REFERENCES AND NOTES

1. J. Marburger, *Science* **308**, 1087 (2005).
2. A. B. Jaffe, M. Trajtenberg, R. Henderson, *Q. J. Econ.* **108**, 577–598 (1993).
3. S. Kantor, A. Whalley, *Rev. Econ. Stat.* **96**, 171–188 (2014).
4. P. Shu, "The long-term impact of business cycles on innovation: Evidence from the Massachusetts Institute of Technology" (HBS Working Paper, Harvard Business School, Cambridge, MA, 2015).
5. H. Sauermann, M. Roach, *PLOS ONE* **7**, e36307 (2012).
6. A. J. Sumell, P. E. Stephan, J. D. Adams, in *Science and Engineering Careers in the United States: An Analysis of Markets and Employment*, R. B. Freeman, D. L. Goroff, Eds. (Univ. of Chicago, Chicago, 2009), pp. 257–287.
7. B. Cronin, C. Sugimoto, *Scholarly Metrics Under the Microscope* (ASIST Titles, Information Today Inc, Medford, NJ, 2014).
8. J. Lane, *Nature* **464**, 488–489 (2010).
9. D. Sayer, "Five reasons why the REF is not fit for purpose." *Guardian*, 15 December 2014; www.theguardian.com/higher-education-network/2014/dec/15/research-excellence-framework-five-reasons-not-fit-for-purpose
10. J. I. Lane, J. Owen-Smith, R. F. Rosen, B. A. Weinberg, *Res. Policy* **44**, 1659–1671 (2015).
11. B. A. Weinberg *et al.*, *Science* **344**, 41–43 (2014).
12. R. S. Jarmin, J. Miranda, The Longitudinal Business Database (Working Paper no. 02-17, Center for Economic Studies, U.S. Census Bureau, 2002); https://ideas.repec.org/p/cen/wpaper/02-17.html.
13. S. Davis, J. Haltiwanger, R. Jarmin, C. J. Krizan, J. Miranda, A. Nucci, K. Sandusky, in *Producer Dynamics: New Evidence from Micro Data*, T. Dunne, J. B. Jensen, M. J. Roberts, Eds. (Univ. of Chicago Press, Chicago, 2009), pp. 329-368.
14. C. Syverson, *J. Econ. Lit.* **49**, 326–365 (2011).
15. National Science Foundation Committee of Visitors, "Business R&D Innovation Survey" (NSF, Arlington, VA, 2013).
16. G. S. Becker, *Human Capital: A Theoretical and Empirical Analysis, with Special Reference to Education* (Univ. of Chicago Press, Chicago, 2009).
17. R. Decker, J. Haltiwanger, R. Jarmin, J. Miranda, *J. Econ. Perspect.* **28**, 3–24 (2014).
18. J. Haltiwanger, R. S. Jarmin, J. Miranda, *Rev. Econ. Stat.* **95**, 347–361 (2013).
19. P. Stephan, in *Innovation Policy and the Economy*, vol. 7, J. Lerner, S. Stern, Eds. (MIT Press, Cambridge, MA, 2007), pp. 71–98.
20. K. B. Whittington, J. Owen-Smith, W. W. Powell, *Adm. Sci. Q.* **54**, 90–122 (2009).

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SUPPLEMENTARY MATERIALS

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SOCIAL BEHAVIOR

Sexual fidelity trade-offs promote regulatory variation in the prairie vole brain

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Individual variation in social behavior seems ubiquitous, but we know little about how it relates to brain diversity. Among monogamous prairie voles, levels of vasopressin receptor (encoded by the gene *avpr1a*) in brain regions related to spatial memory predict male space use and sexual fidelity in the field. We find that trade-offs between the benefits of male fidelity and infidelity are reflected in patterns of territorial intrusion, offspring paternity, *avpr1a* expression, and the evolutionary fitness of alternative *avpr1a* alleles. DNA variation at the *avpr1a* locus includes polymorphisms that reliably predict the epigenetic status and neural expression of *avpr1a*, and patterns of DNA diversity demonstrate that *avpr1a* regulatory variation has been favored by selection. In prairie voles, trade-offs in the fitness consequences of social behaviors seem to promote neuronal and molecular diversity.

Social behavior emerges from the complex, dynamic, and often strategic interactions of individuals—a complexity that places it among the most challenging and interesting behaviors to study. Neuroscience has elucidated many mechanisms of social behavior (*1*, *2*). In parallel, evolutionary biology has outlined how social interaction can promote variation within a species (*3*–*5*). Frequency- or density-dependent selection, for example, maintains individual differences in the parental care of sunfish (*3*), the territorial defense of lizards (*4*), and the cannibalistic behavior of tadpoles (*5*). Among humans, similar forces have been proposed to explain differences in personality, resilience, and psychiatric risk (*6*–*8*). Given that social diversity is central to behavioral ecology, social psychology, and mental health, it is surprising that we know so little about natural variation in the social brain, how it emerges from the interaction of genetic and epigenetic processes, or how it has been sculpted by evolutionary forces.

We explored individual differences in neuronal gene expression in the monogamous prairie vole, *Microtus ochrogaster*, a small North American rodent whose males and females form pair bonds and share parental care (*9*). Prairie vole pair-bonding is governed by multiple modulators and brain regions (*2*, *10*, *11*). Of these genes, the vasopressin 1a receptor (V1aR, encoded by *avpr1a*) is particularly well studied (*2*, *11*–*15*). V1aR expression can vary profoundly across individual prairie voles (*12*), and its abundance in a spatial-memory circuit predicts sexual fidelity in males (*13*, *14*) but not females (supplementary materials), a finding consistent with male-specific vasopressin effects in other contexts (*15*). We used the relationship between *avpr1a* expression and male fidelity to examine how social forces contribute to brain diversity. Specifically, we asked whether the fitness consequences of male sexual fidelity promote genetic and epigenetic variation in *avpr1a*.

Although prairie voles are socially monogamous, they are not sexually exclusive (*16*). Approximately 25% of young are conceived outside a pair bond (termed extra-pair fertilizations, or EPFs). Male fidelity is often thought to depend on spatial strategies that balance the demands of mate-guarding against the value of mating multiply (*17*, *18*). To examine the relationship between space use and sexual fidelity among male prairie voles, we estimated the intensity of a male's space use by fitting kernel density estimates to animal positions measured over several weeks by radiotelemetry (Fig. 1, A and B, and fig. S1). By overlaying these maps of space-use intensity, we could estimate how often males encounter other individuals either at home or in neighboring territories. We found that the spatial behavior of EPF males differs from that of males who sire young only with a partner (intra-pair fertilizations, IPF). EPF males have larger home ranges ($P < 0.05$; Fig. 1C), and they more frequently encounter extra-pair females ($P < 0.0001$; Fig. 1D), intrude on territories ($P < 0.01$; Fig. 1E), and are intruded upon ($P < 0.01$; Fig. 1F). The rate at which a male intrudes on a neighbor's territory is correlated with the rate at which he encounters extra-pair females [Pearson's correlation coefficient (r) = 0.69, $P < 0.0001$], but also with the rate at which he is intruded upon by other males (r = 0.83, $P < 0.0001$; Fig. 1G). Overall, the data suggest that venturing away from a male's core home range increases encounters with both extra-pair females and their aggressive mates; these intrusions may offer the opportunity for extra-pair paternity, but they also increase the rates at

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which a male's home range is visited by neighboring males. This pattern is consistent with data suggesting that pair-bonded EPF males are more likely to be cuckolded (*14*). Increasing the extra-pair female encounter rate seems to come at the expense of intra-pair mate-guarding.

Among prairie voles, we find that neuropeptide receptors show profound variation in nodes of a spatial memory circuit including the hippocampus, laterodorsal thalamus (LDThal), and retrosplenial cortex (RSC; Fig. 1H). Remarkably, variation in each of these regions predicts aspects of space use and paternity in the field (*13*, *19*). The relationship between spatial memory and sexual fidelity is not clear, but males with low V1aR in RSC or LDThal have been hypothesized to have a poor memory for locations of aggressive interactions, a cognitive strategy that could promote territorial intrusion and extra-pair encounters (*14*). In contrast, a male with abundant V1aR may better monopolize a mate but might encounter fewer extra-pair females. To look for evidence of fitness trade-offs that could promote forebrain diversity, we examined the relationship between

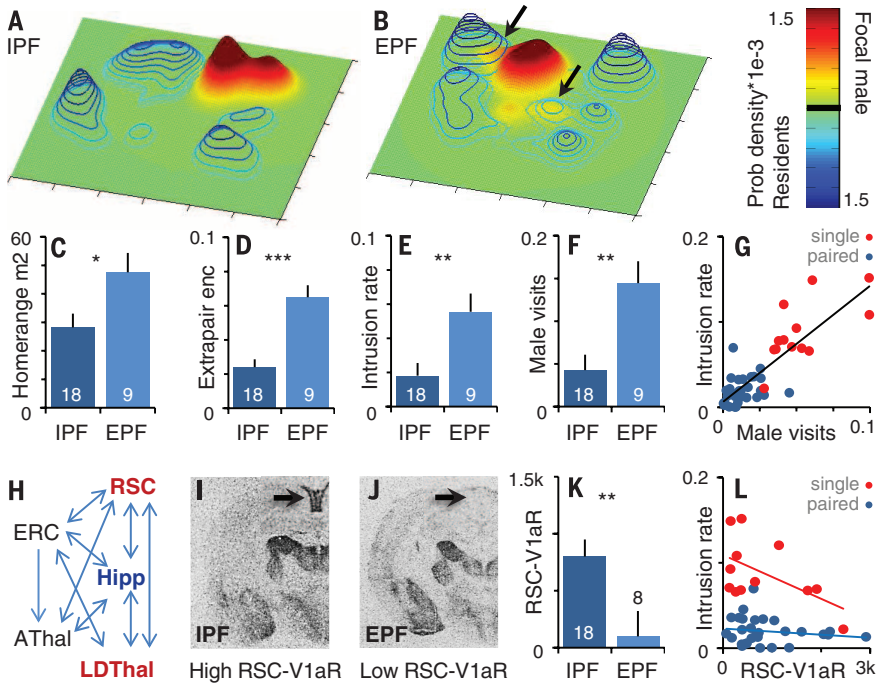

Fig. 1. Male sexual fidelity predicted by patterns of space use, social interaction, and V1aR. (**A** and **B**) Intensity of male space use. The *x* and *y* axes are enclosure dimensions (20 m × 30 m); the height and color of the peaks indicate probability densities. A focal male is indicated as a solid peak; nonfocal males are indicated as blue-contoured peaks. Single males are not shown. Arrows indicate the regions of likely intrusion by the focal male. (**C** to **F**) EPF and IPF males differ in space use. (**G**) Rates of intrusion and of male visitation are correlated. (**H**) Regions of a spatial-memory circuit (*31*) vary in receptors for vasopressin (red) or oxytocin (blue) (*13*, *19*). Abbreviations are as follows: ERC, entorhinal cortex; Hipp, hippocampus; AThal, anterior thalamus. (**I** to **K**) Autoradiograms for V1aR in the RSC. RSC-V1aR abundance (in dissociations per minute per milligram of tissue) predicts sexual fidelity and (**L**) intrusion rate. All bars show mean ± SE. $^{*}P \leq 0.05$, $^{**}P \leq 0.01$, $^{***}P \leq 0.001$.

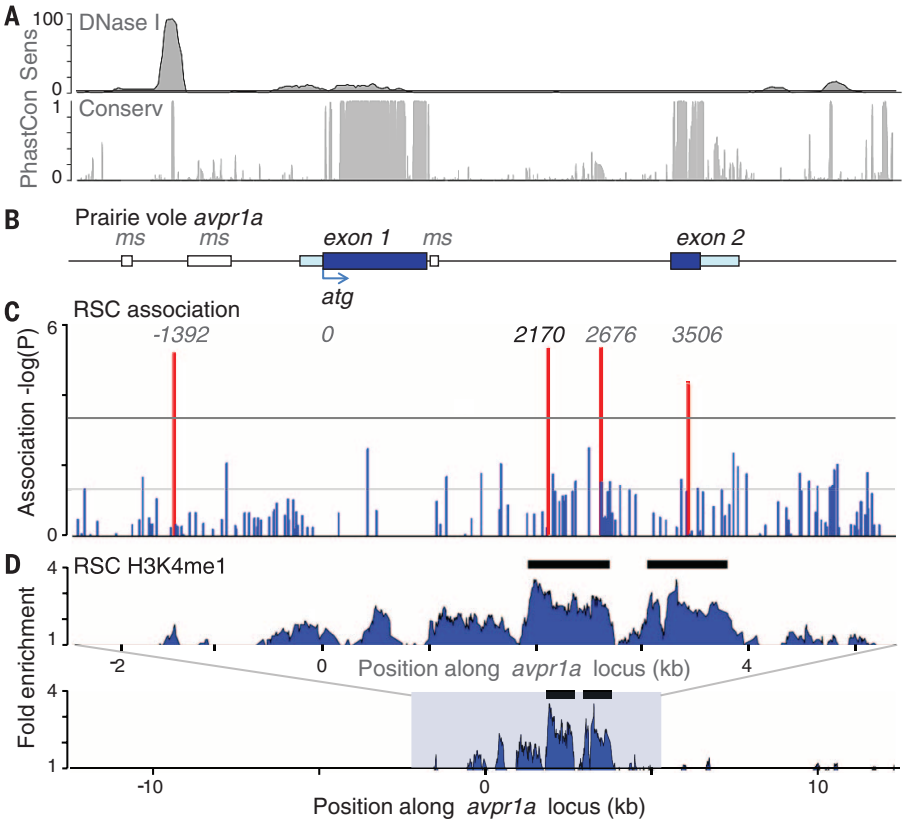

Fig. 2. SNPs in regulatory regions of the *avpr1a* locus predict RSC-V1aR. (**A**) DNAse I hypersensitivity in *Mus* brain and mammalian conservation (*22*). (**B**) Structure of prairie vole *avpr1a* locus (exons, blue; microsatellites, white). (**C**) Association of *avpr1a* SNPs with RSC-V1aR abundance. Each bar is a SNP; the *x* axis depicts position along the *avpr1a* locus; the *y* axis depicts strength of association [$-\log_{10}(P)$]. The lower horizontal gray line shows uncorrected $\alpha = 0.05$; the upper horizontal gray line shows corrected $\alpha = 0.00054$. (**D**) Fold enrichment by H3K4me1 ChIP-seq compared to input chromatin. Horizontal bars mark peaks corresponding to putative enhancers.

RSC-V1aR and our measures of space use. As reported previously, faithful IPF males have more RSC-V1aR than EPF males [$P < 0.001$, Fig. 1, I to K; (*13*)]. Low levels of RSC-V1aR were also associated with high intrusion rates (RSC, $P < 0.01$; pairing status, $P < 0.0001$; RSC × status, $P < 0.05$; Fig. 1L) and poor mate-guarding (male visits received: RSC, $P < 0.05$; pairing status, $P < 0.0001$; RSC × status, $P > 0.10$). V1aR levels in another node in this circuit (the LDThal) also predicted sexual fidelity and space use, whereas brain regions associated with pair-bonding and aggression (the ventral pallidum and lateral septum) did not [supplementary materials (*13*)]. These data suggest that trade-offs between the fitness benefits of intra-pair and extra-pair paternity could contribute to diversity in this memory circuit.

In order for selection to have promoted neuronal diversity, such variation must be heritable. We asked whether single-nucleotide polymorphisms (SNPs) in *avpr1a* predicted individual differences in V1aR abundance. We sequenced ~8 kb of the *avpr1a* locus (Fig. 2 and fig. S2) from lab-reared males with substantial field data [Fig. 1 (*13*)] and from wild-caught adults. Of 151 SNPs, 4 tightly linked polymorphisms predicted RSC-V1aR (Fig. 2, multiple-test corrected $\alpha = 5.4 \times 10^{-4}$). These SNPs were upstream of the coding sequence (SNP –1392, $P = 6.3 \times 10^{-6}$), in the intron (SNPs 2170 and 2676, $P = 4.7 \times 10^{-6}$), and in the second exon (SNP 3506, $P = 5.0 \times 10^{-5}$). We refer to the genotypes defined by these linked SNPs as HI (high)– and LO (low)–RSC alleles. The effects of HI and LO alleles were stronger among lab-reared animals ($P < 0.0001$) than wild-caught animals ($P < 0.05$; genotype × rearing $P = 0.002$; fig. S3), which suggests that population structure or developmental environment may influence cortical V1aR. We also found that a distinct SNP predicted V1aR in the LDThal (SNP 5168, $P = 3.6 \times 10^{-4}$), but none of the 151 SNPs predicted V1aR in the ventral pallidum or lateral septum (fig. S4). Thus, V1aR levels in regions implicated in spatial memory and sexual fidelity were linked to *avpr1a* sequence variation, whereas regions important in pair-bonding and aggression were not.

We examined the stability and specificity of the HI- and LO-RSC associations with a breeding design that controlled for potential confounds of our initial study. We obtained a new genetic stock from a third site >100 miles from prior sites. Heterozygous HI/LO parents were crossed to produce siblings that differed in their genotypes but shared a common genetic background, rearing environment, and lack of sexual experience. We again found that HI and LO alleles influenced V1aR in the RSC ($P < 0.0001$; Fig. 3A), but not in other brain regions (fig. S5). Thus, our data demonstrate a replicable, robust, and specific association between the HI-RSC allele and high RSC-V1aR expression. However, differences between wild-caught and lab-reared animals (fig. S3), as well as previously reported developmental manipulations (*20*), suggest that epigenetic variation may also be at play.

If individual differences in RSC-V1aR abundance are due to differences in the regulation of *avpr1a*, then HI/HI and LO/LO genotypes should differ in *avpr1a* transcript abundance. We dissected the RSC of the lab crosses reported above and used quantitative polymerase chain reaction to quantify *avpr1a* mRNA. Genotypes differed significantly in *avpr1a* transcript abundance (ΔCt versus β-*actin*, $P < 0.001$, Fig. 3B). Moreover, individual

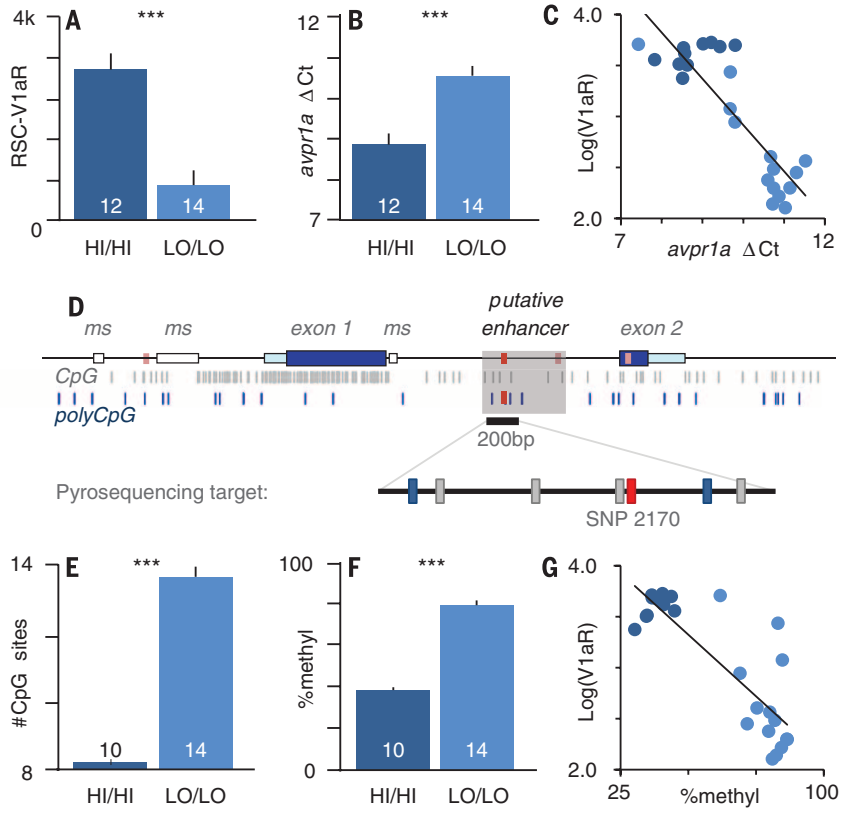

Fig. 3. Genotype differences in regulation of *avpr1a*. (**A**) Homozygotes differ in abundance of V1aR (dissociations per minute per milligram) and (**B**) *avpr1a* mRNA in the RSC. (**C**) RSC *avpr1a* transcript abundance correlates with V1aR protein. (**D**) Fixed (gray) and polymorphic (blue) CpG sites along *avpr1a*. The red bars are SNPs associated with RSC-V1aR. The shaded gray box indicates a putative intron enhancer. A cluster of CpG sites were selected for pyrosequencing, including polymorphic CpG SNP 2170 in red. (**E**) HI/HI males have fewer CpG sites in the intron and (**F**) lower levels of enhancer methylation. (**G**) RSC enhancer methylation correlates with V1aR abundance (R^2 = 0.70, $P < 0.0001$). Bars are means ± SE. ***$P \leq 0.001$.

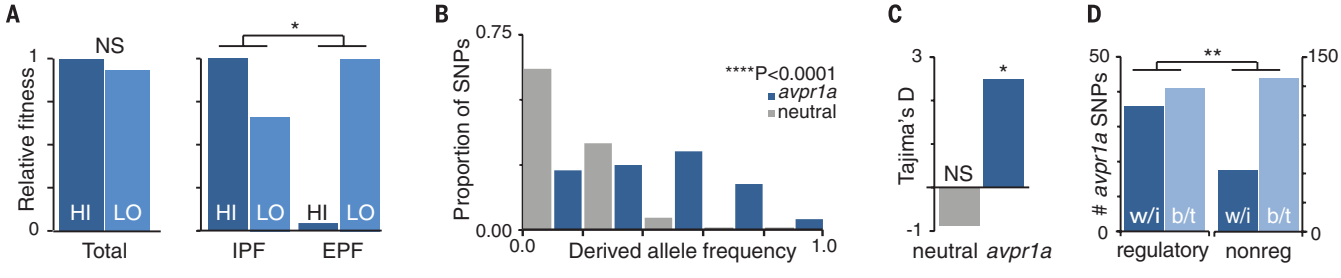

Fig. 4. Selection maintains regulatory variation at *avpr1a*. (**A**) Context-dependent selection on HI-RSC and LO-RSC alleles in the field. (**B**) *avpr1a* has more intermediate frequency alleles than do neutral markers. (**C**) Tajima's D value is significantly positive for *avpr1a* but not for neutral loci. (**D**) Regulatory regions of *avpr1a* had higher ratios of within:between species differences than nonregulatory regions. *$P < 0.05$, **$P < 0.01$, not significant = $P > 0.10$.

differences in *avpr1a* mRNA were strongly associated with RSC-V1aR protein [linear regression coefficient (R^2) = 0.75, $P < 0.0001$, Fig. 3C].

To determine whether any RSC-associated SNPs were within DNA sequences that might contribute to *avpr1a* regulation, we performed chromatin immunoprecipitation sequencing (ChIP-seq) targeting the histone modification H3K4me1, a marker for regulatory sequences known as enhancers (*21*). We dissected RSC samples from eight new lab-reared animals. Within a 25-kb sequence centered on the *avpr1a* translation start site (Fig. 2D), the H3K4me1 mark was specifically associated with two regions within the *avpr1a* locus [$P < 1 \times 10^{-7}$, false discovery rate (Q) < 0.0001; supplementary materials]. One putative enhancer was in the center of the intron, including both intron SNPs of the HI/LO alleles; the second overlapped the second exon and included the fourth linked SNP (Fig. 2C). Three of the polymorphisms that define the HI and LO alleles are within putative enhancer regions, and the fourth is within a conserved deoxyribonuclease I (DNAse I) hypersensitive site [Fig. 2A (*22*)]. Thus, all four RSC-associated SNPs coincide with markers of transcriptional regulation.

We next asked whether differences in RSC *avpr1a* transcript and V1aR protein abundance reflected differences in the epigenetic state of the *avpr1a* locus. We focused on the putative intron enhancer: This sequence had strong evidence of H3K4me1 enrichment and included the two SNPs most strongly linked to RSC-V1aR. SNP 2170 proved to be a G/T polymorphism that altered the presence of a CpG site, a common target of DNA methylation (*23*). Moreover, this CpG/CpT polymorphism is linked to a cluster of CpG polymorphisms within the enhancer (Fig. 3D). HI-RSC alleles have fewer CpG sites than LO alleles ($P < 0.0001$, Fig. 3E), suggesting fewer opportunities for methylation. We isolated DNA from the RSC, treated it with bisulfite, and performed pyrosequencing of this enhancer. HI/HI animals had less enhancer methylation than LO/LO animals ($P < 0.0001$, Fig. 3F). Genotypes also differed in enhancer methylation if we focused solely on nonvariable CpG sites [mean (μ) ± SE, HI/HI 67.6 ± 1.6%, LO/LO 75.6 ± 1.3%; $P = 0.001$]. Moreover, *avpr1a* enhancer methylation is significantly associated with RSC-V1aR abundance ($P < 0.0001$, Fig. 3G). Methylation at noncoding CpG sites is known to recruit methyl-binding proteins, histone de-acetylases, and other silencing proteins (*24*); our data suggest that SNP 2170 and neighboring CpG polymorphisms may alter the function of an intron enhancer by changing the number of CpG sites available for methylation.

Our molecular data indicate that specific alleles are robust predictors of RSC-V1aR, and they suggest mechanisms by which specific SNPs might exert influence on *avpr1a* expression. If genetic differences in RSC-V1aR are adaptive—a "balanced polymorphism" of the brain—we might expect differences in how HI- and LO-RSC alleles gain fitness. Using data from lab-reared animals monitored in the field (Fig. 1), we calculated the number of embryos that each male sired either with a partner (IPFs) or non-partner (EPFs) and estimated the relative fitness of HI and LO alleles in each context. Although the alleles had similar fitness overall, selection favored HI alleles in the context of IPFs and LO alleles in the context of EPFs (Fig. 4A, $P < 0.05$). Thus, fluctuations in the defensibility of females could profoundly influence the strength and direction of selection on HI and LO alleles. Prairie voles exhibit wide fluctuations in population density, ranging from ~25 to 600 voles per hectare in a year (*25*); high densities increase the rate of extra-pair interactions (*26*) and reduce the defensibility of prairie vole females (*27*). Manipulative studies will be needed to test whether fluctuations in population density or allele frequency promote variation in *avpr1a* and related behaviors.

If genetic variation at *avpr1a* produces variation in memory regions, and this in turn influences space use and sexual fidelity, then over time we expect selection to have influenced patterns of *avpr1a* nucleotide variation. We tested for a history of balancing selection by comparing the frequencies of SNPs at *avpr1a* to three putatively neutral nuclear loci among our original wild-caught samples. We found that the *avpr1a* locus was strongly skewed toward an excess of intermediate-frequency alleles, a classic signature of balancing selection (Fig. 4B, likelihood ratio = 120.3, df = 4, $P = 4.7 \times 10^{-25}$). Similarly, *avpr1a* had a positive Tajima's D value ($P < 0.05$) (*28*), whereas our neutral loci had negative values ($P > 0.10$, Fig. 4C). Lastly, a Hudson Kreitman Aguade test (*29*) comparing the number of within- and between-species differences indicated an excess of standing variation within regulatory regions (defined by H3K4me1 ChIP-seq and DNAse hypersensitivity $P < 0.01$, Fig. 4D). We conclude that balancing selection has actively maintained regulatory variation at the *avpr1a* locus. This regulatory variation seems to be specifically associated with brain regions related to memory and space use.

These data provide a remarkably coherent perspective on the origin and maintenance of diversity in the social brain. V1aR levels in memory structures predict whether males will intrude on neighbors and gain extra-pair paternity, or exclude intruders and improve intra-pair paternity. Nucleotide polymorphisms within regulatory sequences robustly and specifically predict V1aR variation in these same brain regions. Within the RSC, we find that low-expressing alleles differ in CpG abundance and methylation status. Because CpG sites can be gained or lost easily [~25% of single nucleotide differences between humans and chimps, for example, consist of the gain or loss of a CpG site (*30*)], we hypothesize that CpG polymorphisms may often shape heritable variation in environmental sensitivity. Genetic markers for this neuronal phenotype exhibit strong evidence of balancing selection. Together these data suggest that trade-offs in the fitness consequences of spatial behaviors promote diversity in the social brain. By focusing on what would seem to be the simplest of social phenotypes—the neural expression patterns of a single gene—we gain insights into the complex interplay of forces that shape both gene function and social evolution.

REFERENCES AND NOTES

1. R. Adolphs, *Nat. Rev. Neurosci.* **4**, 165–178 (2003).
2. L. J. Young, Z. Wang, *Nat. Neurosci.* **7**, 1048–1054 (2004).
3. M. R. Gross, *Philos. Trans. R. Soc. London Ser. B* **332**, 59–66 (1991).
4. B. Sinervo, C. M. Lively, *Nature* **380**, 240–243 (1996).
5. D. W. Pfennig, *Evolution* **46**, 1408–1420 (1992).
6. K. J. H. Verweij *et al*., *Evolution* **66**, 3238–3251 (2012).
7. B. J. Ellis, M. J. Essex, W. T. Boyce, *Dev. Psychopathol.* **17**, 303–328 (2005).
8. M. C. Keller, G. Miller, *Behav. Brain Sci.* **29**, 385–404, discussion 405–452 (2006).
9. L. L. Getz, B. McGuire, T. Pizzuto, J. E. Hofmann, B. Frase, *J. Mammal.* **74**, 44–58 (1993).
10. C. S. Carter, L. L. Getz, M. Cohen-Parsons, *Adv. Stud. Behav.* **16**, 109–145 (1986).
11. B. S. Cushing, K. M. Kramer, *Neurosci. Biobehav. Rev.* **29**, 1089–1105 (2005).
12. S. M. Phelps, L. J. Young, *J. Comp. Neurol.* **466**, 564–576 (2003).
13. A. G. Ophir, J. O. Wolff, S. M. Phelps, *Proc. Natl. Acad. Sci. U.S.A.* **105**, 1249–1254 (2008).
14. S. M. Phelps, A. G. Ophir, in *Cognitive Ecology II*, R Dukas, J. M. Ratcliffe, Eds. (Univ. of Chicago Press, Chicago, IL, 2009), chap. 9.
15. G. J. De Vries, G. C. Panzica, *Neuroscience* **138**, 947–955 (2006).
16. A. G. Ophir, S. M. Phelps, A. B. Sorin, J. O. Wolff, *Anim. Behav.* **75**, 1143–1154 (2008).
17. S. T. Emlen, L. W. Oring, *Science* **197**, 215–223 (1977).
18. H. Kokko, D. J. Rankin, *Philos. Trans. R. Soc. Ser. B* **361**, 319–334 (2006).
19. S. M. Phelps, P. Campbell, D.-J. Zheng, A. G. Ophir, *Neuropharmacology* **58**, 17–28 (2010).
20. K. L. Bales *et al*., *Neuroscience* **144**, 38–45 (2007).
21. N. D. Heintzman *et al*., *Nat. Genet.* **39**, 311–318 (2007).
22. K. R. Rosenbloom *et al*., *Nucleic Acids Res.* **41** (D1), D56–D63 (2013).
23. A. Razin, A. D. Riggs, *Science* **210**, 604–610 (1980).
24. X. Nan *et al*., *Nature* **393**, 386–389 (1998).
25. L. L. Getz, J. E. Hofmann, B. McGuire, T. W. Dolan, *J. Mammal.* **82**, 22–34 (2001).
26. B. McGuire, T. Pizzuto, L. L. Getz, *Can. J. Zool.* **68**, 391–398 (1990).
27. C. A. Streatfeild, K. E. Mabry, B. Keane, T. O. Crist, N. G. Solomon, *Anim. Behav.* **82**, 1387–1398 (2011).
28. F. Tajima, *Genetics* **123**, 585–595 (1989).
29. R. R. Hudson, M. Kreitman, M. Aguadé, *Genetics* **116**, 153–159 (1987).
30. Chimpanzee Sequencing and Analysis Consortium, *Nature* **437**, 69–87 (2005).
31. J. P. Aggleton, *Proc. Biol. Sci.* **281**, 20140565 (2014).

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SUPPLEMENTARY MATERIALS

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