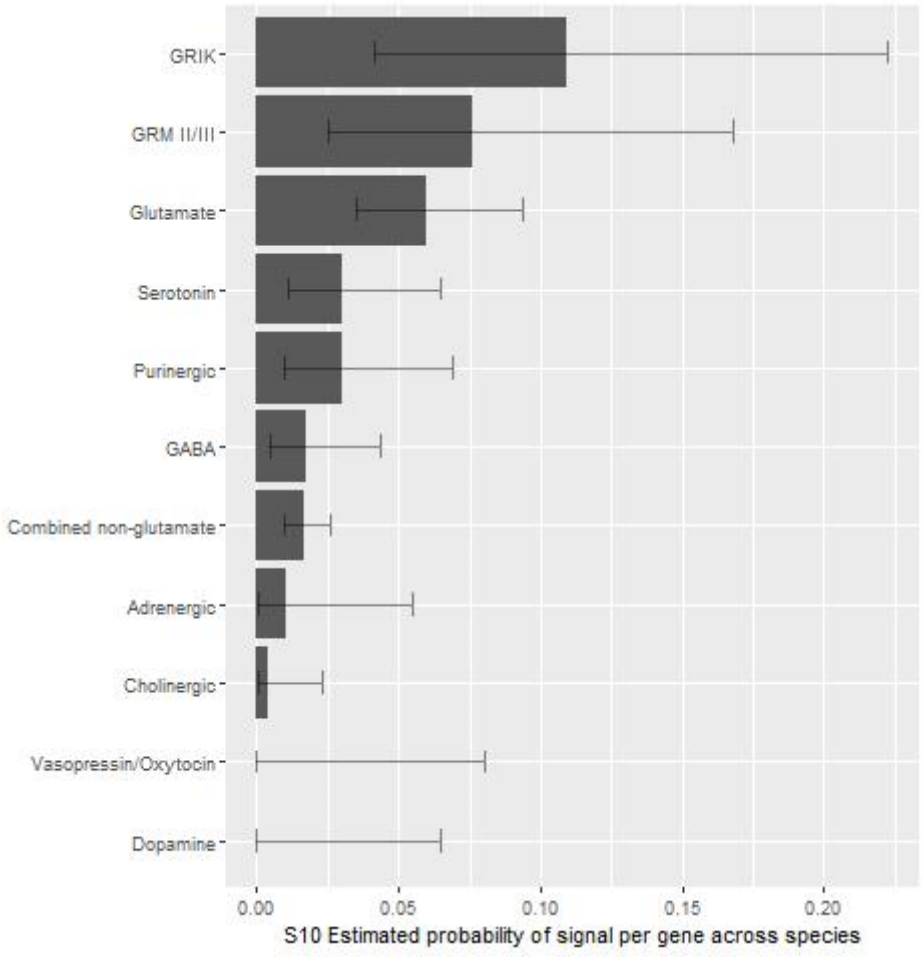

Figure S10 – Comparison of proportions of domestication-related signals across major receptor gene types from domesticate selective sweep studies only (excludes expression, adaptive introgression, fox high-frequency allelic divergence, and all human studies). Error bars represent the exact confidence interval for the data summarized in each rectangular bar.

	Adrenergic	Cholinergic	Dopamine	GABA	Purinergic	Serotonin	Vasopressin / Oxytocin	Combined non-glutamate
GRIK	0.0086578	**0.0001917**	0.0270697	**0.0044**	0.0306672	0.025605	0.06626551	**0.0006541**
GRM II/III	0.0381623	**0.0019961**	0.0624555	0.0283	0.153807	0.14927	0.16105571	0.0079243
Glutamate	0.0518707	**0.0003654**	0.0860251	0.0229	0.2556066	0.191841	0.19557768	**0.0002049**

Table S10a: Results from Fisher's exact test comparing kainite, group II/III metabotropic, and glutamate receptor-gene (sub)families with other major receptor-gene types for data summarized in Figure S10: $p > 0.05$ shaded in grey; for $p \leq 0.05$, text is not highlighted; Bonferroni adjusted p-value ($p \leq 0.00625$) **highlighted in bold**.

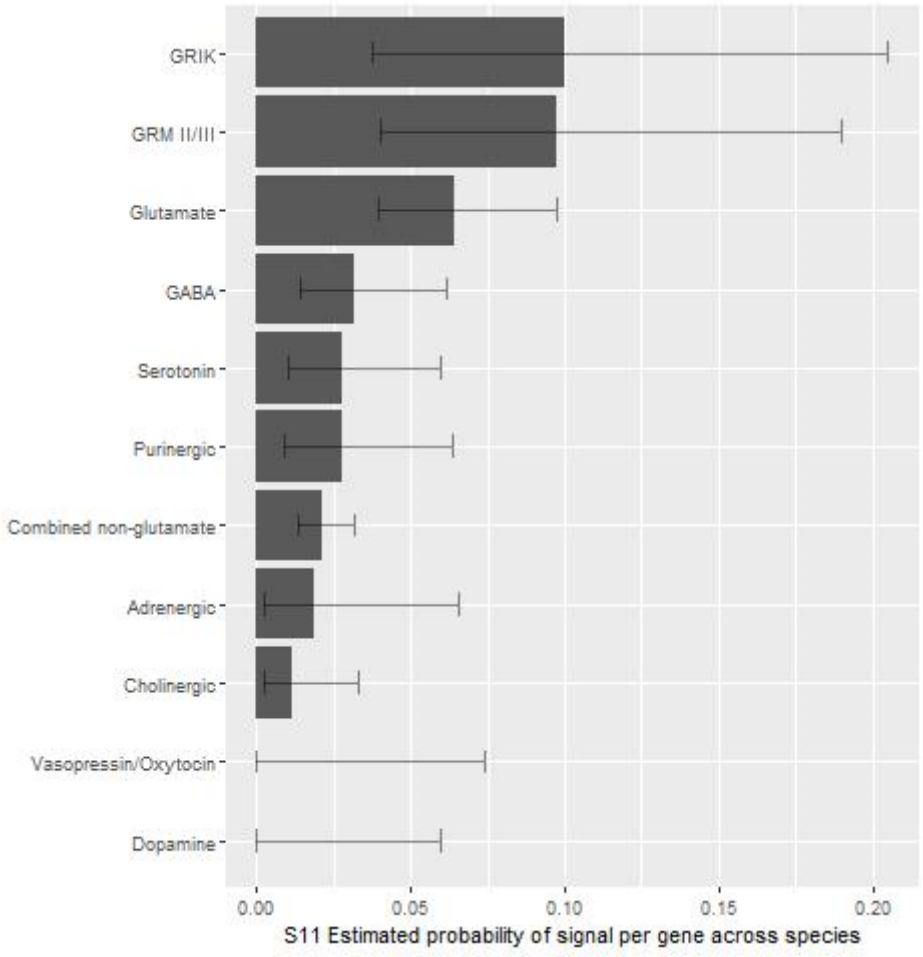

Figure S11 – Comparison of proportions of domestication-related signals across major receptor gene types from domesticate selective sweep and fox high-frequency allelic divergence studies only (excludes expression, adaptive introgression, and all human studies). Error bars represent the exact confidence interval for the data summarized in each rectangular bar.

	Adrenergic	Cholinergic	Dopamine	GABA	Purinergic	Serotonin	Vasopressin / Oxytocin	Combined non-glutamate
GRIK	0.0251001	**0.0017114**	0.027412	0.033	0.030973	0.02587	0.06699523	**0.002962**
GRM II/III	0.0309367	**0.001111**	0.015777	0.049	0.042407	0.021586	0.06745584	**0.00172**
Glutamate	0.0797425	**0.0010437**	0.05455	0.083	0.089751	0.066457	0.14250163	**0.000318**

Table S11a: Results from Fisher's exact test comparing kainite, group II/III metabotropic, and glutamate receptor-gene (sub)families with other major receptor-gene types for data summarized in Figure S11: $p > 0.05$ shaded in grey; for $p \leq 0.05$, text is not highlighted; Bonferroni adjusted p-value ($p \leq 0.00625$) **highlighted in bold**.

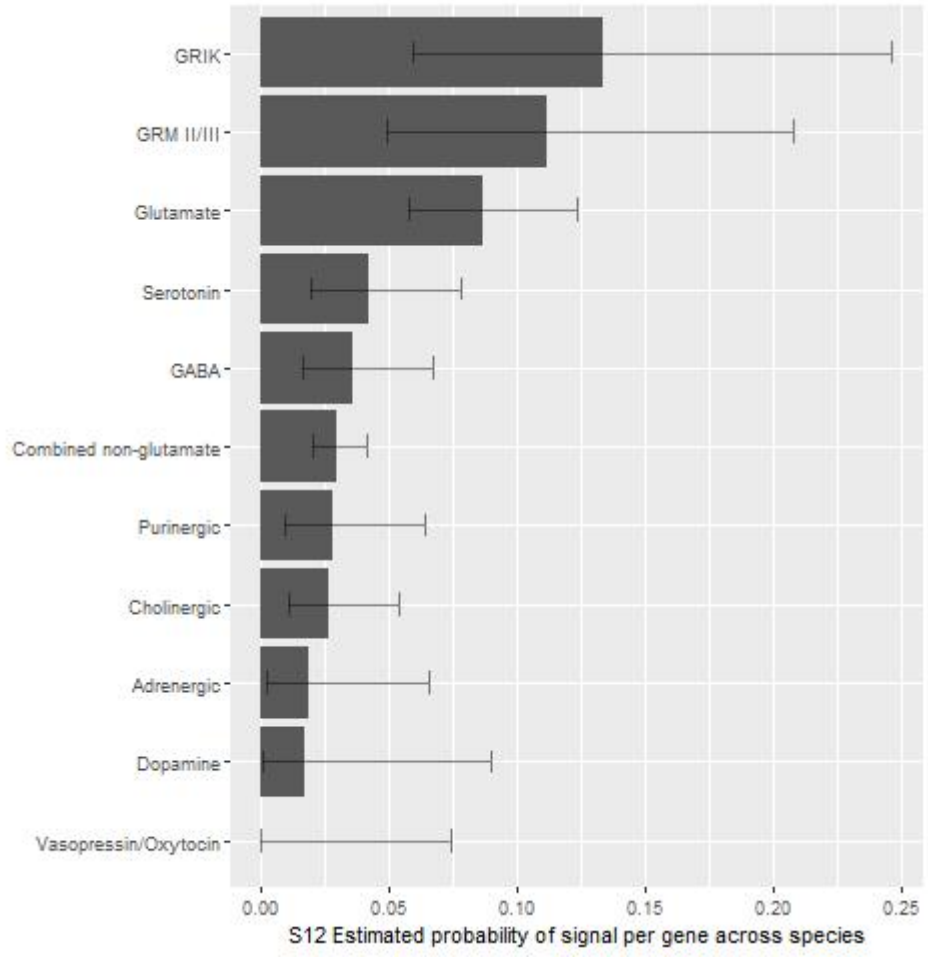

Figure S12 – Comparison of proportions of domestication-related signals across major receptor gene types from domesticate selective sweep, fox high-frequency allelic divergence, and adaptive introgression studies only (excludes expression and all human studies). Error bars represent the exact confidence interval for the data summarized in each rectangular bar.

	Adrenergic	Cholinergic	Dopamine	GABA	Purinergic	Serotonin	Vasopressin / Oxytocin	Combined non-glutamate
GRIK	**0.004381**	**0.0019677**	0.03219	0.00691	**0.004463**	0.014973	0.02386128	**0.000678**
GRM II/III	0.0154174	**0.0054836**	0.039505	0.030013	0.011347	0.041944	0.04370091	**0.002183**
Glutamate	0.0144754	**0.0022794**	0.063265	0.015083	0.012528	0.052949	0.06803232	**3.71E-05**

Table S12a: Results from Fisher's exact test comparing kainite, group II/III metabotropic, and glutamate receptor-gene (sub)families with other major receptor-gene types for data summarized in Figure S12: $p > 0.05$ shaded in grey; for $p \leq 0.05$, text is not highlighted; Bonferroni adjusted p-value ($p \leq 0.00625$) **highlighted in bold**.

Ionotropic

NMDA			AMPA			Kainate		
HUGO	Aliases		HUGO	Aliases		HUGO	Aliases	
GRIN1	NR1	GluN1	GRIA1	GLUR1	GLUA1	GRIK1	GLUR5	GLUK1
GRIN2A	NR2A	GluN2A	GRIA2	GLUR2	GLUA2	GRIK2	GLUR6	GLUK2
GRIN2B	NR2B	GluN2B	GRIA3	GLUR3	GLUA3	GRIK3	GLUR7	GLUK3
GRIN2C	NR2C	GluN2C	GRIA4	GLUR4	GLUA4	GRIK4	KA1	GLUK4
GRIN2D	NR2D	GluN2D				GRIK5	KA2	GLUK5
GRIN3A	NR3A	GluN3A						
GRIN3B	NR3B	GluN3B				Delta		
						GRID1	GLuD1	
						GRID2	GLuD2	

Metabotropic

Group I			Group II			Group III		
HUGO	Aliases		HUGO	Aliases		HUGO	Aliases	
GRM1	mGluR1	mGlu1	GRM2	mGluR2	mGlu2	GRM4	mGluR4	mGlu4
GRM5	mGluR5	mGlu5	GRM3	mGluR3	mGlu3	GRM6	mGluR6	mGlu6
						GRM7	mGluR7	mGlu7
						GRM8	mGluR8	mGlu8

Table S16: Glutamate receptors. (Throughout the present study we use HUGO nomenclature to refer to both receptor genes and proteins, with gene names *italicized*.)

Chapter 3

Capturing the effects of domestication on vocal learning complexity

Under review as:
O'Rourke, T., Martins, P. T., Asano, R., Tachibana, R., Okanoya, K., Boeckx, C. Capturing the effects of domestication on vocal learning complexity

Capturing the effects of domestication on vocal learning complexity

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Key Words: Vocal learning; domestication; stress response; dopamine; glutamate

Abstract

Domesticated and vocal learning species can serve as informative model organisms, respectively, for the reduction of reactive aggression and emergence of speech in our lineage. There is mounting evidence that vocal repertoires are modified under domestication across a range of species. Here we focus on the domesticated Bengalese finch, where the modifications brought about by domestication include a more complex song compared to that of the wild-type white-rumped munia. We put forward an explanation for this effect that revolves around the glutamate neurotransmitter system. Glutamate signaling (i) is broadly implicated in the vocal-learning abilities of songbirds, (ii) controls dopamine activity in neural circuits crucial for vocal learning, (iii) is disproportionately targeted in the evolution of domesticated species, and (iv) regulates stress responses and aggressive behaviors attenuated under domestication. We propose that attenuated excitation of stress-related neural circuits potentiates vocal learning via altered dopaminergic signaling, and suggest that this modification happened in the course of our evolution as a vocal learning, self-domesticate.

Glossary

- **Convergent evolution**: The independent emergence in different species of adaptive traits that were absent in their last common ancestor.
- **Domestication syndrome**: A set of phenotypical traits, at least some of which are proposed to characterize domesticated species. These traits include reduced fear and reactive aggression as well as increased affiliative behaviors towards humans, depigmentation, reductions in skull and brain size, changes to braincase shape, reductions in tooth size, shortening of the muzzle / flattening of the face, and the development of floppy ears.
- **HPA axis**: Hypothalamic-pituitary-adrenal axis, a set of connected structures that regulate the brain–body response to stress. The hypothalamus is a subcortical brain region, activated by neural responses to stressors. It stimulates the pituitary gland, a protrusion from the ventral aspect of the brain, which, in turn activates the adrenal glands, located above the kidneys. The adrenal glands produce corticosteroid hormones — the primary output of the HPA stress-response cascade —, which relay feedback signals to the brain, acting on limbic structures in the hippocampus, amygdala, and prefrontal cortex, implicated in memory, social and emotional cognition. In the text we often use the term "stress circuits" to to refer to interactions of the limbic system and HPA axis.
- **Neural crest cell**: Embryonic cells produced in vertebrates, which migrate away from their transitory origins in neural crest and differentiate into multiple cell types in different parts of the embryo. These include melanin-producing skin cells, cartilage, craniofacial bone, and the norepinephrine (adrenaline) producing adrenal medulla. Mild hypofunction of the neural crest cell signaling ('neurocristopathy') has been proposed to drive the multiple phenotypic changes of the domestication syndrome.
- **Reactive aggression**: Emotional, impulsive aggression, driven by the immediate presence of a perceived threat. There is evidence that reductions in reactive aggression have come under positive selection in domesticates and in recent human evolution. This contrasts with deliberate, planned (and often cooperative) proactive aggression, proposed to have been potentiated in the recent evolutionary history of our species.
- **Self-domestication**: A term often applied to domestication events in which wild animals gain a survival advantage (such as attaining more food or better shelter) by having closer contact with human settlements. Cohabitation is enabled by reduced fearfulness and reactive aggression on the part of the animal towards humans and an increase in affiliative behaviors. This can lead to the emergence, over generations, of domestication-associated physiological and behavioral traits from natural rather than artificial selection. Once detached from the idea of human-driven, intentional selection, self-domestication can describe situations where natural selection against reactive aggression and in favor of prosociality occurs among conspecifics (e.g. modern humans and bonobos), with certain morphological traits of the domestication-syndrome also emerging from this process.
- **Vocal (production) learning**: The ability to modify vocal output on the basis of experience. Apart from humans, incontrovertible vocal learners are three orders of birds (songbirds, parrots, and hummingbirds), cetaceans, pinnipeds, certain species of bats, and elephants. Recent evidence also points to different primate suborders as vocal learners, with the marmoset as one such example. Vocal production learning is often distinguished from vocal usage learning, whereby species learn to use pre-existing calls to encode different messages in new contexts.

1 An interaction of characteristic human traits

Modern humans exhibit a behavioral profile that measurably sets us apart from all other extant primate lineages in the expression of certain complex traits. Perhaps chief among these are our capacity for unboundedly productive language, undoubtedly important for the maintenance of modern human society in any of its guises, and our intraspecific tolerance and cooperation, which, while clearly variable among individuals and subject to environmental influences, falls far outside the range of our primate relatives across multiple measures [1]. In recent years it has become clear that when the individual traits that compose each of these broad capacities are properly fractionated, they can be subjected to comparative and experimental inquiry into how they evolved.

Any adequate evolutionary account of language should eventually seek to explain how individual subtraits interact with each other across cognitive domains. In the present paper we take advantage of the progress made in understanding both vocal learning and domestication, and propose a mechanism for how attenuated stress signaling resulting from the process of **(self-)domestication** (see Glossary) interacts with **vocal learning** circuits to support increases in the complexity of vocal output. A simplified version of our mechanistic proposal linking the prosocial and vocal/linguistic phenotype is presented in Figure 1.

Songbirds currently offer the best developed animal models to study vocal learning in humans, including its neural and genetic basis. Research in mammals, most notably bats, but also marmosets, has begun to uncover viable new models for the study of vocal learning in humans [3, 4]. This effort goes hand in hand with a broadening of interest in the subcomponents that make up the vocal learning phenotype and how these vary across species [5, 6]. A recent finding that the extent of marmoset forehead depigmentation—a commonly occurring trait of the **domestication syndrome** [7]—correlates with the amount of affiliative vocal responses that are produced adds exciting new evidence that domestication-related traits are linked to the evolution of vocal flexibility in primates. Indeed, the rate of white patch growth during development significantly correlated with the amount of vocal feedback received by marmoset offspring [8]. This research is in the spirit of the present review, which ultimately aims to shed light on mechanistic interactions that contribute to our species' complex vocal abilities.

Marmosets are not alone in providing suggestive evidence for a link between mammalian domestication and modified vocal behavior. Experimentally domesticated foxes show a surge of vocal activity in the first minute of exposure to an unfamiliar human, a behavior which quickly fades. On the other hand, non-selected foxes and those selected for aggressiveness vocalize indiscriminately. Moreover, the kinds of vocalizations most produced by domesticated foxes in these conditions ('cackles' and 'pants') are not produced by aggressive foxes, which instead produce 'coughs' and 'snorts' [9]. The vocalizations of dogs are higher pitched, harmonically richer, and much diverse compared to European wolves [10]. Moreover, it has been shown that humans can identify and associate different dog barks with different emotional contexts [11]. Guinea pigs produce calls that differ in rhythm and length from those of the wild cavy [12], cats display domestication-related differences in call frequency (pitch) and repertoire [13, 14], while bonobos show call repertoire differences compared to chimpanzees [15].

We consider that the evidence we present here below pertains mostly to enhanced plasticity in vocal learning circuits, rather than the *de novo* emergence of vocal learning. Nonetheless, experimentally increased stress signaling during development has been shown to negatively affect both song copying and song complexity in non-domesticated species [16, 17]. In the eastern phoebe, a non-vocal-learning suboscine (closely related to vocal-learning songbirds [oscines]), glutamatergic signaling changes, a basic circuitry for vocal control, and an extended period of plastic song development have been proposed as possible evolutionary substrates for the emergence vocal learning [18]. Future research may determine whether domestication-like attenuation of stress signaling in the wild can act as a more fundamental step in the emergence of vocal learning.

Our present focus on the interaction between domestication and vocal learning across levels of analysis, from genes to brain

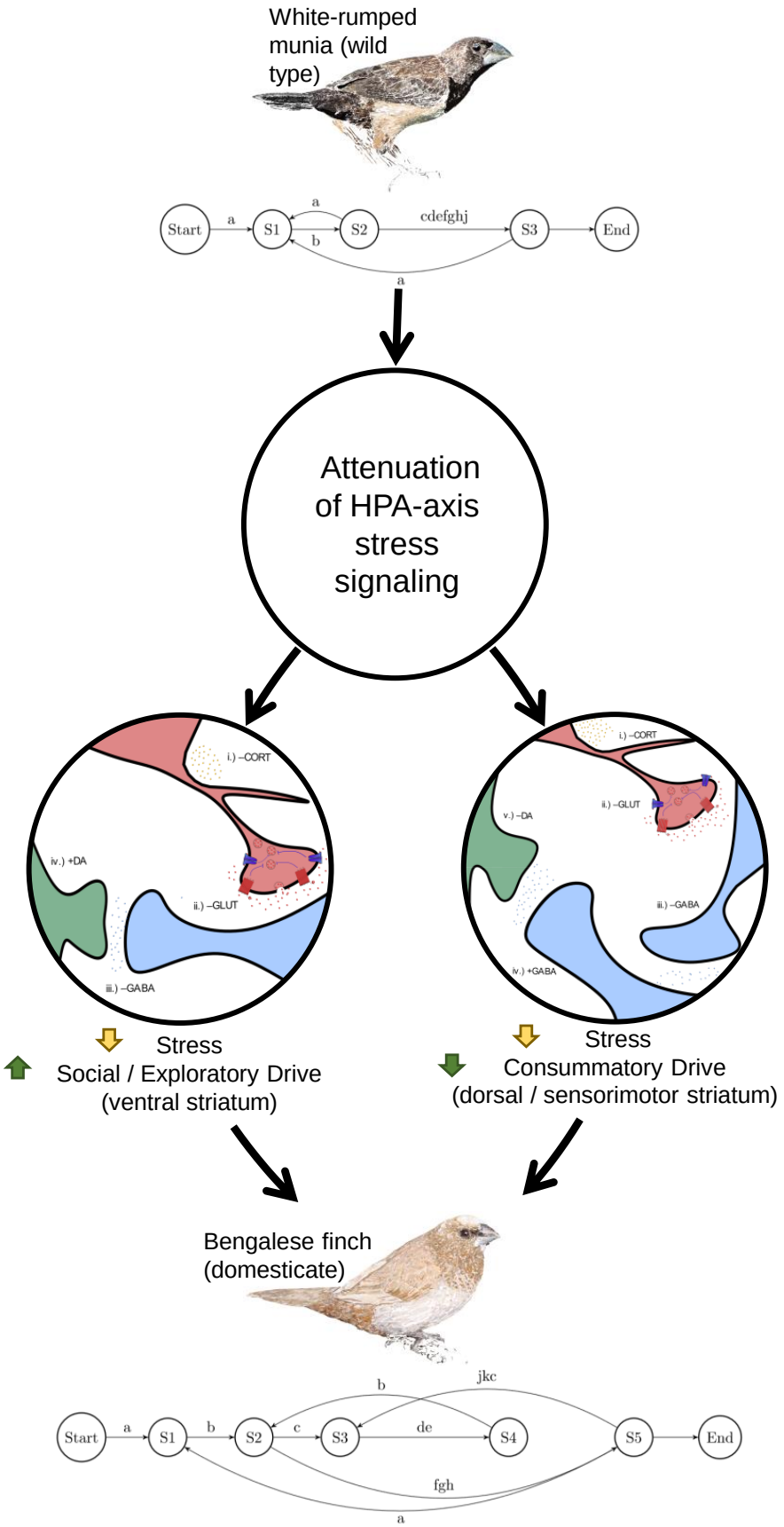


Figure 1: **Glutamate–dopamine interactions in increased vocal learning complexity:** Markov models of song complexity are shown for the wild white-rumped munia (top) and the domesticated Bengalese Finch (bottom) (based on [2]). End state is provided for illustrative purposes. The number of different notes (represented by lowercase letters) is similar in the two species, but the song of the white-rumped munia is more linear than that of the Bengalese Finch, which displays more complex transitions between different states. Under our proposed neurobiological mechanism, attenuated stress signaling (–CORT) results in reduced glutamatergic innervation (–GLUT) of inhibitory neurons (GABA) that regulate dopamine release from different regions of the striatum. We review evidence that glutamate receptors implicated in domestication and modern human evolution (in dark red and dark blue here) play a role in downregulating excitation of striatal circuits. Downstream effects on inhibitory GABAergic signaling (simplified here) result in modulated dopaminergic activity in the ventral striatum (–GABA ⇒ +DA) and dorsal striatum (+GABA ⇒ –DA). Striatal dopaminergic signaling is crucial for song copying, and in humans is implicated in aberrant or stereotyped vocalizations and tics that can emerge as part of neurodevelopmental and neuropsychiatric disorders. Here below we explore evidence that modulated dopamine signaling during critical developmental periods — downregulated in the dorsal striatum and upregulated in the ventral striatum — contributes to increased vocal exploration and enables the production of more complex and varied motor sequences in adulthood.

to cognition and behavior, leads us to prioritize the songbird literature at this point of time. In particular, we capitalize on studies of the Bengalese finch, a species with a well-documented domestication history and detailed phenotypical characterization, including the neural structures that underlie its song system. We build on genomic, neurobiological, and clinical evidence that songbird and human vocal learning depend on shared neurobiological substrates, likely the result of **convergent evolution** (see Box 1). Such detail allows us to articulate a causal hypothesis for how evolutionary pressures affect brain signaling, resulting in altered developmental trajectories and the emergence of a novel adaptive behavior. In so doing, we aim to adhere to the multilevel agenda set by Nikolaas Tinbergen for adequate biological explanation of complex traits [19], a central challenge for the cognitive sciences to this day [20].

Box 1: Homologous circuits in songbird and human vocal learning.

Brain structures recruited for vocal learning in songbirds are likely homologous (i.e. share the same evolutionary origins) with similarly connected structures in humans: these include the midbrain, thalamus, and striatum [21]. Certain structures may be either homologous or analogous (i.e. share structural properties but evolved independently), such as the avian pallium (organized in nuclei) and human cortex (organized in layers) [22, 23]), while others are more incontrovertibly analogous (e.g. human forebrain–larynx and songbird forebrain–syrinx axonal projections) [24]. Songbirds and humans have homologous structural connectivity, with avian pallio-striato-thalamic and human cortico-striato-thalamic loops both crucial for vocal-learning abilities [25]. Songbird vocal learning and vocal production circuits are summarized in Figure A.

Similarities between humans and avian vocal learners (hummingbirds, parrots, and songbirds) extend to neural gene expression. Specialized nuclei in the pallium and striatum (songbird Area X) — share convergent gene-expression patterns, respectively, with the human laryngeal motor cortex and dorsal striatum, critical for our vocal-learning abilities [26].

Using birdsong and its underlying neurobiology as a model for human speech is not without issues: for example, around half of avian studies (as of 2018) focused on the zebra finch, a species which learns a short stereotyped song [4]. Moreover, in many songbird species, including zebra finches and Bengalese finches, females do not typically sing. On the first of these caveats, the structural connectivity patterns of vocal learning circuits we highlight here are shared across songbirds and avian vocal learning species studied to date (including the Bengalese finch [25, 27, 28]). On the second, despite sex differences in song production in certain model species, the majority of female songbirds do, in fact, sing [29]. Female zebra finches, when exposed to the sex hormones estrogen, androgen, and/or testosterone during development learn to sing using the same neural apparatus as males [30, 31].

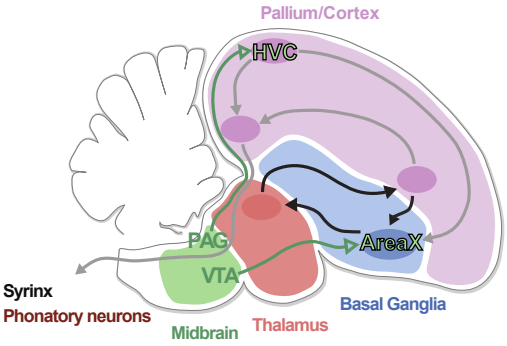


Figure A: **Songbird vocal learning and production circuits:** Lightly coloured portions highlight anatomical regions that are homologous (in the case of the pallium, potentially analogous) with structures of the mammalian brain. Darker colours denote song nuclei. Black arrows represent the anterior forebrain pathway, a loop of projections crucial for vocal learning and plasticity, which shares structural connectivity patterns with human striatal circuits: inputs from the pallium to striatal Area X are relayed back to the pallium via the thalamus, similarly to the human cortico-striato-thalamo-cortical loop [32]. The midbrain periaqueductal gray (PAG) and ventral tegmental area (VTA) provide dopaminergic inputs (green) to the pallial and striatal song nuclei HVC and Area X. HVC (used as a proper name) is a central node connecting auditory, vocal learning, and motor output pathways, forming part of the posterior motor pathway (grey arrows), which supports adult song production.

Just as for cross-species comparison of vocal learning capabilities, the identification of convergent biological substrates for reduced **reactive aggression** in humans and domesticated species can prove highly informative as to the emergence of our species' capacity for tolerance and cooperation. Variability in measures of aggression correlate with differential activity of the hypothalamic-pituitary-adrenal (HPA) stress-response cascade. Hyper-arousal of the **HPA axis** correlates with increased reactive aggression, whereas proactively aggressive individuals tend to have a dampened HPA response to stressors [33]. Domesticated species—for which a reduction of reactive aggression and increased affiliative behaviors towards humans are defining traits [7]—display an attenuated stress response relative to their wild counterparts.

Alterations to the stress-response system in the emergence of the Bengalese finch (*L. striata* var. *domestica*) places this songbird at the evolutionary intersection of traits relevant to domestication and vocal learning. This domesticated strain of the white-rumped munia (*L. striata*), bred in Japan over the last 250 years for its white plumage [27], displays an array of neuroendocrine (HPA-axis), anatomical, and behavioral changes reminiscent of the effects of the domestication syndrome [34]). Apart from depigmentation, these include alterations to HPA-axis signaling, a reduced fear response, attenuated aggression (reduced propensity to bite and reduced biting force), and increases in exploratory and socially driven reactions to the environment [27, 35, 36].

Most relevant to the behavioral considerations we focus on here, the vocal learning capabilities of the Bengalese finch have changed considerably in the course of the domestication process, suggesting an enhanced mechanism for song control: Although Bengalese finches average the same number of notes as their wild counterparts, they produce more syntactically varied songs, introducing more complex note-to-note transitions [37]. Bengalese finches subjected to conditions of stress during developmentally critical periods produce syntactically simpler songs [38]. Available records documenting the domestication process for the Bengalese finch detail that these birds have been bred for their white plumage, with no evidence that they have been bred for their song [27]. This contrasts with other domesticated birds, such as canaries (*serinus canaria domestica*), which have been bred specifically for features of their song, leading to the production of more stereotyped sequences. Canary breeds that have undergone artificial selection primarily on physical characteristics do not show such a marked reduction in song variability, although there is evidence that wild canary (*serinus canaria*) tones perceived as harsh to the human ear may have been selected out across all domesticated breeds [39].

2 Mechanisms of domestication

A leading mechanistic hypothesis for the emergence of domestication traits such as depigmentation, altered facial and cranial shape, reduced tooth size, and the development of floppy ears, proposes that these result from a mild hypofunction of **neural crest cell** signaling [34]. In humans, clinical hypofunction of the neural crest can lead to the emergence of Williams-Beuren syndrome, a developmental disorder for which the typical characteristics include craniofacial alterations, hypersociability, and loquaciousness (OMIM database: #194050). As in marmosets, here too there is a correlation between the emergence of domestication-like features and alterations to vocal traits. Interestingly, it has recently been shown that genes differentially regulated in Williams-Beuren Syndrome patients show above chance intersection with those that have changed in the modern human lineage following the split from Neanderthals and Denisovans [40].

While the hypofunction of the neural crest provides a mechanistic explanation of the broad syndromic changes that often occur in domesticated species, these transient embryonic cells are not directly involved in building the brain nor in its adult functioning, nor do they give rise to the corticosteroid ('stress hormone') producing adrenal cortex [34]. We see this as an important limitation of the neural crest based hypothesis in its potential to explain crucial behavioral aspects of domestication.

Reductions in circulating or, most consistently, stress-response spiking of corticosteroids — marking an attenuation of HPA-axis signaling — occur in multiple domesticated species, including non-aggressive versus aggressive foxes and rats, guinea pigs, sheep, ducks, chickens, and Bengalese finches, as well as in modern humans relative to other extant primates [41–48].

In the case that concerns us directly here, Bengalese finches have two to threefold lower fecal corticosterone (a corticosteroid similar to cortisol) than white-rumped munias, representing lower reactivity to daily stressors [49]. This reduction may have resulted from a process of self-domestication, whereby Bengalese finch lineages with lower stress responses to being caged and handled by humans gained a survival advantage. This may also have contributed to the depigmented phenotype preferred by breeders, as HPA-axis activity can alter the fates of neural crest cells, including those responsible for pigmentation [50, 51].

As for selective pressures affecting neuronal signaling systems in the context of domestication, there is strong evidence that signals of selection in domesticates and in recent human evolution disproportionately affect genes in the glutamate system (the brain's principal excitatory neurotransmitter, including in stress circuits, innervating the hypothalamus, see Box 2).

Box 2: Alterations to glutamatergic signaling in modern humans and domesticates.

Alterations to glutamatergic signaling genes are a remarkably consistent correlate of domestication, having been detected in domesticated foxes, dogs, cats, cattle, sheep, horses, yaks, goats, pigs, rabbits, ducks, and chickens [51] (and references therein). Multiple paleogenomic studies have also found glutamate signaling-gene changes in modern relative to archaic humans [52–54]. In both bonobos and Sumatran orangutans, which exhibit decreased aggression and more prosocial behaviors compared to their closest respective relatives (chimpanzees and Bornean orangutans), signals of selection disproportionately target glutamate receptor genes, which form the top-enriched functional categories in each of the former species [55, 56].

In a recent analysis of genomic changes and gene expression differences among 488 neurotransmitter receptor genes across 14 domesticated species and modern humans, kainate and groups II and III metabotropic glutamate receptor genes emerged as showing disproportionately high rates of changes. These genes' respective receptors are distinct from other glutamate receptors in that their actions tend to downregulate glutamate release, including in stress circuits [51].

Glutamate provides the major excitatory drive in limbic circuits that regulate HPA-axis signaling [57]. Pharmacological studies have shown that metabotropic receptors targeted in domestication and recent human evolution contribute to the attenuation of stress responses [58]. The actions of these receptors primarily dampen net excitation of the HPA axis and are spread across multiple limbic structures such as the hippocampus and the amygdala, the prefrontal cortex, and intermediary structures connecting to the hypothalamus [51]. Kainate receptors are highly modulated by corticosteroid feedback in the hippocampus: under low circulation of these stress hormones, kainate receptors tend to increase in expression, while at higher circulation, their expression tends to decrease [59]. Furthermore, under high glutamatergic excitation, kainate receptors inhibit glutamate release, while in moments of low excitation they promote signaling [60] (thus potentially contributing to the maintenance of low spiking activity relative to basal levels). The actions of metabotropic and kainate receptors contrast with other glutamate receptors, which increase in expression under stress and primarily potentiate excitatory signaling [61].

Pharmacological and knockout studies have shown that both kainate and metabotropic receptors attenuate glutamatergic signaling in the dorsal striatum that acts (via GABAergic inhibitory connections) to regulate dopamine release ([62, 63], see below). Kainate and metabotropic receptors are also implicated in a range of anxiety, stress, mood, and neuropsychiatric disorders, for which developmental stress is a major risk factor and aberrant striatal dopaminergic signaling a biomarker [51]. Interactions between glutamate and dopamine in striatal circuits are a substrate for the motor output of both aggression and learned vocalizations in humans and songbirds [64, 65].

Undoubtedly, the neural crest hypothesis goes a long way to explaining how physical traits are altered in similar ways across multiple domesticated species. Nonetheless, the fact that such changes are variable among domesticates, while tameness is ubiquitous [7, 66] strongly suggests that neural and neuroendocrine signaling are central to the (self-)domesticated behavioral phenotype. We have argued elsewhere that changes to genes involved in regulating glutamatergic signaling can help to fill a missing link in the evolutionary mechanisms driving (self-)domestication [51]. As we argue in the next section, these changes can also provide a mechanistic basis for how motor output for both reactive aggression and learned vocalization interact, particularly if we focus attention on the striatum where this interaction is likely to take place (but see also Box 3 for remarks about the role of other relevant brain structures).

Box 3: Beyond striatal circuits: the periaqueductal gray and vocal learning.

Separate bodies of literature have implicated the midbrain periaqueductal gray (PAG) in divergent phenotypical expressions both of aggression (reactive versus proactive) and vocalizing capabilities (innate versus learned). Activations of distinct subregions within the PAG or of connecting structures crucial to stress-response signaling — including the amygdala, and different hypothalamic subregions — can bring about diverging manifestations of aggression across different species. Proactive and reactive aggression, proposed to be under divergent positive and negative selection in our species, depend on similarly divergent activation patterns of the PAG and upstream hypothalamic structures [1].

Recently it has been shown that a special subset of predominantly glutamatergic neurons within the PAG are activated when male mice make socially motivated ultrasonic vocalizations during courtship [67]. Evidence from wider network gating of these social vocalizations suggests that amygdalar GABAergic projections synapse directly on PAG glutamatergic neurons to inhibit vocal output, while inhibitory projections from the hypothalamus synapse on PAG inhibitory interneurons, resulting in GABA-on-GABA disinhibition of glutamatergic neurons subserving social vocalization [68]. This finding prominently implicates the hypothalamus — a crucial connector of brain and body reactivity to psychogenic stressors — in the ability of mammals to modulate calls according to social context. This capacity has been proposed as a possible evolutionary substrate of vocal production learning capabilities of humans [69]. In the PAG of the vocal-learning pale spear-nosed bat (*P.discolor*), differentially expressed glutamatergic signaling genes form part of the most highly connected functional gene network of any identified [70, 71].

The songbird PAG has multiple connections to striatal and pallial song nuclei [72], and provides an important link between neuroendocrine and vocal learning systems, including stress-dependent influences to song complexity. Seasonal testosterone-driven increases in canary singing have been shown to depend on hypothalamic innervation of PAG dopaminergic neurons, suggesting an important role for interactions of the stress response cascade with production circuits in the social motivation of birdsong [73]. Dopaminergic connections from the PAG to HVC — a pallial song nucleus important for processing auditory inputs and integrating these with learned motor output —, are particularly sensitive to social cues, such as the presence of a singing tutor. These inputs are necessary for successful juvenile song copying [72].

3 Vocal learning under domestication: stress and striatal circuits

The human striatum is divisible into two broad anatomical regions: the ventral striatum (nucleus accumbens) and the dorsal striatum (caudate–putamen). Dopaminergic signaling from separate midbrain structures to each of these striatal regions is mediated by glutamate. In terms of function, the dorsal striatum can itself be divided in two. The dorsolateral portion ("sensorimotor striatum") is most prominently implicated in goal-directed action and in the attribution of salience to relevant stimuli, while the ventromedial aspect, bordering the nucleus accumbens, enables behavioral flexibility (often termed the "associative striatum", given prominent connections to cortical association areas). Midbrain dopaminergic inputs to the nucleus accumbens — also often called the "limbic striatum", because of prominent connections to the amygdala, hippocampus and orbitofrontal cortex — subserve reward and motivation [74]. Other functional characterizations consider that dopaminergic signaling in the ventral portion predominantly supports more exploratory appetitive behaviors, while the dorsal striatum subserves more repetitive consummatory behaviors [75].

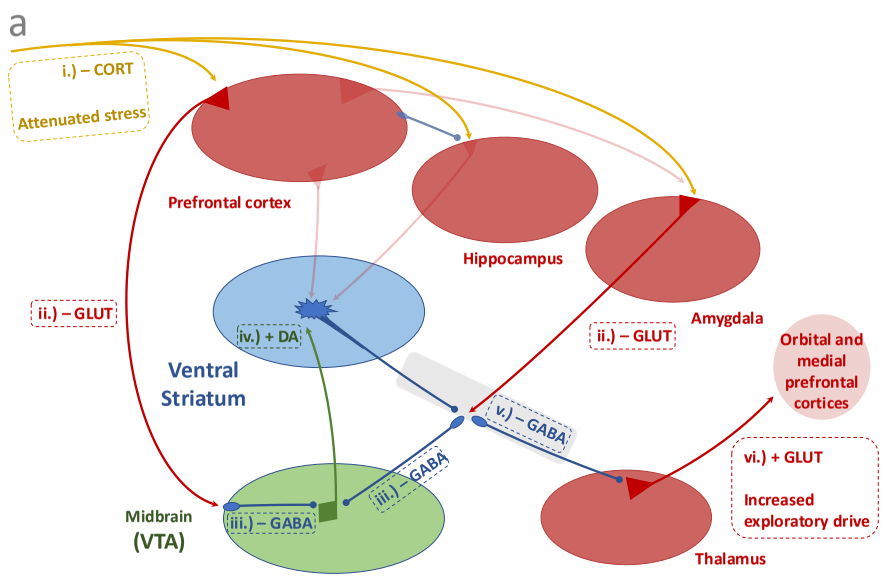
Evidence from neuropsychiatric disorders has made it clear that glutamate mediates striatal and prefrontal dopamine release from the midbrain in a stress-dependent manner [76, 77]. Acute corticosteroid spiking, acting on glutamatergic neurons can promote excitatory signaling in circuits innervating midbrain dopaminergic neurons [61]. Separately, an extensive body of work points to striatal dopaminergic signaling as being important for the vocal learning abilities of songbirds and humans ([64, 78]).

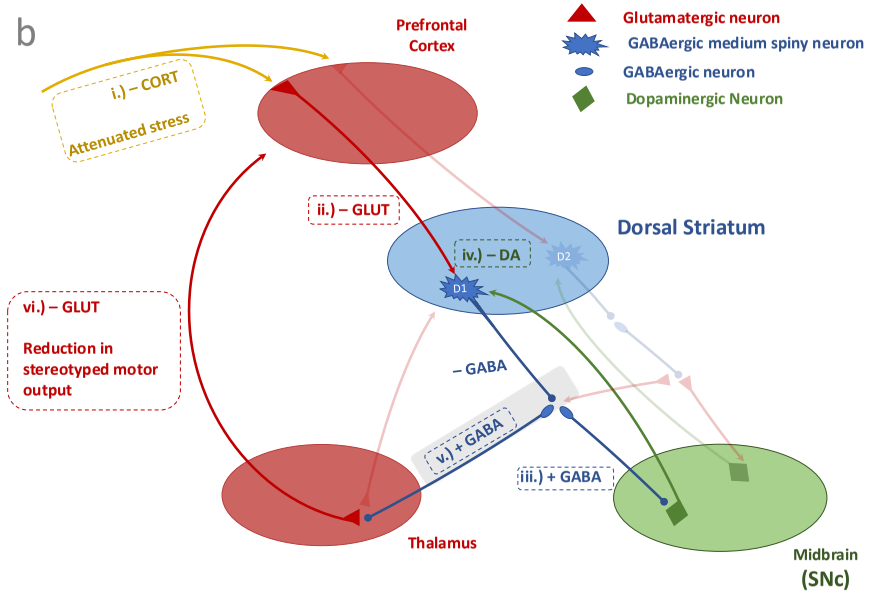
We present the case that attenuated stress signaling can lead to concomitant attenuation of glutamatergic networks, decreasing dopamine spiking in the dorsal striatum while increasing dopamine signaling in the ventral striatum. Because of differential connectivity patterns, not only can downregulated glutamate signaling reduce the stereotyped motor behaviors driven by dopamine efflux in the dorsal striatum, it can also increase the exploratory drive enabled by ventral-striatal dopaminergic signaling. Particularly, in vocal learning species, this is proposed to have enabled increased potential for variation in the production of vocalizations. These mechanistic interactions are summarized in Figure 2.

Clincal studies highlight the net effects of attenuated or hyperexcited glutamatergic signaling on dopamine release in striatal circuits. For the ventral striatum (nucleus accumbens), recent research on schizophrenia has shown that depleted glutamatergic inputs to midbrain dopaminergic regions, on balance, lead to hyperdopaminergic signaling, despite this no longer being considered the primary correlate of psychosis in the disease [74, 79]. By contrast, anhedonia (loss of the ability to experience pleasure), a principal diagnostic of major depressive disorder, is thought to be driven by hypoactive dopaminergic inputs to the ventral striatum. This can be brought on by exposure chronic social stress and is often associated with decreased exploratory drive [80]. Reduced ventral striatal dopaminergic signaling can also result from hyperactive glutamatergic connections from limbic structures , which, in turn, activate GABAergic inhibitory connections to dompamine neurons in the midbrain ventral tegmental area (VTA) [81]. Evidence across these studies points to the attenuation of glutamatergic signaling in limbic and prefrontal structures, promoting dopamine signaling in the ventral striatum. Figure 2a captures the major ways in which glutamate, GABA, and dopamine interact in ventral striatal pathways.

As for the dorsal striatum, disruption of glutamatergic circuits can have extensive effects on motor coordination and learning, often resulting in stereotyped behaviors [74, 75, 82]. Hyperglutamatergic activity in the dorsal striatum and limbic connections affecting these circuits has been implicated in Obsessive Compulsive Disorder (OCD) [83]. Similarly, comorbid Tourette's Syndrome and OCD are associated with hyperglutamatergic signaling from cortical and limbic structures to the striatum. In transgenic mice, putative comorbid OCD and Tourette's-like behaviors may be potentiated by downregulating glutamatergic innervation of GABAergic connections and/or potentiation of further glutamatergic afferents from the amygdala [84].

Figure 2





(a) **Effects of attenuated stress signaling on ventral striatal circuits:**[1]
i.) Reduced corticosteroid feedback acting on glutamatergic neurons in prefrontal and limbic regions leads to ii.) attenuated glutamatergic projections from the prefrontal cortex to the midbrain ventral tegmental area (VTA), as well as from the amygdala to the ventral pallidum (not named). iii.) These inputs typically innervate GABAergic neurons that iv.) inhibit dopaminergic signaling from the VTA to the ventral striatum. Thus, attenuation of upstream glutamatergic signaling disinhibits dopamine inputs to the ventral striatum. v.) Increased dopamine activity activates GABAergic medium spiny neurons, which act on other downstream inhibitory projections in ventral striatal output circuits (grey background). These GABA-on-GABA actions disinhibit ventral striatal output circuits, vi.) leading to increased activity in thalamic projections back to the orbital and medial prefrontal cortices, which support exploratory behaviors [85].

(b) **Effects of attenuated stress signaling on dorsal striatal circuits**
i.) Attenuated corticosteroid signaling leads to ii.) reduced stress-induced spiking of glutamatergic neurons in cortical structures that project to the dorsal striatum iii.) Downregulated excitatory inputs to the dorsal striatum are especially marked in the (D_1 dopamine receptor-expressing) direct pathway, where glutamate receptors targeted in domestication and recent human evolution have widespread actions. iv.) Medium spiny neurons of the direct pathway promote dopamine release by preventing GABAergic neurons in basal ganglia relay structures (simplified here) from inhibiting dopaminergic neurons of the midbrain substantia nigra pars compacta (SNc). By contrast, the indirect (D_2 dopamine receptor-expressing) pathway downregulates dopamine release. Attenuated upstream glutamatergic innervation of the D_1 pathway reduces midbrain dopamine efflux back to the dorsal striatum. v.) Reduced dopamine signaling results in increased GABAergic outputs (grey background), vi.) reducing thalamic excitation of cortical regions that promote stereotyped motor behaviors.

[1]The mechanism presented here is based primarily on clinical research in humans and model animals. Nonetheless, many of these mechanistic interactions in striatal circuits have also been demonstrated in songbirds (discussed overleaf). We have highlighted only central mechanistic interactions that support alternate stereotyped and exploratory motor outputs. For reasons of accuracy, in lighter shades we have also included circuits (e.g. the indirect D_2 pathway) that make important contributions to these behaviors. A more detailed review of glutamate receptor actions in dorsal and ventral striatal circuits can be found in supplemantary section S1

Increased dopaminergic signaling is a primary correlate of Tourette's syndrome [83]. Patients have been shown to have heightened striatal glutamatergic signaling, which has been proposed to cause imbalance of inhibitory–excitatory actions on dopaminergic neurons [86] (see circuitry in Figure 2b). Hyperexcitatory signaling from the prefrontal cortex, as well as tic-related activity in the primary motor cortex and Broca's area, increased thalamic glutamtergic signaling, and aberrant dopaminergic signaling from the midbrain have all been implicated in Tourette's syndrome [82, 87].

In a simiar vein, there is evidence implicating hyperdopaminergic striatal signaling and its downstream effects on motor output pathways in stereotyped vocalizations of songbirds. Microinjection of dopamine (but not saline) into the striatal nucleus Area X in live birds leads to a decrease in song variability. This is mediated by activation of D_1 dopamine receptors that tend to promote excitation in motor output regions (predominant in the direct pathway, as in humans) but not by D_2 (indirect pathway) receptors that tend to attenuate such excitatory outputs [88].

In male zebra finches, neuronal firing in the primarily dopaminergic midbrain VTA, which projects to Area X (see Figure A), correlates with the singing of a more stereotyped female-directed song [89]. Social-context–dependent alterations to dopaminergic signaling regulate the change from juvenile exploratory vocalizations to the adult crystallization of a more stereotyped song [90].

Independently of the influences of social context on song learning, stimulation or inhibition of midbrain (VTA) dopaminergic projections to the songbird striatum, driven by auditory feedback, is sufficient to guide syllable pitch learning [91]. The songbird midbrain receive glutamatergic input from and sends dopaminergic output to forebrain structures crucial for auditory processing of a tutor's song during juvenile learning and for vocal production as an adult [72, 92, 93]. Glutamatergic connections to the VTA are also causally implicated in online evaluative auditory feedback during song performance. As in humans (see Figure 2a), glutamate also innervates GABAergic interneurons in the songbird midbrain, which inhibit dopaminergic signaling to striatum, negatively reinforcing target syllable pitch learning [93].

The evidence reviewed in this section implicates hyperdopaminergic striatal signaling and its downstream effects on motor output pathways in stereotyped vocalizations of both humans and songbirds. Meanwhile, glutamatergic innervation of striatal inhibitory signaling is crucial for exploratory vocalization.

Homologues of glutamate receptor subunits targeted in recent human evolution are highly expressed in striatal input and output circuits that underlie vocal learning across different avian species ([94, 95]. Glutamatergic signaling genes are differentially expressed in Bengalese finch song nuclei relative to surrounding brain regions [96], and glutamate receptor genes have been reported to be differentially expressed in the song nuclei of the Bengalese finch compared to the white-rumped munia [50]. Preliminary reports of genomic differences between the Bengalese finch and white-rumped munia also highlight changes to dopaminergic signaling [97]. We consider that altered glutamatergic regulation of striatal dopaminergic signaling, resulting from domestication, is a strong candidate for having contributed to the plastic and variable vocalizing abilities characteristic of our species (for other candidates, see Box 4).

Our hypothesis is in line with the recent claim that certain "externally motivated behaviors" (increased concern for how one is viewed by others, increased social conformity, reduced aggression, and resultant increases in exploratory drive and behavioral flexibility) came under positive selection in great-ape ancestors of the human lineage. This saw the imposition of a "ventral striatum-dominant" phenotype that differentiates our lineage from the "dorsal striatum-dominant" phenotype exhibited by other extant great apes (marked by autonomous, goal-directed behaviors, relative unresponsiveness to social stimuli, and increased aggression) [98].

Box 4: Beyond Glutamate: neurotransmitter interactions in stress, aggression, and vocal learning.

Although other major neurotransmitter systems show evidence of comparative conservation in modern-human and domestication studies when compared with glutamate [51], this is not to say that they do not play an important role in stress-dependent potentiation of vocal learning. Indeed, glutamatergic effects on dopamine efflux occur as part of a triadic relationship with *GABA*: glutamate either predominantly innervates dopaminergic neurons, promoting signaling, is itself inhibited by GABAergic inputs on excitatory neurons, or innervates GABAergic interneurons, which in turn inhibit dopamine release.

Oxytocin and its avian homologue vasotocin have been proposed to contribute to the social motivation of vocal learning in humans and songbirds [99]. Vasotocin injection in hatchling zebra finches increases affiliative behaviors and improves song copying. Dense expression of vasotocin receptors suggested avian midbrain structures as possible mediators of this effect [100]. In mice, oxytocin acts on midbrain neurons to increase dopaminergic signaling in circuits that primarily project to the ventral striatum, while for midbrain projections to the dorsal striatum, oxytocin innervates GABAergic neurons that inhibit dopamine release [101]. Oxytocin is synthesized in hypothalamic regions crucial for processing psychogenic stressors and acts on circuits implicated in both vocal learning and stress-related psychiatric disorders. Domestication-implicated glutamatergic signaling genes can drive oxytocinergic signaling [51, 102].

Serotonin has long been implicated in aggressive behaviors, and both glutamatergic and serotonergic signaling genes display changes differentiating aggressive from non-aggressive rats and farm-bred foxes as well as in different domesticated species [103–106]. Like glutamate, serotonin mediates oxytocinergic signaling, and in the dorsal PAG of mice this has anxiolytic effects resulting in decreased defensive behaviors [107]. Of note, serotonin receptors are differentially expressed in distinct song nuclei of zebra finches when compared with adjacent tissues [95].

Depletion of *norepinephrine* (noradrenaline) in the zebra finch brain has been shown to disrupt the context-dependent reduction in Area X activity during female-directed singing [108]. Also, socially-tutored juvenile zebra finches show increased noradrenergic (and dopaminergic) activity as well as more exact song copying than those tutored using audio recordings [109].

Compared to other extant great apes, humans show a marked reduction of acetylcholine levels in the striatum, a neurochemical signature that supports the lower levels of reactive aggression in our species [98]. Chronic blockade of cholinergic receptors in a pallial song production nucleus of juvenile zebra finches leads to inexact copying of the tutor song, including abnormally high variability in the production of syllables [110].

In both songbirds and humans, *endocannabinoids* regulate glutamatergic synaptic plasticity at inhibitory medium spiny neurons of the striatum [63, 111]. Cannabinoid receptors also downregulate excitation of the hypothalamus as part of feedback stress signaling acting directly on the hypothalamus [112]. In zebra finches, cannabinoid receptor expression increases throughout development, peaking around the time of song crystallization. Agonism of these receptors in juvenile zebra finches decreases stereotypy in adults without impeding the development of a mature song [113]. Given this evidence, endocannabinoids may well be worthy of research as to domestication-driven enhancement of vocal-learning abilities in the Bengalese finch (see also [114]).

4 Concluding remarks and future perspectives

Our proposal provides a concrete claim regarding how self-domestication, a recent evolutionary event in our lineage [115], may have modified a preexisting capacity for vocal learning [116, 117]. We build our case on an analogy involving the song contrast between the munia and the domesticated Bengalese finch. The paleogenomic, anatomical, neurobiological, and behavioral evidence reviewed here points to the glutamatergic system as an important biological substrate of both domestication and vocal learning. Indeed, differential glutamatergic signaling-gene expression in Bengalese finch song nuclei place this system at the crux of potentiated vocal learning under domestication.

We have argued that selective pressures on reduced stress reactivity in our species have led to attenuated excitation of stress circuits and concomitant reduction of midbrain dopaminergic signaling in the dorsal striatum. The opposite pattern occurs in the ventral striatum, with increases in dopaminergic innervation occurring. We propose that such modulation of dopamine via attenuation of glutamate signaling has contributed to increased innovation and variability in the vocal production abilities of our species.

Feedback from stress hormone signaling not only affects striatal signaling and motor learning, but also targets structures such as the orbitofrontal cortex, amygdala and hippocampus, implicated in social, emotional, spatial, and verbal memory encoding, language processing, and conceptual learning more broadly [118]. Our model invites the possibility that other language-related and cognitive competences should be affected by altered stress signaling under domestication. There is evidence for increased social learning capabilities in domesticated species, including the ability to read communicative signals in dogs and foxes [119, 120]. Dogs and bonobos are also proficient word learners [121, 122]. Sumatran orangutans, which display domestication-related phenotypes relative to their Bornean counterparts, show increases social learning, and innovative tool use [123, 124].

This and other issues (see Outstanding Questions box) will have to be left for the future, but we hope to have convinced the reader that progress in comparative cognitive neuroscience, paleogenomics, and paleoanthropology, can, as proposed by [125], open up a rare window into the evolutionary steps that may have contributed to the modern human linguistic phenotype.

Outstanding Questions

- Correlations between domestication-related traits and the vocalizing abilities of marmosets may provide a window into to the cognitive and neural subcomponents that make up our own species' vocal learning abilities. As for the Bengalese finch, our hypothesis predicts that domestication-associated alterations to vocalization are mediated by attenuated stress signaling acting on glutamatergic networks. The marmoset may prove a highly informative model for the mechanistic study of behavioral and physical trait interactions under domestication.
- Manipulation of developmental stress in songbirds, including the Bengalese finch, can lead to the production of a syntactically simpler song. The behavioral and neurobiological effects of corticosteroid treatment on the Bengalese finch song have yet to be investigated. Under our proposal, chronic corticosteroid treatment during development should lead to the production of a simpler song in adulthood, and should lead to hyperglutamatergic signaling in juvenile vocal learning circuits, inducing increased dopaminergic spikes in Area X.
- Further genomic and neurobiological comparisons between the Bengalese finch and white-rumped munia are crucial to advancing research into domestication and vocal learning. Restrictions due to avian influenza on the international import and export of munias have hindered efforts to carry out such comparisons. Differential glutamatergic receptor gene expression identified in songbirds relative to non-vocal-learning birds has been reported in the Bengalese finch relative to the white-rumped munia. These preliminary reports await confirmation.
- Determining the altered brain expression of neuronal signaling genes associated with stress-driven production of simpler songs may help to identify targets for pharmacological manipulation. This could provide unique therapeutic potential in treating stress-driven vocal stereotypies and tics, including those typical of Tourette's syndrome.

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Supplementary Information: Capturing the effects of domestication on vocal learning complexity

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S1 Glutamate signaling genes in the regulation of striatal dopamine signaling

Here below, we review how glutamatergic signaling genes that show signals of selection and differential expression in modern humans modulate dopamine efflux in distinct striatal networks. We argue that the maladaptive behavioral traits resulting from stress and preservative disorders can help to inform how glutamate–dopamine interactions in mesolimbic (ventral striatal) and cortico-striato-thalamo-cortical (dorsal striatal) networks enable the enhancement of vocal-learning capabilities.

The kainate and groups II and III metabotropic receptor gene (mGluR) (sub)families that disproportionately fall within selective sweep regions under domestication and in recent human evolution have substantial influence on striatal glutamatergic transmission and have been implicated in glutamate–dopamine interactions in stress and preservative disorders. Beyond these (sub)families, individual NMDA and AMPA glutamate receptor genes (particularly GRIN3A and GRIA2) also appear in multiple studies of selective sweeps under domestication and recent human evolution [1].

Loci and actions of kainate and metabotropic receptors are shown in Figure S1. Evidence for these interactions is detailed throughout the remainder of this supplementary section.

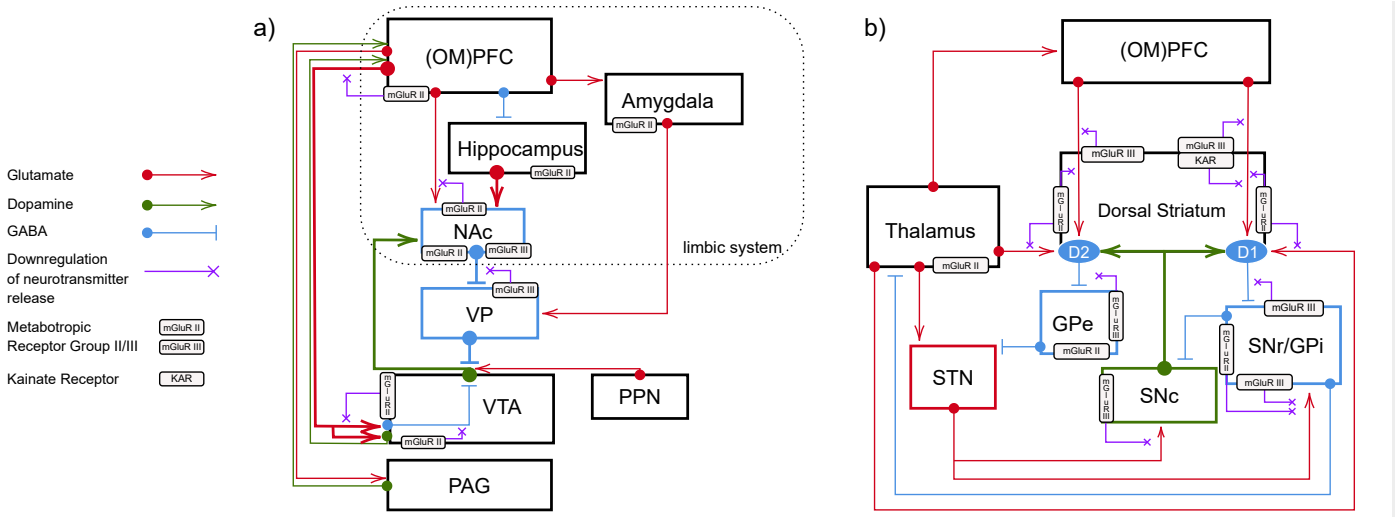

Figure S1: a) Kainate (KAR) and groups II and III metabotropic receptor actions in a) ventral striatal circuits and b) dorsal striatal circuits: Knockout and pharmacological manipulation of group II mGluRs have shown these to contribute, on balance, to the promotion of dopaminergic signaling in the ventral striatum. Meanwhile, KARs and mGluRs attenuate excitatory signaling in corticostriatal and thalamostriatal projections, broadly contributing to a reduction of dopaminergic efflux to the dorsal striatum.
D1 - D_1 dopamine-receptor expressing direct pathway; D2 - D_2 dopamine-receptor expressing indirect pathway; GPe - Globus Pallidus externa; GPi - Globus Pallidus interna; (OM)PFC - (orbital and medial) prefrontal cortices; NAc - Nucleus Accumbens; PAG - Periaqueductal Gray; PPN - Pedunculopontine nucleus; SNc - Substantia Nigra pars compacta; SNr - Substantia Nigra pars reticulata; STN - Subthalamic Nucleus; VP - Ventral Pallidum; VTA - Ventral Tegmental Area

S1.1 Group II mGluR actions in the regulation of ventral striatal dopaminergic signaling

Among high frequency changes and selective sweeps differentiating modern from archaic humans, changes on group II metabotropic receptor genes (*GRM2* and *GRM3*) are identified across more studies than on any other neurotransmitter or nuclear hormone receptor (sub)family [1]. As well as signals of selection in modern humans, a protein-coding change on *GRM3* differentiating tame from aggressive foxes has been considered one of the strongest potential candidates for having resulted directly from the domestication process [2]. *GRM2* shows signals of selection in modern humans [3]).

Double knockout of *GRM2* and *GRM3* has been shown to lead to a hypodopaminergic striatum in mice. However, this depletion is particularly marked in the ventral striatum (nucleus accumbens [NAc]), rather than in the dorsal striatum [4]. Double-knockout mice have deficits in motor co-ordination and appetitively motivated spatial working-memory, are hypoactive and show decreased preference for novel spatial exploration [4, 5]. The mice also have attenuated amphetamine-induced arousal as well as altered noradrenaline signaling in the prefrontal cortex (PFC) [4]. *GRM2*/*GRM3* double knockout does not affect measures of anxiety in mice, despite the fact that agonism of these receptors consistently shows anxiolytic effects [5].

Findings on the effects of agonism and antagonism of group II mGluRs on dopamine signaling are both consistent and contrasting with double knockout, but overall provide support for these receptors as potentiating dopaminergic signaling in the NAc [4]. Apparent contradictions may stem from whether administration of (ant)agonists is systemic or local [6]. For example, in rat NAc tissues measured in dialysis buffer, group II antagonists dose dependently increased extracellular dopamine levels

[7]. Similarly, local antagonism of the group II receptors in the NAc shell using *in vivo* microdialysis leads to an increase in dopamine release in this region [8, 9], a finding complemented by the fact that agonism in NAc slices has an inhibitory effect on dopamine release [10]. Mild agonism of NAc group II receptors in dialysis buffer reduces extracellular dopamine transmission, while no effects were found at low or high doses [7].

Conversely, systemic administration of group II antagonists has been shown not to affect dopamine signaling at basal levels in either control or chronic corticosterone-treated mice (the latter being used as a model for depression), but did *reduce* K+ induced spikes in dopamine release in the PFC of corticosterone-treated animals [11]. In a separate study, systemic antagonism was shown to increase firing of dopaminergic cells in the rat ventral tegmental area (VTA) and to increase dopamine efflux in the medial prefrontal cortex (mPFC) (alongside other neurochemicals such as acetylcholine). These effects were similar to those of the NMDA receptor antagonist ketamine in both neurochemical and behavioral (antidepressant) profiles. Metabolomic analysis showed that the actions of the antagonists involved activation of GRIA2 (an AMPA receptor gene implicated in multiple domestication and modern human evolution studies) [1, 12]. Although the effects on dopamine efflux in the NAc were not measured in this study, increased mesocortical dopaminergic signaling (VTA-PFC) does not always correlate that of mesolimbic (VTA-NAc) dopamine efflux. This is because descending glutamatergic connections to the VTA alternately synapse directly on mesocortical dopamine neurons that project back to the PFC or on GABAergic neurons that predominantly inhibit mesolimbic dopaminergic release [13, 14].

In a rat model of schizophrenia, systemic pretreatment with an mGluR group II agonist can attenuate the increase in glutamatergic transmission brought about by NMDA antagonism (using phencyclidine [PCP], known to elicit or exacerbate psychosis in humans). This reduced locomotor activity and stereotypy in the animals, but increased the spike in dopaminergic release brought about by PCP in the nucleus accumbens and the prefrontal cortex [15]. In another study using systemic administration, group II mGluRs led to increases in the turnover/utilization (as determined by metabolite measures) of both dopamine and serotonin in rat mPFC, NAc, and dorsal striatal slices [16]. Local agonism of group II receptors in the nucleus accumbens causes long term depression of excitatory axon terminals from the prelimbic cortex [17]. Within the VTA, group II mGluRs attenuate direct glutamatergic innervation of dopaminergic neurons innervating the nucleus accumbens, but they also downregulate GABAergic inhibition of these dopaminergic efferents. Perhaps for this reason, there have been contradictory findings as to the effect of mGluR II pharmacological manipulation in the VTA on dopamine-associated behaviors such as the stimulation of locomotor activity or cocaine seeking [18, 19].

S1.2 Group II mGluR regulation of dorsal striatal dopaminergic signaling

In adult human brains, the *GRM2*-coded receptor subunit (mGluR2) is localized across the basal ganglia, perhaps at levels higher than in any other broadly-defined brain region. This includes very intense immunolabeling in the caudate, putamen, and globus pallidus externa, with intense staining in the globus pallidus interna. Very intense staining is also detected in pars reticulata of the substantia nigra (SNr) and intense to very intense staining across most regions of the thalamus [20]. A Northern blot study has also shown particularly high expression in the human caudate nucleus, with very high expression in the thalamus. Expression was also detected at in the amygdala, hippocampus, and substantia nigra, with lower levels in the hypothalamus and subthalamic nucleus (STN) [21].

Pharmacological activation of mGluR2 in mice strongly inhibits glutamatergic release from thalamostriatal projecting neurons and at medium spiny neurons (MSNs) of the dorsal striatum, inducing reversible long-term depression (LTD). Meanwhile, agonism of both group II subfamily members leads to LTD at corticostriatal synapses. This attenuation of glutamatergic release has the

downstream effect of reducing phasic dopamine release mediated via cholinergic interneurons in the dorsal striatum [22].

Group II mGluR agonists lead to a reduction in excitatory signaling from STN synaptic terminals on GABAergic projection neurons in the SNr. The behavioral effect of agonism was to reverse catalepsy resulting from dopamine receptor antagonism. This may be due to reduced SNr inhibition of nigrostriatal dopamine output as a result of decreased glutamatergic innervation of GABAergic neurons. No behavioral effects were noted where dopamine receptors were not antagonized [23]. In the rat, group II mGluRs have been shown to downregulate excitatory signaling on STN synaptic terminals in the Substantia Nigra pars compacta (SNc), which provides the major dopaminergic input to the dorsal striatum [24].

However, separate expression studies of rats have failed to detect either *GRM2* or *GRM3* mRNA in the Substantia Nigra, when considered as a whole [25, 26]. In a mouse study, mGluR3 was not detected and mGluR2 only moderately expressed in SNc [27], while a human study found mGluR2 to be barely detected in the STN and not at all in the SNc [20]. Although we are unaware of any such detailed human expression or immunolabeling studies for *GRM3*/mGluR3, Northern blot analysis has shown moderate expression in the substantia nigra as a whole [21]. All things considered, group II metabotropic receptor actions at glutamatergic afferents to the SNc are unlikely to greatly affect dopaminergic signaling to the dorsal striatum. Stronger regulatory actions of these receptors are likely to occur in corticostriatal and thalamostriatal glutamatergic networks.

S1.3 Group III mGluR actions in the regulation of dorsal striatal dopaminergic signaling

Selective sweeps, high-frequency changes, or differences in brain expression occur on group III metabotropic receptor genes (*GRM4*, *GRM6*, *GRM7*, *GRM8*) at higher rates across domesticated species and modern humans than any other receptor (sub)family [1]. Three of the respective receptor subunits (mGluR4, mGluR7, and mGluR8) are extensively expressed in networks affecting nigrostriatal dopaminergic signaling and the resulting excitatory outputs from this. This includes corticostriatal glutamatergic afferents, subthalamic connections to both SNc and SNr, and striatal efferents to the SNr and globus pallidus. For this reason they have been considered potential targets for the treatment of Parkinson's Disease (PD), the primary etiology of which involves a depletion of dopamine release from the SNc to the dorsal striatum, and which can result from excitotoxicity of glutamatergic afferents [28].

Given this group III attenuation of excitatory drive, in non-Parkinsonian (non-dopamine depleted) populations, these receptors are strong candidates for the regulation of dopaminergic inputs to the dorsal striatum. Systemic administration of a group III agonist over two weeks attenuates motor deficits in a rat model of Parkinsons Disease that involves chemical lesion of SNc, in turn resulting in severe reductions in dopamine signaling in the dorsal striatum. This was considered to be the result of a reversal of subthalamonigral glutamatergic overactivity that had led to excitotoxicity in the SNc. However, this same chronic administration of the mGluR III agonist in control animals that had received no nigrostriatal dopaminergic depletion, brought about comparable motor deficits to the dopamine depleted animals and increased neuronal activity in SNr, a major output region of the dorsal striatum. This led the authors to suggest that the opposing effects of mGluR III activation were mediated alternately by the different tonic dopamine levels [29].

Agonism of mGluR4 in rat brain slices presynaptically attenuates excitation of SNc dopaminergic neurons by subthalamic nucleus fibres. In mice, but not rats, mGluR8 was shown to functionally overlap with mGluR4, reducing glutamatergic inputs to nigral dopaminergic neurons [30]. Agonism of group III mGluRs more broadly, following microinjection to the dorsal striatum of rats, has been shown to reduce basal extracellular dopamine levels, while antagonism had the opposite effect of increasing extracellular dopamine. Agonism also had the effect of reducing amphetamine-induced dopaminergic spiking in the dorsal striatum [31].

mGluR4 attenuates excitatory signaling in the corticostriatal pathway and inhibitory signaling in the indirect striato-pallidal D_2 pathway. Systemically administered positive allosteric modulation of this receptor increases premature responding and decreases attentional accuracy in mice, while decreasing motor activity and choice impulsivity (as measured by preference for a large-magnitude delayed reward). The effects on premature responding (motor impulsivity) were attenuated by antagonism of the D_2 dopamine receptor, suggesting that mGluR4 effects are mediated via dopaminergic signaling in the indirect pathway. This mechanism is thought to lead to an increase in the pallidal inhibition of subthalamic excitatory drive acting on the Substantia Nigra [32].

S1.4 Summary of groups II and III metabotropic receptor actions on striatal signaling

The actions of groups II and III receptors in striatal circuits strongly suggest divergent effects on dopaminergic signaling and resulting excitatory output from these striatal regions. On balance, studies suggest that the net systemic actions of group II receptors are to promote dopaminergic signaling in the nucleus accumbens, despite evidence that, locally, receptors act to inhibit dopamine release. Meanwhile, in the dorsal striatum, both group II and group III receptors act to attenuate cortico- and thalamostriatal excitatory inputs, with group III receptors also prominently attenuating subthalamonigral glutamatergic inputs.

S1.5 Kainate receptor regulation of downstream striatal signaling

Kainate receptor genes (*GRIK1-GRIK5*) encode for low-affinity (GRIK1-GRIK3, GLUK1-GLUK3, or GLUR5-GLUR7) and high-affinity (GRIK4-GRIK5, GLUK4-GLUK5, or KA1-KA2) receptors. In a recent comparison of the genomic signals associated with domestication events, signals occurred on *GRIK3* across the highest number of domesticated species of any neurotransmitter receptor gene, closely followed by *GRIK2* [1]. *GRIK3* has also been a target of a selective sweep in recent human evolution [33]. NETO1, a kainate receptor accessory subunit, shows differential expression in the lateral magnocellular nucleus of the anterior nidopallium (LMAN), Area X, and HVC song nuclei of the Bengalese finch compared to surrounding areas [34].

Kainate receptor genes are highly expressed in the rodent and primate basal ganglia, with relative abundances varying across studies and according to species. *GRIK2*, *GRIK3*, and *GRIK5* — the kainate receptor genes most often implicated in modern-human and domesticate evolution — are consistently found to be most prominently expressed in the rat, mouse, monkey, and human dorsal striatum [35, 36, 37, 38, 39, 40]. GRIK2 and GRIK3 receptors are more abundant and more predominantly presynaptically expressed in the primate caudate and putamen than in those of the rodent, making them more likely to be involved in regulation of glutamate release [39]. High-affinity subunits are necessary for ionotropic but not metabotropic function of kainate receptors, the latter instead being subserved by low-affinity receptors [41]. A comparison of expression levels of neuronal signaling genes in humans, chimpanzees, and macaques identified *GRIK3* among genes showing differential expression in the human striatum (dorsal caudate nucleus and putamen). *GRIK3* is listed in four of the five most significantly enriched functional categories for human differentially expressed genes, including the most significantly enriched [42].

Knock-out of all five receptor genes (*GRIK1-5*) in mice leads to abnormalities in corticostriatal signaling over and above that of any other brain region, including reductions in striatal NMDA-mediated synaptic plasticity and decreased spine densities in direct and indirect projecting MSNs. Knockout led to increased preservative and decreased exploratory behaviors typical of OCD model animals, as well as to motor deficits [43].

Kainate receptors containing the GRIK2 (GLUK2/GLUR6) subunit (one of the most prominently expressed in the striatum) have been shown to inhibit glutamate release through the mobilization of endocannabinoids in direct (D_1 dopamine-receptor expressing) MSNs of the dorsal striatum, while not affecting the indirect (D_2 dopamine-receptor expressing) pathway [44].

Activation of the direct pathway further potentiates glutamatergic signaling in thalamocortical circuits, via a disinhibitory mechanism (in turn facilitating motor activity), while the indirect pathway has the opposite effect (inhibiting thalamocortical excitatory outputs, and reducing motor activity). Thus, kainate receptors appear to play a prominent role in modulating the excitatory downstream effects of dorsal striatal dopamine. In the comparison of human, chimpanzee, and macaque neuronal signalling-gene expression that listed *GRIK3* among genes differentially expressed in the human striatum, the dopamine receptor genes *DRD1*, *DRD2*, and *DRD3* were all significantly downregulated in the human striatum [42].

Experiments in cats have shown that kainate receptors in the caudate nucleus regulate dopamine signaling: Kainate stimulates dopamine release in the presence of the sodium ion channel blocker tetrodotoxin (TTX), and is thus thought to act directly on dopaminergic nerve terminals (an effect not seen for NMDA or the potent AMPA receptor agonist quisqalate), whereas, in the absence of TTX, and at high concentrations, kainate inhibits dopamine release (and potentiates GABA) [45].

S1.6 Combined effects of kainate and metabotropic receptor regulation of striatal signaling

Overall, strong evidence is beginning to emerge for a prominent role of kainate receptors in the modulation of dorsal striatal dopaminergic signaling. Similarly to group II and III metabotropic receptors, the low affinity kainate receptors, which are most often associated with domestication events, attenuate glutamate actions on (and downstream excitatory output of) dopaminergic signaling in the striatum.

As with metabotropic receptors, loss of function of kainate receptors can lead to a reduction in exploratory behaviors. Ablation of kainate receptors can also lead to an increase in stereotyped behaviors, and activation of group II mGluRs has been shown to reduce these, again suggesting a similar directionality in the actions of these receptors.

Apart from the attenuation of excitation by all three receptor (sub)families in dorsal striatal networks, there is also evidence that the net actions of group II activation across basal ganglia networks is to promote dopaminergic signaling in the nucleus accumbens. As mentioned further above, there is strong evidence that dopaminergic signaling in the NAc subserves the motor implementation of exploratory or appetitive behaviors, while dorsal striatal signaling enables more stereotyped consummatory behaviors [46].

It is, as yet, unknown how the signals of selection in recent human evolution may have affected the brain expression and functions of the receptor genes highlighted here. However, given that these changes are predominantly regulatory rather than protein coding, it seems reasonable to posit that expression of these receptors has been altered in number, rather than kind, as a result of the regulation of excitatory signaling coming under selection in our lineage. In short, these signals of selection are strong candidates for having contributed to an increase in exploratory behaviors in our species. Convergent signals on the same genes across domesticated species suggest that these genes may subserve increased exploratory or appetitive social behaviors in domesticates as a result of selection for tameness, including the more complex vocalizations of the Bengalese finch. Altered glutamate-mediated dopaminergic signaling in striatal networks, as outlined above, provides explanatory potential for the increase in complexity of the Bengalese finch song as compared to the white-rumped munia.

S1.7 Domestication, modern-human, and vocal-learning associated genes implicated in striatal signaling

In songbirds, GRM8, GRIK2, and GRIN2B receptor genes, each of which have been implicated in multiple domestication studies, are transcriptional targets of *FOXP2*, an important regulator of the highly striatally dependent vocal-learning abilities of both songbirds and humans [1, 47, 48]. Mutations on *FOXP2* in humans can lead to a heritable speech disorder in which decreases

in dorsal striatal volume (specifically in the caudate nucleus) are among the most prominent neural correlates [49]. Knockdown of *FoxP2* in Area X of songbirds interferes with dopaminergic signaling and abolishes the LMAN-dependent switch from a more variable undirected song to restricted directed singing [50]. Dopaminergic signaling in Area X is also attenuated by non-selective agonism of both groups I and II metabotropic receptors [51].

Various glutamate receptor genes show differential expression in the human striatum when compared with those of the chimpanzee and macaque. Apart from the kainate receptor gene *GRIK3*, implicated in multiple domestication studies and targeted by a modern-human selective sweep (see further above), the NMDA receptor genes *GRIN2A* and *GRIN2B*, the group I metabotropic receptor genes *GRM1* and *GRM5*, and the AMPA receptor gene *GRIA4* are all differentially expressed in the human striatum [42]. Also differentially expressed is *NETO2*, which encodes a kainate receptor accessory subunit and has been identified as showing signals of selection in modern humans [52, 3] as well as of ancient introgression from cattle to domesticated yaks [53].

Many other glutamatergic signaling genes that show differential expression in the human striatum have been identified as having changed in recent human evolution or under domestication. These include the sorting receptors *SORCS1* and *SORCS2*, the latter of which has been the target of a selective sweep in modern human evolution [33]. Both *SORCS1* and *SORCS3* had also been identified in an earlier draft of this modern-human selective sweep study, before correction for gene length was accounted for [54]. The SORCS2 receptor is highly enriched at post-synaptic densities in the striatum and hippocampus, where it is implicated in neurite outgrowth and spine formation. *SORCS2* knockout mice show increased susceptibility to stress, hyperactivity, risk-taking, reduced NMDA-dependent synaptic plasticity, and impaired long-term memory and prepulse inhibition of the startle response (a typical feature of schizophrenia) [55]. *SORCS1* is among the genes with most significant SNP frequency differences between tame and aggressive foxes [2]. Knockout in mice has been shown lead to a reduction in both AMPA and NMDA receptor surface trafficking as well as to both GABAergic and glutamatergic transmission at synapses [56].

NBEA, which encodes a scaffolding protein that regulates trafficking of glutamate and GABA receptors to synapses, is differentially expressed in the human striatum, has been identified as showing signals of selection in the course of recent human evolution, and has been associated with the domestication events of goats, sheep, cattle, and yaks [57, 42, 3, 58, 59, 60, 53].

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Chapter 4

Names and their meanings: A dual-process account of proper-name encoding and retrieval

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Review article

Names and their meanings: A dual-process account of proper-name encoding and retrieval

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ABSTRACT

The ability to pick out a unique entity with a proper name is an important component of human language. It has been a primary focus of research in the philosophy of language since the nineteenth century. Brain-based evidence has shed new light on this capacity, and an extensive literature indicates the involvement of distinct fronto-temporal and temporo-occipito-parietal association cortices in proper-name retrieval. However, comparatively few efforts have sought to explain how memory encoding processes lead to the later recruitment of these distinct regions at retrieval. Here, we provide a unified account of proper-name encoding and retrieval, reviewing evidence that socio-emotional and unitized encoding subserve the retrieval of proper names via anterior-temporal–prefrontal activations. Meanwhile, non-unitized item–item and item–context encoding support subsequent retrieval, largely dependent on the temporo-occipito-parietal cortex. We contend that this well-established divergence in encoding systems can explain how proper names are later retrieved from distinct neural structures. Furthermore, we explore how evidence reviewed here can inform a century-and-a-half-old debate about proper names and the meanings they pick out.

1. Introduction: Dual processes in proper-name encoding and retrieval

Proper names are lexical items that can pick out unique entities that are either perceived in the world around us (as in *Venus,* also known both as *the Morning Star* and *the Evening Star)* or are conjured from our internal conceptual structures (as in *Clark Kent* and his alias *Superman*). Proper names have been subject to debates in the philosophy-of-language literature since the nineteenth century, largely stemming from disagreement as to whether they directly denote entities in the external world, or, instead, pick out more complex meanings associated with the entity being named (Mill, 1858; Frege, 1948; Russell, 1911; Kripke, 1972).

More often than not, the people or entities named with a proper name are unambiguously unique and are familiar to speakers who use the name in common. Despite this shared usage, distinct speakers (or even a single speaker) may hold contradictory beliefs about the entity being named. For example, Venus can be called the Morning Star when it appears in the east but the Evening Star when appearing in the west. If one is unaware that the same planet is appearing in different contexts, one can affirm that Venus is the Morning Star while denying that it is the Evening Star (Frege, 1948). In the philosophy of language, debates about the semantics of such contradictory usages of proper names sought to elucidate questions about the nature of meaning, belief, and the interactions of language, mind, and world around us.

From the point of view of cognitive neuroscience, research on the ability to express meaning largely involves studying processes of memory encoding and lexical retrieval. However, despite extensive literature on the networks involved in face–name encoding and proper-name retrieval, few proposals have sought to integrate findings from these studies to inform the nature of proper names and the meanings they pick out. Here, we review neuroanatomical, lesion, and functional imaging evidence for the networks supporting the encoding of knowledge about unique entities and the later accessing of that knowledge during the retrieval of lexical items.

We propose that certain white-matter tracts, most saliently the left

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uncinate fasciculus (UF), but also the inferior longitudinal fasciculus (ILF), and the inferior fronto-occipital fasciculus (IFOF), and grey-matter structures that they connect — left orbital and medial prefrontal cortices (OMPFC), temporal pole, medial temporal lobe (MTL), and posterior temporo-occipito-parietal region, as well as the thalamus — are integrated into an encoding and retrieval network for proper names. We argue that the interactions of these regions with contralateral homologue structures during lexical retrieval and in broader aspects of cognition provide key insights into the kinds of meanings that proper names pick out.

Bilateral UF connections to the anterior MTL enable the encoding of information about unique entities that is later accessed via the orbito-frontal cortex and temporal pole during proper-name retrieval (Alm et al., 2016; Damasio et al., 1996; Kirwan and Stark, 2004; Papagno et al., 2011; Sperling et al., 2003; Zeineh et al., 2003). Moreover, the UF's important role in social and emotional cognition (Craig et al., 2009; Kitis et al., 2012; Motzkin et al., 2011; Olson et al., 2007; Von Der Heide et al., 2013) is suggestive of the nature of information encoded in anterior regions that enables subsequent retrieval.

We review evidence indicating that this network supports the encoding of unitized memories that often enable subsequent familiarity judgements at retrieval, but which more readily support explicit recall when socio-emotional information is encoded as a feature of items (see Dolcos et al., 2004; Yonelinas, 2002; Yonelinas et al., 2010; Fenker et al., 2005; Rugg and Curran, 2007; Murray and Kensinger, 2013; Yonelinas and Ritchey, 2015). We propose that unitization potentiated by socio-emotional arousal — enabling associative encoding of memories that are subsequently retrieved as a single integrated entity — supports the later recall of proper names via the UF-connected anterior temporal–prefrontal network.

Temporal regions lying immediately caudal to the UF-connected temporal pole, as well as posterior temporal regions, bordering the occipital and parietal lobes, have also regularly been evidenced to support both common-noun and proper-name retrieval (Damasio et al., 1996; Gorno-Tempini et al., 1998; Grabowski et al., 2001; Mehta et al., 2016; Semenza, 2006, 2011; Semenza and Zettin, 1988). We propose that the hippocampus and parahippocampal cortex encode information later accessed at retrieval by a second network running along this rostro-caudal axis of the temporal lobe, with both encoding and retrieval being supported by the ILF and the IFOF's posterior temporal connections. This (para)hippocampal item–item and item–context encoding forms non-unitized mnemonic associations that are typically implicated in recollection-based retrieval, supported primarily by posterior temporal and parietal regions (Eichenbaum et al., 2007; Yonelinas, 2002; Yonelinas et al., 2005; Diana et al., 2010). This memory system is posited to support the retrieval of both proper names and common nouns from a posterior projecting network connecting the temporo-occipito-parietal region.

Under this account, then, information enabling the retrieval of proper names is encoded via two distinct processes, one that forms mnemonic units that tend to encode socio-emotional information, the other non-unitized item–item and item–context associative memories that tend to be less emotionally arousing. Both the anterior fronto-temporal and posterior temporo-occipito-parietal networks supporting these processes are integrated via shared connections with the anterior MTL and PFC (Amaral and Lavenex, 2007; Papinutto et al., 2016; Van Hoesen and Pandya, 1975; Van Hoesen et al., 1975; Thiebaut de Schotten et al., 2012).

In Section 2, we explore in detail the networks involved in proper-name retrieval, as evidenced through semantic dementia, lesion, and functional imaging studies. Following this, in Section 3 we review the literature on face–name encoding, before spelling out the dual-process model of proper-name encoding and retrieval defended here. In Section 4, we explore the implications of the dual-process account for theories of proper naming, long debated in the philosophy of language but rarely considered in terms of neuroscientific evidence. We also propose means by which our model can be experimentally tested.

2. Proper-name retrieval networks

Lexical retrieval is a complex and integrative process, depending on many brain regions and multiple cognitive resources. These include accessing perceptual and conceptual representations, engaging control mechanisms to select suitable lexical items among various competitors, linking from conceptual to lexico-semantic or semantically categorized conceptual representations at distinct 'convergence zones' and/or at a single 'semantic hub', and, finally, accessing phonological and motor output systems, with their own fine-grained functional subdivisions (Damasio, 1989; Damasio et al., 1996; Patterson et al., 2007; Jefferies et al., 2008; Friedmann et al., 2013; Lewis and Poeppel, 2014; Gainotti, 2017). As we are most concerned here with the meanings that names pick out, most of our discussion concerns the conceptual–semantic systems supporting lexical retrieval rather than phonological (or graphemic) output systems.

The separation and definition of the above cognitive domains remains controversial, including disagreement as to whether conceptual and semantic knowledge should be considered distinct from each other, whether this information is stored in modality-specific or in amodal format, and whether different conceptual and semantic categories are stored in separate modules in the brain (see e.g. Damasio, 1989; Barsalou et al., 2003; Rogers et al., 2004; Patterson et al., 2007; Barsalou, 2008; Gainotti, 2017). Here below we review lesion evidence that predominantly leftward temporal lobe structures support the retrieval of lexical items including proper names, while damage to right temporal and bilateral orbital and medial prefrontal regions consistently leads to deficits in retrieving knowledge about individuals, rather than anomias. While this may suggest a qualitative left–right distinction between lexico-semantic and conceptual knowledge, it may also reflect effects on left-dominant language processing acting over conceptual representations that are otherwise qualitatively similar in both hemispheres (Gainotti, 2017). As such, we remain agnostic as to whether the anomias described here below are symptomatic of inherently semantic or conceptual deficits.

2.1. The temporal pole and proper names

Converging evidence from semantic dementia, lesion, and functional imaging studies leaves little doubt as to the importance of the left temporal pole in proper-name retrieval. The right temporal pole supports the recognition of unique individuals.

Proper names are frequently the first lexical items lost in semantic variant primary progressive aphasia (svPPA or PPA-S) (Papagno and Capitani, 1998; Snowden et al., 2004). Left anterior temporal lobe (ATL) deterioration is a feature of svPPA, which has sometimes been equated with semantic dementia (SD) or the fluent variant of PPA (Mummery et al., 2000). Mesulam et al. (2009) distinguish between svPPA and SD, with deficits in the former being language-specific (loss of semantic knowledge), whereas, in the latter, impaired face and object recognition can accompany semantic deficits. SD is usually marked by bilateral deterioration of the ATL, with most severe damage occurring in the left temporal pole, where the atrophy is thought to originate (Papagno and Capitani, 1998; Mummery et al., 1999, 2000; Gorno-Tempini et al., 2011; Collins et al., 2017).

Papagno and Capitani (1998) found that a svPPA patient with circumscribed atrophy in the left ATL had no deficits for retrieving common nouns, but significant deficits in retrieving proper names for famous people, places, and brands. Naming deficits for famous people were not accompanied by concomitant deficits in relaying knowledge about those people. As atrophy progressed throughout the left temporal lobe, common nouns began to be affected. Snowden et al. (2004) found that the more significant the atrophy in the left ATL in SD, the greater the deficits in recognizing and identifying famous names. Atrophy in

the right ATL correlated with deficits in face recognition and identification.

Damasio et al. (1996) found that left temporal-pole lesions across numerous patients significantly correlated with deficits in naming famous people (without deficits in recognizing images of them), while no subjects with retained people naming had temporal-pole lesions. Where patients had deficits in people naming only, lesions were limited to the most anterior portion of the left temporal pole. In the same study, Positron emission tomography (PET) scans of healthy subjects also showed activations in the left temporal pole for the retrieval of people's names. In another PET study, Grabowski et al. (2001) found left temporal-pole activations to be the main effect of naming famous faces and landmarks versus processing unknown entities. The right temporal pole was most significantly activated for the recognition of famous faces.

The evidence reviewed above suggests that the left temporal pole is particularly important in retrieving lexico-semantic information relevant to unique entities, while its rightward homologue supports the retrieval of non-lexical conceptual and perceptual information about unique entities.

2.2. Beyond the temporal pole: A dispersed network for proper-name retrieval

Functional imaging studies have indicated that an extensive network beyond the temporal pole supports proper-name retrieval. The extent of this network, which includes subcortical and limbic structures, underscores the point that proper-name retrieval does not solely depend on language-dominant regions of the temporal cortices.

Structures implicated in proper-name retrieval include the left inferior frontal cortex, left medial prefrontal cortex, left retrosplenial region, left collateral sulcus, left central cortex, right posterior superior parietal lobe, left temporo-parietal junction, left posterior temporal/occipital region, left basal ganglia (including the left thalamus), the amygdala, and the right cerebellum (Gorno-Tempini et al., 1998; Grabowski et al., 2001; Semenza, 2006, 2011). Based on a combined PET and lesion study, Damasio et al. (2004) proposed a predominantly leftward proper-name retrieval network that includes both temporal poles, the left anterior inferior temporal gyrus, left anterior superior temporal sulcus, left frontal operculum (pars orbitalis), left anterior medial prefrontal cortex, and left anterior cingulate gyrus. These authors suggest a rightward network for person-related concept retrieval that includes the temporal pole, anterior inferior temporal gyrus, anterior parahippocampal gyrus, lateral occipital lobe, and temporo-occipital junction.

There is much convergence among the above studies, although Gorno-Tempini et al. (1998), Grabowski et al. (2001), and Semenza (2006, 2011), unlike Damasio et al. (2004), all highlight the importance of left posterior temporal regions bordering the occipital and parietal lobes in proper-name retrieval. As with studies of SD patients, lesion–deficit correlations can help to pinpoint which parts of the proper-naming network are especially important for the retrieval of conceptual or lexico-semantic information that supports the recall of a name. Cases of near global proper-name anomia have occurred in patients with two very different neural pathologies: left parieto-occipital stroke and left fronto-temporal lesion (Semenza and Zettin, 1988, 1989), lending support to the idea that both anterior and posterior cortical regions are engaged in proper-name retrieval.

Anterior and mediodorsal thalamic damage can result in naming deficits similar to those associated with the temporal pole, including increased susceptibility to person over place-name loss (Lucchelli and De Renzi, 1992; Damasio et al., 1996; Miller et al., 2003) and improved naming performance when given phonemic as opposed to semantic cues (Lucchelli and De Renzi, 1992; Semenza and Sgaramella, 1993; Cohen et al., 1994; Otsuka et al., 2005). We consider there to be strong evidence from lesion and functional imaging studies that left thalamic, inferior prefrontal–temporal pole, and temporo-occipito-parietal regions are most consistently implicated in proper-name retrieval. Further below, we present evidence for these regions' structural and functional integration via white-matter tracts.

2.3. Proper-name and common-noun retrieval deficits: Convergent and divergent patterns

Although we are primarily concerned with proper-name retrieval deficits, it should be noted that, as atrophy extends posteriorly in the left temporal lobe of svPPA or SD patients, lexical retrieval deficits become more extensive, including both proper and object naming, as well as word association deficits. Grammatical competence and non-verbal object matching often remain normal (Mesulam et al., 2013). This raises the possibility that posteriorly connected networks for proper-name retrieval identified in studies reviewed above are engaged in broader lexical retrieval.

Nonetheless, evidence of extensive and selective proper-name anomias (as in Semenza and Zettin, 1988, 1989) suggests that proper-name retrieval depends, at least in part, on a separate network from that of other lexical items. In healthy populations, proper names are generally more difficult to retrieve than common nouns, even in cases where these lexical items are matched in their phonological form (e.g. Baker/baker: McWeeny et al., 1987). Cases of selective proper-name anomias can extend to names of personally familiar people, including friends and family members, which should presumably be relatively easy items to retrieve, while sparing infrequently occurring common nouns (Semenza and Zettin, 1988; Miceli et al., 2000). Lexical retrieval deficits that pattern with or dissociate from proper-name loss can tell us much about shared and distinctive cognitive resources upon which proper-name retrieval depends. We explore these patterns here.

The loss of highly specific common nouns (as in *sparrow* rather than *bird*) can accompany that of proper names in SD patients with predominantly left ATL atrophy (Gorno-Tempini et al., 2004). This observation has been corroborated by functional imaging data from healthy individuals, showing similar activations in the temporal pole for the retrieval of person names and specific common nouns (Rogers et al., 2006). This finding contrasts with Damasio et al. (1996), who had found that patients with lesions mainly in the inferior temporal lobe typically exhibited deficits in naming animals, while more posterior temporal lobe lesions, often encroaching on occipital and parietal regions, led to deficits in naming tools. Unlike in SD studies, these authors did not observe significant correlations between posterior temporal lesion and proper-name retrieval deficits.

These discrepancies may be explained by partially overlapping white-matter networks connecting posterior and anterior temporal regions subserving distinct lexical retrieval processes. Mehta et al. (2016) have shown that, within the left ATL, lesions limited to the temporal pole correlate with the loss of proper names, while anterior temporal lesions lying caudally to the polar region correlate with both proper-name and common-noun loss. These authors also show that such partial dissociations of lexical retrieval deficits are likely to emerge from distinct patterns of long-range-association-tract disconnection, with left UF disconnection from prefrontal areas correlating uniquely to proper-name loss and left ILF damage, disconnecting posterior temporal and occipital areas leading to both proper-name and common-noun loss.

These findings suggest that the retrieval of both proper names and common nouns engages shared cortical regions and white-matter tracts along the longitudinal axis of the left temporal lobe, whereas the most anterior portion of the left temporal pole, with its distinctive white-matter connections, is more specifically engaged in the retrieval of proper names. Below, we detail the white-matter tracts integrating thalamic, inferior prefrontal, temporal-pole, and temporo-occipito-parietal regions often associated with these distinct retrieval deficits.

2.4. White-matter connections integrating proper-name retrieval regions

Prefrontal and anterior temporal regions implicated in processing information about individuals and in proper-name retrieval are connected by the uncinate fasciculus (UF). These include the orbitofrontal cortex (OFC: BA 10, 11, and 47), (ventro)medial prefrontal cortex ([V]MPFC: BA 12, 25, and 32), temporal pole (BA 38), amygdala, anterior parahippocampal gyrus (divisible into the entorhinal [BA 28 and 34] and the perirhinal cortices [BA 35 and 36]), and perhaps the anterior inferior temporal gyrus (BA 20) (Ebeling and von Cramon, 1992; Chabardès et al., 2002; Kier et al., 2004; Martino et al., 2011; Thiebaut de Schotten et al., 2012; Catani et al., 2013; Dick et al., 2014; Vassal et al., 2016). Atrophy in SD is thought to spread from the anterior temporal cortex to the VMPFC and the amygdala via progressive degeneration of the UF (Mummery et al., 2000; Agosta et al., 2009).

Papagno et al. (2011) found that glioma patients who had temporal-pole and medial temporal portions of the UF removed, showed the clearest deficits in proper-name retrieval, followed by those who had the frontal portion resected. On the whole, patients for whom the UF was preserved retained proper-naming abilities. In a follow-up study, performance for proper naming remained pathological in patients with the UF resected, while any other deficits, including the retrieval of common nouns, had returned to normal. Nonetheless, even in cases of total or near total UF resection, proper-naming deficits are not total: On average, patients without the UF scored half as well as those with fully-retained connections (Papagno et al., 2014). This fact led the authors to argue, following Semenza (2006), that if there is anything like a module for proper names, it is not uniquely located in UF-connected regions. This is supported by the lesion and imaging evidence cited above, which points to thalamic and temporo-occipito-parietal involvement in proper-name retrieval.

Given these lesion–deficit associations, white-matter connections to the thalamus and posterior cortical regions must be integrated in any full account of proper-name retrieval networks. The ILF runs from the occipital lobe along the inferior temporal gyrus, connecting the inferior portion of the temporal pole (Kondo et al., 2003; Papinutto et al., 2016). The temporal pole's dorsal portion connects to the auditory cortex via the middle longitudinal fasciculus (MLF) (Dick and Tremblay, 2012; Dick et al., 2014; Vassal et al., 2016). Yasuda et al. (2000) proposed that the inferior longitudinal fasciculus (ILF) integrates a semantic hub for proper names in the left posterior temporal/occipital region with a phonological hub in the temporal pole. However, this proposed network for proper names does not take UF contributions into account and would have a hard time explaining proper-name retrieval deficits associated with damage to prefrontal regions.

There is evidence that the ILF relays visual content from occipital to anterior temporal regions: The extent of degradation of bilateral ILF fibers in children with cerebral visual impairment has been shown to correlate with the extent of object recognition deficits (Ortibus et al., 2012). Right ILF degradation has been implicated in both face and object recognition deficits with retained semantic knowledge (Grossi et al., 2014), while left ILF dysfunction has been implicated in object-naming deficits (Shinoura et al., 2010). However, brain stimulation tasks have failed to confirm ILF involvement in object naming, instead strongly suggesting a role for the IFOF, which connects occipital and posterior temporal regions to the OFC (Mandonnet et al., 2007; Duffau et al., 2005). Damage to the IFOF and UF have also been associated with loss of recognition of famous individuals from the presentation of voice stimuli (Papagno et al., 2018). Given the evidence for the ILF's involvement in object and face recognition, this tract is a strong candidate for relaying visual inputs about people and objects to the anterior temporal lobe. This may go some way to explaining left temporal-pole involvement in retrieving specific common nouns (Gorno-Tempini et al., 2004a; Rogers et al., 2006), with the ILF relaying detailed object information anteriorly, while more general (superordinate) object distinctions are processed in the posterior temporal/occipital region.

As for the thalamus, its mediodorsal, anteromedial, midline, and intralaminar nuclei connect to the orbital and medial prefrontal cortices via two separate loops (Price, 2007). The UF has strikingly similar limbic, orbital, and medial prefrontal connections to these loops, and there are direct reciprocal projections from the mediodorsal thalamus to the amygdala and the temporal pole via the inferior thalamic peduncle (Behrens et al., 2003). A plausible explanation as to why thalamic lesions should bring about proper-name anomias is that damage disrupts mechanisms for engaging cortical and subcortical regions "to bind semantic features/concepts to the corresponding lexical representation" (Crosson, 2013).

2.5. Summary of evidence for distinct proper-name retrieval networks

The lesion and functional-imaging evidence reviewed above suggests that distinct cortical regions at either end of the temporal lobe support proper-name retrieval: At the rostral extreme, the ATL bilaterally support the retrieval of information about highly specific entities, with the polar regions supporting the retrieval of information about unique entities. At the caudal end, the posterior temporo-occipito-parietal junction supports the retrieval of information about both superordinate (non-specific) and unique entities. The language-dominant left hemisphere is implicated in the retrieval of lexical items for both unique and non-unique entities, with the left temporal pole supporting the retrieval of proper names, the ATL, caudal to the polar region, supporting the retrieval of highly-specific common nouns, and the posterior temporo-occipito-parietal junction supporting the retrieval of both common nouns and proper names.

The distinct posterior and anterior temporal regions supporting proper-name retrieval are integrated by partially overlapping white-matter connections. The temporal pole is connected to the OMPFC by the uncinate fasciculus (UF). Damage to the left UF in either temporal or prefrontal lobes affects proper-name retrieval over and above any other discernible and lasting language deficits. The temporo-occipito-parietal junction is connected by the inferior fronto-occipital fasciculus (IFOF) to many of the same inferior PFC regions as the UF. The inferior longitudinal fasciculus (ILF) connects posterior temporal and occipital regions to the ATL, terminating caudally to the most anterior temporal-pole connections of the UF. Distinct studies have implicated both the ILF and IFOF in the recognition of both unique and non-unique entities, as well as in naming deficits.

These studies provide strong evidence that the neural substrates of proper-name retrieval partially overlap with those for the retrieval of common nouns, particularly in posterior regions of the temporal lobe connected by the IFOF and ILF. By contrast, when it comes to lexical retrieval, anterior connections by means of the UF-connected temporal pole appear to be exclusively involved in the retrieval of proper names.

These white-matter connections to regions implicated in distinct patterns of proper-name and common-noun retrieval deficits provide evidence for partially overlapping networks subserving partially overlapping processes. Any account of these processes should attempt to explain how and why such divergent patterns should come about, including an explanation of the encoding processes that give rise to the distinct cortical instantiations described above. In Section 3 we review evidence that distinct encoding processes in the MTL can give rise to divergent cortical instantiations of long-term memory that support later retrieval.

3. Cortico-subcortical connections in dual memory encoding processes: A model for the emergence of divergent proper-name retrieval networks

In their studies of the early stages of SD, both Hodges and Graham (1998) and Papagno and Capitani (1998) note that patients with atrophy limited to left ATL scored similarly to controls in providing information about contemporary famous people but worse when it

came to famous people from the past. The former study proposed that preserved structural integrity of, and connections to, the hippocampus in SD allow for the formation of new memories enabling proper name retrieval, despite the erosion of long-term memories. In a follow-up of their study, Papagno and Capitani (2001) found that extensive bilateral atrophy encompassing the parahippocampal gyrus correlated with extended naming deficits including contemporary famous people. As described above, the medial projection of the UF connects to the entorhinal and perirhinal cortices, which, in tracing experiments, have been shown to relay the principal afferent and efferent connections to and from the hippocampus, including major projections from the UF-connected temporal pole and orbitofrontal cortex (Amaral and Lavenex, 2007; Van Hoesen et al., 1975; Suzuki and Amaral, 1994; van Hoesen and Pandya, 1975).

The hippocampal formation has long been known to play an essential role in the encoding of new memories. The UF–anterior parahippocampal connections detailed above, and the association of MTL atrophy with the loss of recently encoded proper names, suggest that these structures may be crucial to the encoding of proper names. Elucidating MTL interactions during encoding with regions that later enable retrieval should give a fuller picture of how the brain processes proper names. Below, we review literature on MTL regions that support face–name encoding. Following this, we detail dual-process accounts of memory encoding, how these point to distinct unitized versus non-unitized memory systems, and how socio-emotional versus neutral encoding processes can help to explain how divergent networks come to subserve subsequent proper-name retrieval.

3.1. Functional interactions of the MTL and UF-connected regions in face–name encoding and retrieval

Temporal-pole and prefrontal activations, as well as diffusion tensor imaging studies, suggest a dual role for the UF in both proper-name encoding and retrieval. Alm et al. (2016) found that left and right fractional anisotropy and leftward diffusivity measures in the UF (but not in the ILF) significantly predicted subjects' accuracy and learning rate in a face–name association task. In another task, UF microstructural measures were shown *not* to predict subjects' ability to memorize faces that were not associated with a name or any other item. A similar study (Thomas et al., 2015) also showed that UF microstructure correlates with the ability to learn face–place associations. The authors of this study viewed the correlation as evidence of the UF's involvement in rapid associative encoding and recall.

Sperling et al. (2003) and Chua et al. (2007) observed increased activity in the bilateral anterior hippocampal formation and left inferior prefrontal cortex during the encoding of face–name associations that were subsequently remembered. The latter study also noted fusiform and entorhinal activations at encoding that correlated with subsequent associative memory, with activity in the perirhinal and fusiform cortices predicting subsequent memory for faces. A separate study has shown subsequent memory for face–name associations to be significantly associated with hippocampal activations during encoding, as well as a tendency (although non-significant) for perirhinal activations to occur more often for successful than non-successful encoding of these associations (Westerberg et al., 2012).

Kirwan and Stark (2004) found that activations during successful encoding of face–name associations occurred in the left amygdala, right hippocampus, and right parahippocampal cortex, while activations in the right perirhinal cortex and parahippocampal cortex predicted subsequent memory regardless of whether single items or associations were remembered. The retrieval of face–name associations correlated with activations in the right entorhinal cortex, right hippocampal region, right parahippocampal cortex, and a subsumed region in the left perirhinal cortex–temporal pole.

Zeineh et al. (2003) found that face–name associative encoding occurred primarily in the dentate gyrus (DG), CA2, and CA3 of the hippocampus, target regions of the entorhinal cortex's perforant pathway. Meanwhile, the retrieval of names upon presentation of a face activated the posterior subiculum and a small area of the anterior parahippocampal gyrus, fitting with the fact that the main efferent hippocampal pathway runs between these two regions. As the task was repeated, and face–name associations became better learned, activations in the hippocampus decreased, while increasing most significantly in the left anterior prefrontal cortex, left posterior superior temporal gyrus, right lateral posterior fusiform gyrus, and left ventral occipital cortex. The strong increase in cortical activity occurred presumably as information became encoded in (and thus retrievable from) cortical areas.

These anterior-versus-posterior cortical activations at retrieval following successful face–name encoding mark a similar pattern to those of retrieval and lesion studies explored in Section 2. Moreover, there is a consistent pattern of dual anterior and posterior MTL activations during face–name encoding. Studies of different mnemonic processes in the MTL can help to sketch out how this pattern emerges and whether it can motivate broad anterior-versus-posterior divergence in proper-name retrieval networks. A similar division has been proposed for a broad range of behaviors in the prominent model of Ranganath and Ritchey (2012), where the UF-connected memory system supports person-specific memory, object perception, assessment of an entity's significance or value, and subsequent familiarity judgements. Meanwhile a posterior system including cingulate and retrosplenial areas, but also thalamic, hippocampal, and temporo-occipito-parietal regions, supports the perceptual processing of scenes, language-based representations of interactions between entities, actions, and outcomes, reasoning about others' mental states (theory of mind), and episodic/recollection-based memory (Ranganath and Ritchey, 2012).

3.2. Divergent mnemonic processes in the emergence of dual proper-name retrieval networks

Lesion and functional imaging studies provide extensive evidence that distinct structures along the longitudinal axis of the MTL support dual memory encoding processes, giving rise to divergent networks at retrieval (Yonelinas et al., 2002, 2004; Bowles et al., 2007; Eichenbaum et al., 2007; Henson et al., 1999; Yonelinas et al., 2005, Vilberg and Rugg, 2008; Ranganath and Ritchey, 2012).

The predominant paradigm used to elucidate the neural basis of divergent memory systems compares the behavioral correlates of *familiarity* (reporting knowledge that an event or item had been presented earlier, without being able to recall any details about it) with those of *recollection* (recalling details about an earlier event or learning task). When scanning is carried out during encoding, multiple studies have found that the anterior parahippocampal gyrus (perirhinal and entorhinal cortices) supports the encoding of memories for single items and item–item associations that are subsequently recognized as familiar (see Eichenbaum et al., 2007 for review; also Haskins et al., 2008). Meanwhile the hippocampus predominantly supports the encoding of single and associated items, allowing for subsequent recollection (Eichenbaum et al., 2007; Staresina and Davachi, 2006), and the (posterior) parahippocampal cortex is often activated at encoding when contexts in which items presented are subsequently remembered (Diana et al., 2007; Staresina et al., 2011).

When scanning happens at retrieval, MTL activations correlating with familiarity and recollection parallel with those often identified at earlier encoding (anterior parahippocampal regions supporting familiarity, the hippocampus supporting recollection, and the parahippocampal cortex supporting both item and context memory: Diana et al., 2007; Eichenbaum et al., 2007). This broad anterior-versus-posterior divergence extends to cortical retrieval networks: Each of Henson et al. (1999), Yonelinas et al. (2005), Vilberg and Rugg (2008), and Ranganath and Ritchey (2012) identify predominant — although not absolute — anterior-versus-posterior divergence in retrieval

networks that largely overlap with the anterior-versus-posterior networks identified in Subsection 2.2 for proper-name retrieval. Moreover, thalamic regions, which when damaged have been associated with proper-name anomias (see also Subsection 2.2), have been shown to engage the distinct MTL structures identified here for the encoding and retrieval of memories supporting both familiarity judgements and recollection (Aggleton and Brown, 1999; Ketz et al., 2015).

That a dual anterior-versus-posterior pattern of MTL activations at encoding should parallel with anterior-versus posterior activations at retrieval is consistent with the view that distinct mnemonic processes can drive the divergence of networks for proper-name retrieval. However, in order to use a name, one always has to *recall* the name being used, so familiarity, as defined in many of the studies reviewed above, would be insufficient. This entails that proper-name retrieval, whether dependent on anterior or posterior networks, must depend on encoding processes that allow for recollection.

Although recollection and familiarity are defined in terms of dichotomous behavioral phenomena at retrieval, the underlying neural mechanisms need not be purely dichotomous. In keeping with this — and despite broad anterior-versus-posterior divergence in memory systems — inferior PFC regions prominently implicated in familiarity judgements have also been associated with recollection, while in the parietal lobe, the angular gyrus has been implicated in familiarity-based retrieval (Ranganath, 2010; Henson et al., 1999; Yonelinas et al., 2005). At encoding, each of the perirhinal cortex, hippocampus, and parahippocampal cortex, or distinct combinations of these regions, have been shown to support the formation of associations that can support subsequent recall (Staresina and Davachi, 2006; Staresina et al., 2011; Ranganath, 2010; Wixted and Squire, 2011). Crucially, however, there is evidence that these associations are distinct in nature, leading to divergence in networks, both of which can support recollection, but with a greater tendency for anterior regions to support familiarity.

Here we review evidence that anterior MTL regions (most prominently the perirhinal cortex, but also the hippocampus) support the encoding of unitized memory (Staresina and Davachi, 2010; Borders et al., 2017). Unitization is prominently associated with subsequent familiarity judgements, but can also support subsequent recall (Graf and Schacter, 1989; Haskins et al., 2008; Ranganath, 2010; Diana et al., 2011; Parks and Yonelinas, 2015). Meanwhile, the parahippocampal cortex and the hippocampus support non-unitized item–context and item–item associative encoding, commonly associated with subsequent recall (Diana et al., 2010; Staresina et al., 2011; Ranganath and Ritchey, 2012; Aminoff et al., 2013).

Unitization is an associative process in which two or more separate items, or features of an item, are combined to form a single mnemonic unit. This is enabled by perceived structural continuity or coherence between items and features, or by conceiving separate items as connected due to their being presented concurrently (Graf and Schacter, 1989). Examples include instances where separate words (e.g. *steam* and *boat*) are combined to form a compound word with a new singular meaning (*steamboat*), when separable features and items (e.g. color and item) are encoded together (Haskins et al., 2008; Staresina and Davachi, 2006, 2010), and when item and source context (e.g. task performance demands) are unitized (Diana et al., 2008). Unitized memories can support both recollection and familiarity judgements, although effects are often found to be greater for familiarity, and the extent to which items are unitized have been shown to increase familiarity-based retrieval but not recollection (Parks and Yonelinas, 2015). Effects of unitization on both recollection and familiarity are greater when associations are made across domains for a range of different stimuli (e.g. face–hobby associations: Parks and Yonelinas, 2015).

The perirhinal cortex has been shown to be particularly implicated in the encoding of unitized memories. Apart from being activated for the encoding of item–feature associations (e.g. color–item unitization) and of stimuli from a single processing domain (word–word compounds), the perirhinal cortex has also been implicated in cross-domain (word–picture) and inter-item visual (picture–picture) encoding of associations that were later recognized as familiar, and which have been suggested to result from unitization processes (Haskins et al., 2008; Park and Rugg, 2011; Staresina and Davachi, 2006, 2010). Based on lesion studies, it has been suggested that inter-item unitized encoding is more prominently supported by the hippocampus and item–feature unitization by the perirhinal cortex, although there is evidence for the involvement of each of these regions in either unitization process (Borders et al., 2017). Visual integration of object fragments to form a unitized item has been shown to occur in the ventral visual stream prior to perirhinal encoding (Staresina and Davachi, 2010). These ventral activations occur in multiple regions connected by the medial branch of the ILF (Latini et al., 2017; Staresina and Davachi, 2010).

Despite the fact that stimuli used to detect unitized encoding can vary broadly across studies, the associative processes identified provide plausible means by which one may attach a name to a unique entity. For example, face–name and picture–word encoding tasks are comparable in that they both involve cross-domain (visual–lexical) associations. Ostensibly, both types of tasks also test memory for item–item associations, as is clear in instances where scenes are presented alongside unrelated words at encoding (Park and Rugg, 2011). Yet proper names, by nature of being fixed identifiers of unique entities, differ considerably from incidental picture–word associations often used in task situations: Because the link (once established) between a unique entity and its name is essentially invariable, the name may also feasibly be encoded as a unitized item–feature association. This seems especially likely when the concurrent association of a unique entity with its name is repeated, underscoring the invariable nature of the association and aiding subsequent unitized recall. A related idea — that names are "attached to the objects themselves" (i.e. that they bear an inextricable and direct link to the unique entities they pick out) — was famously spelled out by John Stuart Mill (1858), spurring much subsequent debate in the philosophy of language.

In the case of unique individuals, face–name item–feature unitization may be comparable to making face–voice associations, especially in cases where individuals introduce themselves by uttering their own name, a common occurrence in initial face–name association. In such instances, both voices and names share the property of being concurrently presented and coherent with the individuals they uniquely identify, as is typical of associations encoded in a unitized manner (Graf and Schacter, 1989). The UF has been proposed to support the integration of both voices and names with information for unique individuals, while the left temporal pole subserves the retrieval of names from voice stimuli (Von Der Heide et al., 2013; Waldron et al., 2014). Hippocampal and perirhinal activations during the encoding of face–-name associations (e.g. Kirwan and Stark, 2004; Chua et al., 2007; Westerberg et al., 2012) may result, respectively, from distinct item–-item (word–image) and intra-item (item–feature) unitization mechanisms.

The converse pattern of hippocampal and posterior MTL (parahippocampal cortex) activations during face–name encoding (e.g. Kirwan and Stark, 2004) may be explained in terms of evidence that these regions support non-unitized item–context and item–item encoding (Diana et al., 2007; Eichenbaum et al., 2007). The associative nature of these encoding processes is perhaps less controversial than that of unitization, in that they often support explicit recollection of associated stimuli at retrieval (Diana et al., 2010; Ranganath, 2010; Ranganath and Ritchey, 2012). As discussed further above, hippocampal activations at encoding often predict subsequent item–item recollection, including face–name pairs, while the hippocampus and parahippocampal cortex have been implicated in subsequent contextual item-and-source memory.

There is strong evidence that item-and-source memory supported by interactions between the hippocampus and parahippocampal cortex is

processed in a non-unitized manner (Diana et al., 2010). In support of this, subsequent associative memory for face stimuli presented at a delay following earlier presentation of place and person names correlated with activations of a left posterior parahippocampal region. On the other hand, subsequent associative memory for names presented concurrently with faces correlated with activations in the hippocampus bilaterally, including an anterior region that also encompassed the amygdala (Qin et al., 2007).

The posterior encoding of non-unitized item–context and item–item information may help to explain why posterior cortical regions often implicated the retrieval of proper names also support common-noun retrieval. The relationship between proper names, common nouns, and contextual associations is apparent if we consider that contextual or episodic details about a person or entity must be relayed with common nouns, as in 'Venus is the star that rises in the east in the morning'.

Conversely, the unitization of associations in memory should make them less amenable to description using common nouns, as in 'Venus is the Morning Star'. Indeed, as this example illustrates, common nouns that themselves may have descriptive meaning, can be combined to form a proper name, where the descriptive value is diluted or may be lost completely. One may think of the many (old) places called *Newtown* in the English-speaking world or the famous Barcelona stadium *el Camp Nou* (literally 'the new field'). Compound proper names bear striking similarities to the novel (and often highly specific and evocative) common-noun compounds considered to be indicative of unitization processes (Haskins et al., 2008; Parks and Yonelinas, 2015). The fact that the UF-connected perirhinal cortex supports the encoding of such associations is suggestive that unitized memory may support the retrieval of proper names via the anterior temporal–prefrontal network.

We consider that available evidence supports a dual-process account whereby unitized (item–item or item–feature) versus non-unitized (item–item and item–context) encoding can support the association of proper names with individuating information relevant to unique entities. This still leaves open questions as to what individuating attributes might bias encoding towards unitized or non-unitized processes, and how these may give rise to divergent networks supporting retrieval. Here below we briefly explore evidence that the encoding of social and emotional information plays a prominent role in the unitization of information about unique individuals, enabled by UF connections from the OMPFC to the MTL. Importantly, the contribution of emotional information to the unitization process tends to support recollection supported by UF-connected regions rather than familiarity, thus enabling name retrieval. Conversely, the associations between less emotionally arousing stimuli tend to be encoded in a non-unitized manner alongside contextual information. As we have proposed above, this contextual encoding process supports the retrieval of proper names from posterior networks.

3.3. The encoding of socio-emotional information supporting the subsequent retrieval of proper names

Activations of the amygdala during face–name encoding have been implicated in subsequent memory effects at retrieval (Sperling et al., 2003; Kirwan and Stark, 2004). There is extensive literature on amygdalar involvement in the processing of facial emotion (prominently, but not exclusively, negative emotions), attractiveness (including attractive and unattractive faces over neutral faces), and in making social judgements, such as evaluations of trustworthiness based on facial attributes (see e.g. Adolphs et al., 1998; Morris et al., 1996; Adolphs et al., 1994; Tsukiura, 2012).

Dolcos et al. (2004) showed that amygdalar activations increase during the encoding of emotional but not neutral images, aiding later retrieval. These activations correlated with those of other anterior MTL structures, most significantly the entorhinal cortex and the anterior hippocampus. Posterior portions of the hippocampus and parahippocampal gyrus were most significantly activated for neutral stimuli (see also Luck et al., 2014 for anterior–posterior MTL divergence in emotional-versus-neutral associative encoding). Within the amygdala, activation for emotional encoding has been shown to occur primarily in its basolateral aspect, which connects to fronto-temporal regions, likely via the UF (Dolcos et al., 2004; Von Der Heide et al., 2013).

In Kensinger and Schacter's (2006) item–source encoding study, amygdalar activations were associated with subsequent memory for both positive and negative emotional word and picture stimuli, but not for neutral stimuli. The entorhinal cortex was activated for items subsequently remembered, regardless of emotional content, while posterior parahippocampal and hippocampal activations correlated with subsequent memory for items and task contexts in which they were presented.

In the prefrontal lobe, the UF-connected OMPFC has been implicated in automatic processing for facial attractiveness, interpreting the friendliness of facial expressions (O'Doherty et al., 2003), and other processes of affective evaluation during impression formation (Mitchell et al., 2005). Functional connectivity between the OFC and hippocampus, as well as increased activations in these regions at encoding, have been shown to predict increased subsequent memory for attractive over neutral or unattractive faces (Tsukiura and Cabeza, 2011). In their review of functional imaging literature, Amodio and Frith (2006) concluded that the anterior medial prefrontal cortex processes perceptual information relevant to people, including observations of social interactions and judgements about the appropriateness of behavior.

Overall, an extensive literature points to bilateral interactions between the OMPFC, amygdala, anterior medial temporal cortex, and ultimately, the ATL in the encoding of social and emotional information. These same regions are also prominently activated at retrieval (for review see Dolcos et al., 2017). The ATL has been shown to be selectively responsive to the learning of information about people over information about tools and buildings, suggesting domain specificity for processing social information (Simmons et al., 2010). In the same study, "resting state" functional connectivity of the ATL pointed to prominent connections with the medial prefrontal cortex, amygdala, and the social cognition network more broadly (including posterior midline regions), as well as regions implicated in domain general processing, such as the hippocampus, perirhinal cortex, and inferior prefrontal cortex (Simmons et al., 2010; see also Simmons and Martin, 2012).

Olson et al. (2007) propose that the right temporal pole is a hub for highly-processed sensory inputs combined with social and emotional responses to those inputs. One possibility is that the right temporal pole acts as a "storehouse" (ibid.) of conceptual information related to people, with storage in the left temporal pole being primarily lexical rather than conceptual (thus supporting the retrieval of proper names). Alternatively, similar person-related conceptual information may be stored in both hemispheres, with only leftward lesions affecting language processes leading to deficits in lexical retrieval (see Gainotti, 2017).

UF dysfunction is associated with deficits and disorders that underscore its crucial role in social and emotional cognition. These include associations with neuropsychiatric disorders (psychopathy, antisocial personality disorder, and deficit schizophrenia), abnormal personality traits related to these disorders (emotional detachment, diminished emotional range, restricted affect, diminished social drive, and antisocial behaviors), and socio-emotional impairments emergent in neurodegenerative diseases, paralleling with those of neuropsychiatric disorders (monotone voicing, loss of facial expressions, loss of empathy, diminished affect, withdrawal) (Craig et al., 2009; Motzkin et al., 2011; Anderson et al., 1999; Harlow, 1993; Motzkin et al., 2011; Thiebaut de Schotten et al., 2015; Kitis et al., 2012; Von Der Heide et al., 2013).

Activations in the OMPFC and hippocampus at encoding, as well as functional connectivity between these regions, have been shown to correlate with increased subsequent memory for names that had been associated with smiling faces over those associated with a neutral

expression. Furthermore, activity and functional connectivity between these regions and the anterior parahippocampal gyrus was associated with improved retrieval performance (Tsukiura and Cabeza, 2008). Within healthy populations, variability in the connectivity of UF from the orbitofrontal cortex (OFC) to the ATL has been shown to predict proficiency in learning face–name associations (Metoki et al., 2017).

Finally, and importantly for the dual-process account presented here, there is strong evidence that the encoding of emotional information influences whether associated stimuli become unitized in memory or not (see Chiu et al., 2013 and Murray and Kensinger, 2013 for reviews). The effects of emotion on item and associative memory often vary according to the nature of stimuli presented, the nature of associations between items, the contexts in which they are presented, how emotionally arousing they are, and whether they are positively or negatively valenced (Dolcos et al., 2017). Nonetheless, there is a general tendency for emotionally arousing stimuli and their constituent features (item–feature unitizations) to be better remembered than are non-emotional stimuli, and that this potentiates recollection rather than familiarity. This effect increases over time and often involves interaction between the amygdala and anterior (para)hippocampal regions (Mather, 2007; Murray and Kensinger, 2013; Yonelinas and Ritchey, 2015).

This last point is especially important given that proper-name retrieval requires mnemonic resources to support explicit recollection, while unitization had been shown to predominantly support subsequent familiarity judgements. The encoding of emotional information as part of unitized associations appears to tip the balance in favor of recollection over familiarity. Increased anterior parahippocampal and OMPFC activations for successful recollection of smiling face–name associations (Tsukiura and Cabeza, 2008) suggest that the retrieval advantage conferred by emotional encoding may be due to unitization processes dependent on the UF-connected network. Conversely, emotion often has null or negative effects on the encoding of contextual details (Yonelinas and Ritchey, 2015). When emotional items are presented as part of a scene, the details of these items are often encoded at the expense of peripheral contextual details, while the opposite is true for neutral items, which are often remembered better when contextually associated (Kensinger and Schacter, 2006; Mather, 2007).

We propose that socio-emotional information, readily derived from the facial (and behavioral) expressions and characteristics of unique individuals, is encoded in a unitized manner alongside proper names. These unitized memories support the subsequent retrieval of names from the UF-connected anterior temporal–prefrontal network. We propose that this unitization process is potentiated by the presentation or utterance of a name concurrently with the encoding of visual information for unique entities. Furthermore, we propose that the hippocampus and parahippocampal cortex enable non-unitized item–item and item–context encoding of less emotionally arousing information relevant to unique entities, supporting the subsequent retrieval of proper names from posterior networks.

3.4. Summary of evidence for dual encoding processes supporting subsequent network divergence in the retrieval of proper names

Naming deficits in neurodegenerative diseases point to the importance of the MTL in supporting the retrieval of recently encoded proper names. Motivated by this region's crucial role in the encoding of new memories, here we have reviewed evidence that multiple structures dispersed along the MTL's longitudinal axis are activated during the associative encoding of proper names and the faces of individuals they pick out. Structures prominently implicated in face–name encoding include the amygdala, entorhinal and perirhinal cortices, hippocampus, and parahippocampal cortex.

Evidence points to anterior-versus-posterior divergence in the encoding processes supported by these structures: Activations of the anterior parahippocampal region are prominently implicated in the encoding of items and associations subsequently recognized as familiar, while hippocampal and posterior parahippocampal activations are more often implicated at encoding when item–item associations and contextual details are later recalled. Similarly, at retrieval, hippocampal and posterior parahippocampal regions are also regularly activated during item–context and item–item associative recall, while perirhinal activations are often associated with familiarity judgements. Anterior-versus-posterior divergence at retrieval extends beyond the MTL, including prominent activations at the temporo-occipito-parietal junction for recollection and anterior temporal and orbitofrontal activations for familiarity. These networks suggest a divergence in retrieval networks similar to that reviewed in Section 2 for proper names.

However, given that the anterior network implicated in proper-name retrieval supports recall and not just familiarity, we have sought to detail the neural processes that underlie each of these behavioral phenomena. Strong evidence points to perirhinal activations in the encoding of unitized associative memories that subsequently support familiarity judgements, largely dependent on anterior temporal–prefrontal connections. Crucially, this UF-connected network also supports recollection of unitized memories, especially potentiated when emotional information is encoded as part of unitized associations. This emotionally supported unitization is enabled by interactions between the anterior parahippocampal gyrus, amygdala, OMPFC, and, possibly, the hippocampus. Indeed, emotionally expressive face–name associations are better remembered than those for neutral faces and names, with both encoding and retrieval of these associations showing increased activations in UF-connected regions. Non-unitized item–item associative, contextual, and non-emotional (neutral) encoding, is predominantly supported by the hippocampus and parahippocampal cortex. We propose that these encoding processes subserve the subsequent retrieval of proper names via activations of posterior cortical regions at the temporo-occipito-parietal junction.

3.5. Dual encoding and retrieval processes in the light of selective proper-name anomias

Given that our exploration of encoding and retrieval networks is partly motivated by lesion evidence that the brain processes proper names in a category-specific manner, our model should be able to account for instances where proper-name anomias are almost total, while the retrieval of common nouns is broadly spared. Although the dual-process account provides relatively clear reasoning for instances — typical in the semantic dementia literature — where the loss of proper names patterns with that of common nouns, or where the retrieval of proper names alone tends to be partially disturbed, our model may have more difficulty where proper names are exclusively and extensively lost.

In the most clear-cut case of which we are aware (Semenza and Zettin, 1988), a patient (PC) following left parieto-occipital stroke, could not name any famous people, cities, countries, rivers, or mountains in an associative recall test. PC could freely recall just five relatives' names and five city names (including his home city) in the space of a minute. At times during assessment he was observed to be able to use the name of his native country (Italy) and to consistently recall the names of his wife and son. Under our model, such near total loss of proper names may be expected to result from damage to both fronto-temporal and temporo-occipito-parietal networks. Nonetheless, the ability to retrieve certain proper names of particular socio-emotional importance is consistent with partial sparing of fronto-temporal connections and/or retained anterior MTL integrity, allowing for the retention or relearning of proper names regularly encountered in daily life.

Another case of near global proper-name anomia (LS), described by the same authors, resulted from left fronto-temporal lesion (Semenza and Zettin, 1989). LS's retrieval of geographical names was better relative to PC, consistent with the prediction of our model that the

sparing of the temporo-occipito-parietal region should allow for comparatively better retrieval of proper names of lesser socio-emotional importance. Seemingly inconsistent with our model is the fact that LS was also better at retrieving relative's names than PC. As the authors note, however, these names had to be relearned subsequent to the lesion and during the months before testing, consistent with retained structural integrity and connections of the anterior MTL, allowing for the encoding of recently encountered names.

Perhaps more challenging to our account is the fact that, in the first case study, PC could recall detailed world knowledge in the form of descriptions about the unique entities he could not name. Our model predicts that posterior damage is more likely to correlate with loss of both common nouns and proper names. Nonetheless, as the authors suggest, PC's deficits point to problems in accessing the output lexicon, connecting to phonological or graphemic form (Semenza and Zettin, 1989). While there is no evidence that the output lexicon is categorically organized in a manner comparable to conceptual or semantic information (see Semenza, 2009), PC's deficits suggest that a category-specific lexical access mechanism may have been damaged (Semenza and Zettin, 1989). Relative sparing of the left posterior temporal lobe may explain the retention of PC's conceptual knowledge associated with unique entities, while access to output systems for proper-name use from this posterior region may have been all but completely lost.

3.6. A model for the encoding and retrieval of proper names in the ventral semantic stream

Accounts of left UF function based largely on early functional imaging studies of language processing had proposed this tract to be involved in basic syntactic processing (Friederici, 2011; Friederici et al., 2006; Friederici and Gierhan, 2013), while more recent accounts (e.g. Friederici and Singer, 2015) propose there to be a dual ventral stream for semantics supported by white-matter tracts connecting prefrontal and temporal lobes. This raises questions as to which semantic processes are subserved by the UF, ILF, and IFOF.

The evidence we have reviewed here suggests one possible answer, with the left UF — connecting the OMPFC, amygdala, and the anterior MTL — enabling unitized proper-name encoding and retrieval, and bilaterally supporting social and emotional processing. Meanwhile the ILF and IFOF are likely crucial for relaying visual information from the occipital lobe to the MTL and OMPFC, respectively, before UF connections integrate these with socio-emotional information. ILF and IFOF connections to the posterior temporo-occipito-parietal region are also likely to support the retrieval of both proper names and common nouns. This may include lexical (indeed sentential) associations between proper names and common nouns that provide contextual information (for example definite descriptions, discussed below). We propose that such associations are enabled by earlier item–item, item–context, and neutral (non-emotional) encoding processes in the hippocampus and parahippocampal cortex. This model is summarized in Fig. 1.

4. Conclusion: Implications of the dual-process account for classical theories of naming and reference, and outstanding issues for further inquiry

Here below we briefly explore the possibility that the dual-process account of proper-name encoding and retrieval can inform long-standing debates about the meanings that these lexical items pick out. We consider three of the most influential perspectives on the matter here.

4.1. Classical theories in the light of evidence for dual processes in the encoding and retrieval of proper names

A prominent view of the semantics of proper names, associated with John Stuart Mill, takes it that they directly refer to unique entities in the world. In Mill's own words, proper names "denote the individuals who are called by them … are attached to the objects themselves, and are not dependent upon the continuance of any attribute of the object" (Mill, 1858, pp. 21–22; see also Kripke, 1972). On Mill's account, naming a unique entity should depend on neural structures necessary for the perception of that entity, the association perceptual information with lexical or phonological form, and the committal of this association to memory, allowing for subsequent retrieval. Mill's proposal is most consistent with evidence that proper names are encoded in a unitized manner alongside information derived from unique entities.

However, this account seems inconsistent with evidence that UF–MTL connections encode socio-emotional evaluations and impressions with perceptual information about unique entities. There is evidence that these processes may be crucial for subsequent unitization-based recall of proper names. Socio-emotional encoding processes also suggest contributions to the meaning of a name that are internal to the speaker who uses it. This goes beyond the perceive–encode–associate–retrieve architecture that would better support Mill's theory of direct reference for proper names.

On the other hand, Frege (1948) considered that proper names do not directly refer, but instead pick out a *sense* of an entity which can vary, roughly, according to the context in which it is presented, or perhaps the perspective from which it is perceived (for Frege, the entity's *mode of presentation*). Thus, the change in context makes it possible for Venus to be called the Morning Star when it appears in the east but the Evening Star when appearing in the west. Frege's argument that proper names, rather than being attached directly to the entity being named, instead pick out an external sense that is determined by context or perspective, shares certain aspects of both the unitized and item–-context accounts of proper-name encoding and retrieval. On the one hand, the observation that contextual factors influence the meaning of a name parallels with evidence that item–context encoding can support proper-name retrieval. However, for Frege, the senses that proper names picked out were inherent in their meaning, which is distinct from the non-unitized associations that item–context memory encodes. If senses are considered to be meanings determined by perspective, this may be more compatible with evidence that information extracted from perceptual inputs is encoded in a unitized manner alongside proper names. Again, however, evidence that socio-emotional encoding makes an important contribution to the unitization process would suggest that senses are internal and variable according to the speaker who uses a name, rather than solely determined by external context.

Finally, influential accounts extending from the work of Bertrand Russell consider meanings of proper names to be equated with descriptions, sets of descriptions, or sets of properties of unique entities (Russell, 1911; Searle, 1958). Thus, a description such as 'The independent senator from Vermont', which picks out a unique entity, could (at least partly) be equated with the meaning picked out by the proper name *Bernie Sanders*. Intriguingly, the detached contextual nature of non-unitized encoding, whereby the associations can be described using common nouns, has parallels with Russell's (1911) account that the meanings which proper names pick out can be equated with definite descriptions. This is underscored by evidence that posterior cortical regions support both proper-name and common-noun retrieval.

However, the contributions of socio-emotional encoding and unitization strongly suggest that definite descriptions cannot, on their own, account for the meanings that proper names pick out. When definite descriptions are converted into proper names (*the white house* versus *The White House*), this may be supported by the unitization of socio-emotional information in anterior regions.

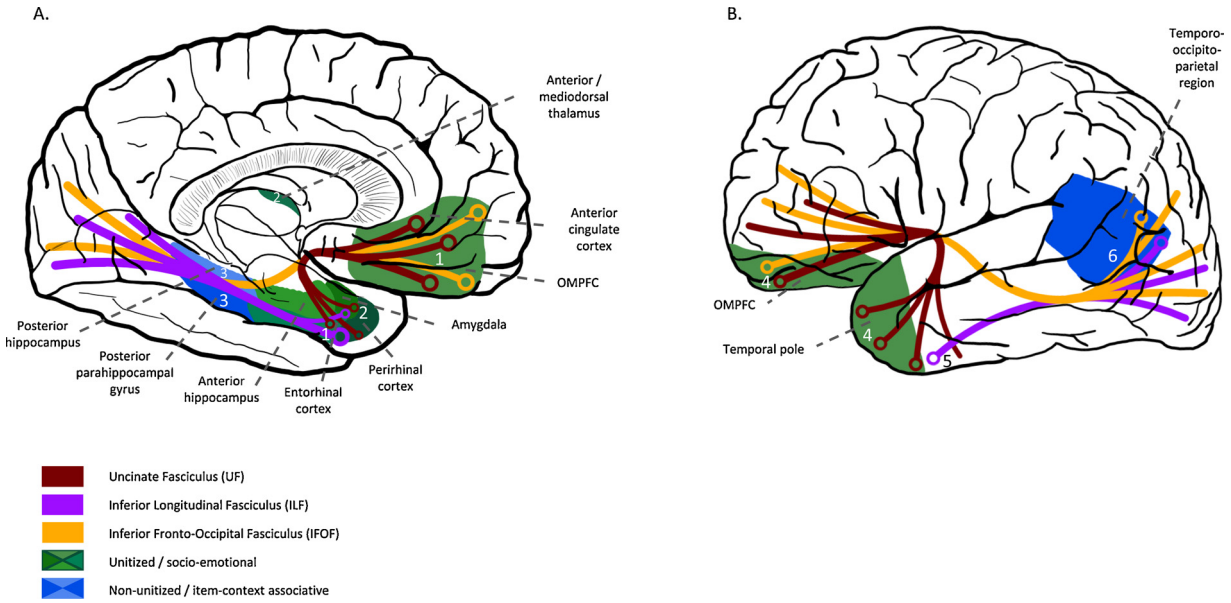

Fig. 1. Illustration of networks related to proper-name encoding and retrieval: A. Proper-name encoding: 1) The IFOF and ILF relay visual information from the occipital lobe to the orbital and medial prefrontal cortices (OMPFC) and anterior medial temporal lobe (MTL), respectively, where processing of social and emotional information relevant to unique entities occurs. 2) The medial UF, connecting both amygdala and OMPFC, integrates socially and emotionally processed information relevant to individuals, encoding this in a unitized manner via perirhinal and, possibly, entorhinal connections in the MTL. Specific object information, relayed by the ILF, may become processed in terms of its social and emotional relevance via the amygdala and OMPFC connections of the UF. The hippocampus is connected to these structures via the perforant path, and subserves both item–item unitization and non-unitized associative encoding. Anterior and mediodorsal thalamic nuclei engage these MTL regions to bind individuating and lexical information. 3) Non-unitized item–item and item–context associations are encoded via interactions of the hippocampus and parahippocampal cortex.
B. Proper-name retrieval: 4) UF connections between the OMPFC and temporal pole enable retrieval of proper names via unitized visual, auditory and socio-emotional information, encoded earlier through anterior MTL structures. 5) Lateral anterior temporal connections of the ILF terminate posteriorly to those of the UF, subserving the retrieval of information relevant to specific common nouns and definite noun phrases. Integration of this information with socio-emotional information in the anterior MTL may enable the retrieval of definite noun phrases as proper names from anterior polar areas. 6) Information encoded in the posterior temporal region, bordering parietal and occipital lobes, supports both common-noun and proper-name retrieval, enabled by previously encoded non-unitized item–item and item–context associative memories.

4.2. Concluding remarks: Future directions for research into proper-name encoding and retrieval

Our proposal that distinct unitized versus non-unitized encoding processes drive the divergence of proper-name retrieval networks makes various predictions that can be experimentally tested. These include predictions of divergence in the associative encoding of proper names versus common nouns, and that both featural emotion and the (non-)concurrent presentation of stimuli should have differential effects on how proper names are associatively encoded. We briefly overview potential ways to test these predictions here below.

The potentiation of subsequent associative memory by emotion — shown to improve retrieval of smiling face–name associations, dependent on UF-connected regions (Tsukiura and Cabeza, 2008) — should be expected to diminish when names are presented non-concurrently with emotional faces. Where non-concurrent emotional face–name encoding is successful, this may be expected to activate the parahippocampal cortex, suggesting non-unitized encoding or non-attendance of emotional information. Qin et al. (2007) found such activations for non-concurrent neutral face–person name and neutral face–place name associations.

Our proposal that emotional face–proper name associations are particularly receptive to unitized encoding, aiding subsequent recall, also entails that associations a.) between emotional faces and common nouns, and b.) between proper names and individuating descriptions, should be less receptive, instead tending towards non-unitized encoding. While it is to be expected that associative memory for common nouns should be better than for proper names (McWeeny et al., 1987; Cohen, 1990), one could measure the effect of emotional facial expression, trustworthiness, or attractiveness on subsequent memory for concurrently and non-concurrently presented faces, names, occupations, or other common-noun descriptors such as possessions. Under our account, the potentiating effect of emotional arousal on subsequent memory would be expected to improve recall of concurrently presented faces and proper names to a greater extent than faces and common nouns, an effect that may increase over time (see Yonelinas and Ritchey, 2015).

The association of names with descriptions of people may be expected to differentially activate hippocampal and posterior hippocampal structures. Under a paradigm where emotional faces, names, and descriptions are presented both concurrently and non-concurrently with each other, our model predicts that encoding and retrieval of emotional face–name associations should depend on structures in the UF-connected network to a greater extent than other types of association. Subsequent memory is expected to be worst for proper nouns associated with non-concurrently presented faces. Where proper names can be successfully retrieved in such instances, this would be expected to depend to a greater extent on successful associations with common-noun descriptors, and less on emotionally arousing facial features. Retrieval in such instances should also be expected to differentially depend on the parahippocampal cortex and, as memories become better encoded, on temporo-occipito-parietal regions.

A related prediction of our model is that subsequent memory for concurrent face–name–voice associations should potentiate subsequent name retrieval due to the unitized nature of the stimuli, where a name, like a voice, may be encoded as a feature of an individual. The unitizing effect of using individuating voices is expected to increase where unique individuals are shown to utter their own names. Encoding and retrieval in these instances is expected to depend on the UF-connected network. Under our account, this effect should be greater for proper

names than for face–voice–description associations, which we expect to comparatively resist unitization. A separate contrast for face–name–description associations could be made where a third-party voice 'introduces' the individual. We consider that use of auditory stimuli in these contrasts would increase the ecological validity for how face–name associations are typically made. If names indeed tend to be differentially encoded as features of individuals, emotional arousal should be expected to potentiate subsequent memory for proper names over descriptions, especially in cases where individuals introduce themselves.

Much of the evidence to support our model, including the manipulations suggested here to test it, are derived from face–name association paradigms. Faces transmit social and emotional signals perhaps more regularly and clearly than any other stimuli, and provide a relatively easy means to control for the influence of these signals on associative encoding. However, a potential criticism stemming from this same evidence is that our model may not extend beyond people's names to those for unique objects, places, or other entities.

Despite these reservations, evidence for similar left temporal-pole activity for both landmarks and people's names (Grabowski et al., 2001), suggests that the influence of socio-emotional and unitized encoding may bear on all proper names. It has been shown that activations in the perirhinal cortex track subjects' cumulative lifetime experience with objects and object concepts (Duke et al., 2017). This may be indicative of increasing unitization processes over time as a result of an object's perceived social relevance and/or the emotion it arouses. It is just such objects that one could expect to be named with a proper name.

An interesting paradigm to test the dual-encoding account for object or place names would be to measure the effect of previous experience with visual stimuli on subsequent memory for definite descriptions, indefinite descriptions, and proper names. Under our account, the effect of increased lifetime experience with an object or location should be expected, relatively speaking, to increase subsequent memory (including the duration of memories) for associated proper names more so than for associated descriptions, with indefinite descriptions showing the smallest effect of previous experience with the object. Conversely, associated descriptions should be better remembered than proper names when attached to recently encountered stimuli. Just as with the Baker/baker paradigm, one could contrast the use of proper names that take the form of capitalized definite descriptions with non-capitalized definitions (e.g. [The] New Harbor versus [the] new harbor).

In terms of the philosophical questions that have interested us here, we do not expect that support or refutation of our model can reconcile age-old debates about how language and the mind interact with unique entities in the world. Nonetheless, we hope that the evidence presented here of how internal neural processes contribute to the meaning of a name may inform these philosophical issues. Similarly, we think that it should be interesting to neuroscientists that findings which have accumulated in distinct research streams over the past three decades point towards a dualism in the brain mechanisms for proper-name encoding and retrieval (unitized versus item–context associative) that parallel in many ways with dual conceptualizations in the philosophy of language (denotational versus descriptive) of how these lexical items pick out unique entities.

Declaration of Competing Interest

None.

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Appendices

Appendix A

Glutamate Receptors implicated in (self-)domestication regulate dopaminergic signaling in striatal vocal-learning pathways

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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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List of publications

The following is a list of papers published over the course of my PhD.

Publications

[1] **O'Rourke, T.** & Boeckx, C. 2020. Glutamate Receptors in Domestication and Modern Human Evolution. *Neuroscience and Biobehavioral Reviews* doi:10.1016/j.neubiorev.2019.10.004.

[2] **O'Rourke, T** & De Diego Balaguer, R. 2020. Names and their meanings: A dual-process account of proper-name encoding and retrieval. *Neuroscience and Biobehavioral Reviews* doi:10.1016/j.neubiorev.2019.11.005

[3] Zanella, M., Vitriolo, A., Andirko, A., Martins, P.T., Sturm, S. **O'Rourke, T.**, Laugsch, M., Malerba, N., Skaros, A., Trattaro, S., Germain, P., Mihailovic M., Merla, G., Rada-Iglesias, A., Boeckx, C., & Testa, G., 2019. Dosage analysis of the 7q11.23 Williams region identifies BAZ1B as a major human gene patterning the modern human face and underlying self-domestication. *Science Advances* doi:10.1126/sciadv.aaw7908

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Proceedings

[5] **O'Rourke, T.**, & Boeckx, C. (2020). Glutamate receptors implicated in (self-) domestication regulate dopaminergic signaling in striatal vocal-learning pathways. *The evolution of language: proceedings of the 13th international conference (Evolang13)* doi:10.17617/2.3190925