6-7-2016

Genes, dopamine pathways, and sociality in primates

Jeffrey French
University of Nebraska at Omaha, jfrench@unomaha.edu

Follow this and additional works at: https://digitalcommons.unomaha.edu/psychfacpub

Part of the Psychology Commons

Please take our feedback survey at: https://unomaha.az1.qualtrics.com/jfe/form/SV_8cchtFmpDyGfBLE

Recommended Citation
French, Jeffrey, "Genes, dopamine pathways, and sociality in primates" (2016). Psychology Faculty Publications. 214.
https://digitalcommons.unomaha.edu/psychfacpub/214

This Article is brought to you for free and open access by the Department of Psychology at DigitalCommons@UNO. It has been accepted for inclusion in Psychology Faculty Publications by an authorized administrator of DigitalCommons@UNO. For more information, please contact unodigitalcommons@unomaha.edu.
Genes, dopamine pathways, and sociality in primates

Jeffrey A. French*1

Unraveling the complex sequence of molecular, biochemical, and neuronal cascades that transpire between gene action and behavioral phenotypes has been an exceptionally tough scientific nut to crack. The difficulties in connecting the links between genes and behavior have been especially problematic for social phenotypes, including species-typical social structures, in which multiple individuals are involved in interactions, and hence the appropriate behavioral responses are conditional on actions of a partner. Forty years ago, Robert Hinde (1) provided a critical insight into the dissection and analysis of social behavior, in which he argued that the social structure of a particular species is an emergent consequence of the nature, quality, and patterning of social relationships across time. These relationships, in turn, are dictated by the quality and content of social interactions among partners that derive from the social dispositions of the participants in the interaction. Although little was known about the neurobiological substrates of social behavior at the time, Hinde was sufficiently prescient to appreciate that individual differences in the propensity to engage in social behavior must be linked to variation in important and pervasive underlying neurobiological substrates. Furthermore, Hinde recognized that some of this variation would ultimately be tracked to genetic origins. Since 1976, much has been learned about the ways in which genes shape neurotransmitter systems, and this work has highlighted the role of genetic variability in both regulatory and coding regions of multiple genes in producing both individual differences (2–4) and species diversity (5–9) in social behavior. In PNAS, Bergey et al. (10) provide support for Hinde’s proposition, through evidence that genomic regions associated with dopamine (DA) signaling have diverged dramatically in two closely related species of baboons with markedly different social systems, despite a recent evolutionary split between the species.

Anubis (Papio anubis) and hamadryas (Papio hamadryas) baboons live sympatrically in eastern Africa, and are found in both distinct populations and in hybridized groups in areas of range overlap in Ethiopia. Despite their relatively recent divergence, estimated at only 0.72 million y ago (11), the two species differ dramatically in social structure: anubis are characterized by multimale:multifemale groups with male dominance hierarchies, whereas male hamadryas recruit from 1 to 10 females of varying ages and reproductive states into “one-male units” that are actively defended from other males. Further distinctions in social phenotypes that contribute to differences in social structure between the species can be found in Fig. 1A. Bergey et al. (10) argue that these species differences could be attributed to species- and age-specific reward structures for impulsive vs. restrained social behavior by males. Previous work on these populations and on other nonhuman primates has implicated variation in the central DA signaling system, as measured by DA metabolite levels in cerebrospinal fluid, as an important correlate of species-typical social structure and behavior (12–15).

In light of these findings, Bergey et al. (10) genotyped thousands of SNPs in samples from over 200 anubis and hamadryas. Using the well-annotated rhesus macaque genome, the authors focused on SNP frequency in functional groups of genes involved in over 160 signaling pathways, including those implicated in behavioral variation, as well as in “control” gene groups (e.g., Wnt signaling and DNA replication pathways). Fixation indices (FST), reflecting the proportion of genetic differences between populations relative to genetic similarity within a population, were calculated for each pathway to estimate population differentiation between the two baboon species. Two multigenic pathways were identified as substantially divergent (i.e., significant FST values) between the two baboon species at three values of the parameter σ: 50, 100, and 150 kb. The first pathway is of little interest from the perspective of social behavior: chemo- and cytokine-mediated inflammatory signaling. However, the second pathway is highly relevant, and includes a cluster of 17 genes involved in the regulation of DA receptor-mediated signaling (table 2 in ref. 10). Not all genes in this DA signaling cluster contributed to the differentiation among species; FST analysis applied to each gene led to the identification of three that serve to differentiate the two species, with FST values > 0.35 (considered a moderate-to-large effect size). Among the genes that emerged as significantly enriched were three

---

*Program in Neuroscience and Department of Psychology, University of Nebraska at Omaha, Omaha, NE 68182

Author contributions: J.A.F. wrote the paper.

The author declares no conflict of interest.

See companion article on page 6178 in issue 22 of volume 113.

*Email: jfrench@unomaha.edu
critical players in DA signaling. SLC6A3 (solute carrier family 6, member 3 or DAT1) codes for the dopamine transport protein, a membrane-bound sodium-activated protein that transports DA from the synaptic cleft into cell bodies for vesicle storage and later release, with the consequence of reducing or terminating dopaminergic synaptic activity. The second gene with enriched differences between species was COMT, which encodes catechol-O-methyltransferase (COMT), an enzyme that metabolizes and deactivates catecholaminergic neurotransmitters, including DA, again exerting a dampening effect on DA neurotransmission. Finally, anubis and hamadryas showed high differentiation for PPP1CC, a gene that codes for protein phosphatase 1y (PP1y) that plays a role in dendritic synaptic morphology in dopaminergic neurons in the striatal regions of the brain, among other functions, thereby influencing the potential connectivity of these neurons. Fig. 1B summarizes the role of these genes in DA neurotransmission.

Although the SNP analysis identified important differentiation in the genes regulating DA signaling between the two species, this tells us little about the potential functional significance of these gene changes. To address this important question, Bergey et al. (10) sequenced genomic coding regions from eight anubis, hamadryas, and hybrid baboons. These sequences were compared with a draft P. anubis reference genome (papAnu2, Baylor College of Medicine) and assessed for either high-impact or loss-of-function variants using PANTHER (16). Of the 164 pathways analyzed, 11 pathways had greater than expected high-impact variants, and 7 had greater than expected loss-of-function variants. In both categories of variants, DA receptor-mediated signaling pathways ranked second highest, suggesting that the differentiation of this cluster of genes between species may have functional significance for DA-mediated behavioral traits. The PANTHER analysis also revealed that many of the 11 high-impact variants derive from genes associated with other neurotransmitter systems (including cannabinoid, glutamate, GABA, and serotonin signaling pathways; see table S1 in ref. 10). This finding suggests that although DA may be an important player in the differentiation of species-specific social traits, the origin of these differences is likely to be polygenic.

Given the central role of DA in both reward (17) and behavioral impulsivity (18), Bergey et al. (10) posit that the differentiation in the genes underlying signaling in this neurotransmitter system may reflect adaptive divergence between the two species of baboons. The authors suggest, for example, that high impulsivity in hamadryas males may lead to greater or earlier success in recruiting females for one-male units, and that male hamadryas may find that interactions with nonreceptive or immature females have greater reward valence than do these same interactions male anubis. However, it is equally plausible that high impulsivity could be adaptive for male anubis; for example, males with high impulsivity might have greater success in working their way up the male-dominance hierarchy. There are a number of testable scenarios, but all require knowledge of the impact of the genetic differentiation between species on overall dopaminergic function.

Given the constraints of work with a wild population of nonhuman primates, Bergey et al. (10) are not in a position to verify the impact of differentiation in the DA signaling system genes on changes in central dopaminergic tone (e.g., ref. 19). Although PANTHER analysis can serve as a guidepost for potentially important and functional genetic polymorphisms, further work on either cell lines or living animals that are engineered to express the identified SNPs is required to confirm both functional changes in DA signaling and the subsequent modification in behavioral phenotypes. A further question is the impact of genetic differentiation between species on female social phenotypes; the present paper by Bergey et al. (10) focuses solely on variation in male social behavior. Because the differentiated DA signaling genes are located on autosomes (SLC6A3, COMT, and PPP1R1B are located on baboon chromosomes 6, 10, and 11, respectively), females also have potentially altered DA function, and hence variation in impulsivity and reward in the social realm, as well. The report (20) that female anubis–hamadryas hybrids show bimodal patterns of social interactions with males (“obedient” and affiliative toward males in some females, avoidant of males in others) suggests that that DA-associated differences in sociality in females may also play a prominent role in shaping differences in social structure. The availability of long-term social, demographic, and genetic data on these populations of baboons places Bergey et al. (10) in an excellent position to address these questions in the future.
These concerns notwithstanding, Bergey et al. (10) provide important results on the ways in which genetic variation may translate into differences in social relationships and ultimately social structure. In this sense, the data in their paper add considerable credence to Hinde's (1) visionary perspective that species-specific social structure can be produced by the nature of social-interaction patterns, which are in turn influenced by genetic differences in neurobiology. Moreover, their results add to the growing knowledge base regarding the molecular origin of normative function in the social brain.

Acknowledgments

J.A.F.’s research is supported in part by funds from the National Institutes of Health (Grant HD042882).