further studies examining local reactivation during sleep: presenting auditory information to only one ear during sleep also primarily activates one hemisphere. Thus, auditory stimuli such as sounds and words may also be useful to reactivate memories locally during sleep.

It also provides further evidence that sniffing a scent with only one nostril does indeed selectively activate one hemisphere. This local selectivity might be particularly strong during NREM sleep, as connectivity between cortical regions is reduced during these sleep stages. This brings me to one of my favorite research questions: How does the nasal cycle influence oscillatory activity and the processes of memory consolidation during sleep? The nasal cycle refers to a particularity of our nose: typically we preferentially sniff with only one nostril. You can try it yourself right now: which nostril has an easier airflow in this moment? Interestingly, the preferential nostril regularly switches sides, with varying duration mostly between 1.5 and 4 hours [10]. While its function is not completely clear, it might serve optimal olfactory perception. Importantly, some authors additionally suspect an association between the nasal cycle and left or right sided activation of our brain [11]. And it occurs during sleep: changes in nostril side occur mostly during REM sleep or with postural changes, but very seldom during deep sleep [12]. Thus, we naturally sniff mostly with our left or right nostril during deep sleep. Does this also relate to differences in slow wave activity in the activated hemisphere? If so, does this relate to differential consolidation and/or reactivation of memories in the stimulated hemisphere? I hope future studies will answer these questions.

Can we translate the reported findings in applied settings, e.g. learning in real-life? First attempts to reactivate foreign vocabulary during sleep at home were not very successful, probably due to sleep disturbances induced by the words [13]. Furthermore, precise presentation of scents is complicated and requires large and expensive olfactometers and nasal masks. However, even very simple ways of presenting odors during sleep at home, using scent diffusers, have revealed promising results [14]. Moreover, engineers have started to develop mobile scent-delivery devices: for example, the device 'Essence' can be worn like a necklace [15]. It releases scent either via a smart-phone application or based on physiological parameters including sleep stage. Because scents do not disturb our sleep, these user-friendly devices will help us greatly to reactivate and boost memories during sleep also in a home setting — be it with the left or right nostril or both.

REFERENCES

1. Bar, E., Marmelstein, A., Arzi, A., Perl, O., Livne, E., Hizmi, E., Paz, R., Sobel, N., Dudai, Y., and Nir, Y. (2020). Local targeted memory reactivation in human sleep. Curr. Biol. *30*, 1435–1446.
2. Rasch, B., and Born, J. (2013). About sleep's role in memory. Physiol. Rev. *93*, 681–766.
3. Rasch, B., Büchel, C., Gais, S., and Born, J. (2007). Odor cues during slow-wave sleep prompt declarative memory consolidation. Science *315*, 1426–1429.
4. Hu, X., Cheng, L.Y., Chiu, M.H., and Paller, K.A. (2020). Promoting memory consolidation during sleep: A meta-analysis of targeted memory reactivation. Psychol. Bull. *146*, 218–244.
5. Zelano, C., and Sobel, N. (2005). Humans as an animal model for systems-level organization of olfaction. Neuron *48*, 431–454.
6. Rihm, J.S., Sollberger, S.B., Soravia, L.M., and Rasch, B. (2016). Re-presentation of olfactory exposure therapy success cues during non-rapid eye movement sleep did not increase therapy outcome but increased sleep spindles. Front. Hum. Neurosci. *10*, 340.
7. Tononi, G., and Cirelli, C. (2020). Sleep and synaptic down-selection. Eur. J. Neurosci. *51*, 413–421.
8. Klinzing, J.G., Niethard, N., and Born, J. (2019). Mechanisms of systems memory consolidation during sleep. Nat. Neurosci. *22*, 1598–1610.
9. Bergmann, T.O., and Born, J. (2018). Phase-amplitude coupling: a general mechanism for memory processing and synaptic plasticity? Neuron *97*, 10–13.
10. Kahana-Zweig, R., Geva-Sagiv, M., Weissbrod, A., Secundo, L., Soroker, N., and Sobel, N. (2016). Measuring and characterizing the human nasal cycle. PLoS One *11*, e0162918.
11. Price, A., and Eccles, R. (2016). Nasal airflow and brain activity: is there a link? J. Laryngol. Otol. *130*, 794–799.
12. Kimura, A., Chiba, S., Capasso, R., Yagi, T., Ando, Y., Watanabe, S., and Moriyama, H. (2013). Phase of nasal cycle during sleep tends to be associated with sleep stage. Laryngoscope *123*, 2050–2055.
13. Göldi, M., and Rasch, B. (2019). Effects of targeted memory reactivation during sleep at home depend on sleep disturbances and habituation. NPJ. Sci. Learn. *4*, 5.
14. Ritter, S.M., Strick, M., Bos, M.W., van Baaren, R.B., and Dijksterhuis, A. (2012). Good morning creativity: task reactivation during sleep enhances beneficial effect of sleep on creative performance. J. Sleep. Res. *21*, 643–647.
15. Amores, J., and Maes, P. (2017). Essence. In Proceedings of the 2017 CHI Conference on Human Factors in Computing Systems - CHI '17, G. Mark, S. Fussell, C. Lampe, M.C. Schraefel, J.P. Hourcade, C. Appert, and D. Wigdor, eds. (New York, New York, USA: ACM Press)), pp. 28–34.

Evolution: Is Recombination Rate Variation Adaptive?

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Recombination rates vary between species and individuals, but the evolutionary significance of this variation remains unknown. A new study demonstrates that recombination rate divergence in two natural populations of *Drosophila pseudoobscura* has been driven by adaptive evolution.

Homologous recombination is the hallmark event of meiosis and a critical force in evolution. By shuffling genetic variants between homologous chromosomes, recombination shapes patterns of genetic diversity within

populations. In addition, recombination can influence the efficacy of natural selection by decoupling linked variants with unequal fitness effects, thereby reducing selective interference. At the same time, the proper genomic distribution and frequency of recombination events safeguard the fidelity of meiosis. Excessively low recombination rates or mal-positioned recombination events confer increased risk for chromosome segregation errors and aneuploidy, whereas high recombination rates may promote ectopic exchanges that lead to deleterious genomic rearrangements [1].

The clear fitness costs associated with extreme recombination rates, coupled with their central importance for evolution, give way to a logical hypothesis: recombination rates should be subject to strong selective constraints that limit the range of this trait in nature. In perplexing contrast to this prediction, recombination rates are remarkably variable between species, individuals, and sexes [2]. The presence of variation in recombination rate has intrigued geneticists for more than a century [3] and classical genetic experiments established its heritable basis nearly 50 years ago [4]. The emergence and application of modern genomic technologies has further energized this research field by refining the scale and scope of recombination rate variation in nature and enabling the identification of loci that influence recombination rates in diverse organisms [5].

Despite these advances, an understanding of the evolutionary forces that give rise to variation in this fundamental meiotic phenotype continues to elude us. Theoretical models have defined potential scenarios under which increases or decreases in recombination rates may be favored by natural selection, but few empirical tests have sought to confirm whether such conditions are realized in nature [6]. Recent studies have uncovered genetic signatures of adaptive evolution in genes that function in the recombination pathway [7,8]. However, it remains unclear whether the recombination *phenotype* is adaptively evolving.

In this issue of *Current Biology*, Samuk *et al.* present technological and conceptual advances that make significant in-roads toward closing this knowledge gap [9]. The authors develop a novel targeted amplicon sequencing approach to construct genome-wide recombination maps for 17 inbred lines of *Drosophila pseudoobscura* derived from populations of wild-caught flies from American Fork Canyon, Utah and Madera Canyon, Arizona, USA. Their innovative strategy uses dual sample indexing to permit pooling, targeted sequencing, and subsequent demultiplexing of large numbers of progeny from multiple mapping populations. With a single library preparation step, the authors genotype thousands of individual flies at hundreds of informative SNPs, obviating two long-standing obstacles to estimating recombination rates: cost and throughput.

The authors' recombination maps localize most crossover events to genomic windows less than 300 kb. While not sufficient to detect fine-scale recombination rate differences, this precision permits comparisons of both global and intermediate-scale recombination rates within and between the Utah and Arizona populations. Samuk et al. document significant variation for recombination rate within each population. However, flies from the Utah population have, on average, 8% higher recombination rates than flies from the Arizona population. Intriguingly, this between-population difference is driven by a near-uniform increase in recombination across the genome, rather than localized differences in recombination rate at a select number of loci. This finding suggests a comparatively larger impact of global (as opposed to local) modifiers on the evolution of recombination rates in this system.

Samuk and team then used this set of 17 recombination maps to carry out one of the first direct tests for adaptive evolution of recombination rates. To do so, they adopt a powerful and widely used paradigm in quantitative genetics — Q_{ST}-F_{ST} analysis — to ask whether the phenotypic variation for recombination rate between populations exceeds the level of variation expected under neutral evolution [10]. Although the Utah and Arizona populations exhibit a modest (~8%) difference in global recombination rates, the authors show that this difference exceeds the level of divergence predicted in the face of genetic drift alone. This finding provides compelling evidence that population-level differences in recombination rate have been driven by adaptive evolution in this system.

Samuk *et al.* were then motivated to identify genetic determinants of this population-level divergence in global recombination rate. Using a candidate-gene driven approach, they identified nonsynonymous differences in two genes, *asp* and *mei-41*, that are associated with moderate (5–7%) differences in global recombination rate between lines. Both genes have biological functions consistent with their plausible role as recombination rate modifiers: *asp* is involved in microtubule organization and spindle formation at meiosis and *mei-41* is the *Drosophila* homolog of ATR, a gene involved in DNA damage surveillance and response. Both *asp* and *mei-41* are strongly linked in the populations surveyed, precluding further efforts to assess their independent effects or identify causal variants.

Samuk *et al.*'s work provides key new insight into the modes of recombination rate evolution and the nature of the evolutionary forces that operate on recombination rates. However, their findings simultaneously raise several new questions.

First, does recombination rate evolution largely proceed via uniform, global shifts in recombination rate, as opposed to localized changes, in other species? Many theoretical models of recombination rate evolution invoke the action of globally acting modifiers [11]. Thus, determining whether global changes are the prevailing mode of evolution across diverse taxa is paramount to assessing the validity of model assumptions. In particular, recombination events in most mammals, including humans, are

restricted to short 1–2 kb 'hotspots' defined by the zinc-finger DNA-binding domain of a histone methyltransferase, PRDM9 [12,13]. Although *Drosophila* exhibit fine-scale variation in recombination rates, they lack *Prmd9* and do not harbor bona fide hotspots [14]. Whether recombination rate evolution in species with and without hotspots proceeds via distinct modalities requires further investigation.

Second, what selective pressures drive adaptive differences in recombination rate? Prior studies have demonstrated plastic shifts in recombination rate in response to diverse external stressors [15], including temperature [3,16]. These observations raise the possibility that different recombination rates may be optimal under specific climatic conditions. It is noteworthy that mean average temperature differs by 11°C in the Arizona and Utah populations profiled in this study. Although tempting to speculate that temperature could drive local adaptation in recombination rate between these two populations, further studies are clearly needed to test this hypothesis. Of course, it is also possible that recombination rates evolve as a correlated response to adaptive changes in a cryptic, secondary trait. Indeed, strong directional selection for unrelated phenotypes can yield correlated changes in recombination rate [17,18]. Additionally, demographic differences between populations [11] and variation in life history traits [19] may also create population genomic environments in which distinct recombination rate values are adaptively favored.

Finally, what is the relationship between variation in recombination rate and evolutionary fitness? Recombination rates and offspring number are significantly positively correlated in humans [20]. However, the presence of significant variation for recombination within populations, including those studied by Samuk *et al.*, would seem to suggest that departures from the adaptive optimum may not be associated with large fitness losses. Further work is needed to determine the intensity of the selection response across a range of recombination rate values.

An extension of this final question concerns whether the relationship between fitness and recombination rate differs between the sexes. If so, recombination rates could serve as a battleground for sexually antagonistic genetic variants that exert opposite effects on male and female fitness. Addressing this possibility will require studies of recombination rate evolution in species other than *Drosophila*, as recombination is restricted to female meiosis in flies. Importantly, the methodological and conceptual framework developed by Samuk *et al.* can be adapted to test for sex-specific mechanisms of recombination rate evolution, as well as experimental tests of recombination rate evolution in other taxa. In this way, Samuk *et al.*'s work moves us significantly closer to understanding of the biological mechanisms that underpin the puzzling diversity of recombination rates in nature.

REFERENCES

1. Hassold, T., and Hunt, P. (2001). To err (meiotically) is human: the genesis of human aneuploidy. Nat. Rev. Genet. *2*, 280–291.
2. Smukowski, C.S., and Noor, M.A. (2011). Recombination rate variation in closely related species. Heredity *107*, 496–508.
3. Plough, H.H. (1917). The effect of temperature on crossingover in Drosophila. J. Exp. Zool. *24*, 147–209.
4. Chinnici, J.P. (1971). Modification of recombination frequency in Drosophila. I. Selection for increased and decreased crossing over. Genetics *69*, 71–83.
5. Zelkowski, M., Olson, M.A., Wang, M., and Pawlowski, W. (2019). Diversity and determinants of meiotic recombination landscapes. Trends Genet. *35*, 359–370.
6. Stapley, J., Feulner, P.G.D., Johnston, S.E., Santure, A.W., and Smadja, C.M. (2017). Variation in recombination frequency and distribution across eukaryotes: patterns and processes. Philos. Trans. R. Soc. Lond. B Biol. Sci. *372*, 20160455.
7. Brand, C.L., Cattani, M.V., Kingan, S.B., Landeen, E.L., and Presgraves, D.C. (2018). Molecular evolution at a meiosis gene mediates species differences in the rate and patterning of recombination. Curr. Biol. *28*, 1289–1295.e4.
8. Dapper, A.L., and Payseur, B.A. (2019). Molecular evolution of the meiotic recombination pathway in mammals. Evolution *73*, 2368–2389.
9. Samuk, K., Manzano-Winkler, B., Ritz, K.R., and Noor, M.A.F. (2020). Natural selection shapes variation in genome-wide recombination rate in Drosophila pseudoobscura. Curr. Biol. *30*, 1517–1528.
10. Leinonen, T., McCairns, R.J.S., O'Hara, R.B., and Merilä, J. (2013). Q_{ST}–F_{ST} comparisons: evolutionary and ecological insights from genomic heterogeneity. Nat. Rev. Genet. *14*, 179–190.
11. Keightley, P.D., and Otto, S.P. (2006). Interference among deleterious mutations favours sex and recombination in finite populations. Nature *443*, 89–92.
12. Baudat, F., Buard, J., Grey, C., Fledel-Alon, A., Ober, C., Przeworski, M., Coop, G., and de Massy, B. (2010). PRDM9 is a major determinant of meiotic recombination hotspots in humans and mice. Science *327*, 836–840.
13. Parvanov, E.D., Petkov, P.M., and Paigen, K. (2010). Prdm9 controls activation of mammalian recombination hotspots. Science *327*, 835.
14. Manzano-Winkler, B., McGaugh, S.E., and Noor, M.A.F. (2013). How hot are Drosophila hotspots? Examining recombination rate variation and associations with nucleotide diversity, divergence, and maternal age in *Drosophila pseudoobscura*. PLoS One *8*, e71582.
15. Singh, N.D., Criscoe, D.R., Skolfield, S., Kohl, K.P., Keebaugh, E.S., and Schlenke, T.A. (2015). Fruit flies diversify their offspring in response to parasite infection. Science *349*, 747–750.
16. Grell, R.F. (1978). A comparison of heat and interchromosomal effects on recombination and interference in *Drosophila melanogaster*. Genetics *89*, 65–77.
17. Flexon, P.B., and Rodell, C.F. (1982). Genetic recombination and directional selection for DDT resistance in *Drosophila melanogaster*. Nature *298*, 672–674.
18. Ross-Ibarra, J. (2004). The evolution of recombination under domestication: a test of two hypotheses. Am. Nat. *163*, 105–112.
19. Burt, A., and Bell, G. (1987). Mammalian chiasma frequencies as a test of two theories of recombination. Nature *326*, 803–805.
20. Kong, A., Barnard, J., Gudbjartsson, D.F., Thorleifsson, G., Jonsdottir, G., Sigurdardottir, S., Richardsson, B., Jonsdottir, J., Thorgeirsson, T., Frigge, M.L., *et al.* (2004). Recombination rate and reproductive success in humans. Nat. Genet. *36*, 1203–1206.