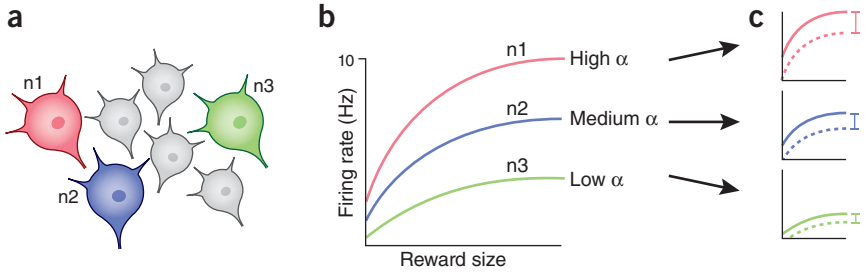


Figure 1 Responses of individual dopamine neurons to varying levels of expected and unexpected reward. (**a**) Recorded population of neurons in the lateral VTA. Reward-responsive dopamine neurons are colored. (**b**) Response of three dopamine neurons to unexpected rewards of varying sizes. As reward increases (horizontal axis), the firing rate of each neuron increases with a common response function, differing only in the gain of the response (α). (**c**) When reward presentation is preceded by a predictive cue (dashed line), the response of each dopamine neuron is reduced in a subtractive manner relative to unexpected reward (solid line). The amount of this subtraction is proportional to the gain of each neuron's response to unexpected reward (see **b**).

The experiments described above characterized dopamine response homogeneity through averaging over repeated trials of the same stimuli. To examine whether dopamine neurons also display homogeneity at the level of individual trials, the authors calculated the noise correlation, a metric of the correlation of activity between two neurons in response to identical stimuli. In contrast to the relatively low noise correlation between non-dopaminergic neurons, dopamine neurons instead showed much higher noise correlation with each other. This high noise correlation provides further support for their conclusion of homogeneity among dopamine neurons. In addition, it indicates that there would be little computational advantage of a downstream neuron integrating information across multiple dopamine neurons, as averaging across inputs with high noise correlations does not improve the signal-to-noise ratio.

Together, these findings provide elegant evidence that the reward-responsive dopamine neurons in the lateral VTA encode RPE with a similar response function that varies solely in gain. At the same time that these experiments point to homogeneity in RPE coding in this region, they in no way rule out functional diversity of dopamine neurons in other regions. In fact, previous experiments have demonstrated that dopamine neurons in different parts of the VTA and substantia nigra project to different regions of the brain, receive inputs from different areas, and have different physiological properties[4,6,9–12]. It will be interesting to learn whether the homogeneity of RPE in dopamine neurons remains when a broader range of recording locations is examined.

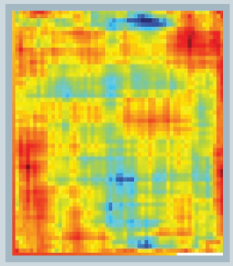
Another source of functional diversity among dopamine neurons may arise under conditions of greater task complexity. In particular, the Pavlovian conditioning task used in this study was carefully designed to assess RPE encoding, but many other behaviors in which dopamine have been implicated are more complex[13–15]. In theory, tasks that involve, for example, instrumental responses, working memory or attention could in turn elicit more heterogeneous coding schemes across dopamine neurons. The uniformity or diversity with which dopamine neurons respond under such conditions remains to be seen. On a related note, it is possible that the neurons with a low gain in their reward prediction error function may preferentially encode some of the other aspects of behavior. In addition, the function of the small subset of recorded dopamine neurons that displayed a phasic suppression of firing rate in response to reward was not characterized in this study. The role of these dopamine neurons, as well as how they may differ in their inputs and projection targets, is a worthwhile question in light of the otherwise homogeneous encoding of RPE across dopamine neurons reported in this paper.

In summary, Eshel *et al.*[8] provide an elegant and convincing demonstration of uniformity in the RPE encoding among dopamine neurons in the lateral VTA: when neurons encode RPE, they use the same response function, diverging only in gain. These results provide valuable support for homogeneity of RPE encoding and have important implications for how downstream neurons could make use of this teaching signal.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

1. Schultz, W. & Dickinson, A. *Annu. Rev. Neurosci.* **23**, 473–500 (2000).
2. Steinberg, E.E. *et al. Nat. Neurosci.* **16**, 966–973 (2013).
3. Chang, C.Y. *et al. Nat. Neurosci.* **19**, 111–116 (2016).
4. Lammel, S. *et al. Nature* **491**, 212–217 (2012).
5. Roeper, J. *Trends Neurosci.* **36**, 336–342 (2013).
6. Lerner, T.N. *et al. Cell* **162**, 635–647 (2015).
7. Neuhoff, H., Neu, A., Liss, B. & Roeper, J. *J. Neurosci.* **22**, 1290–1302 (2002).
8. Eshel, N., Tian, J., Bukwich, M. & Uchida, N. *Nat. Neurosci.* **19**, 479–486 (2016).
9. Lynd-Balta, E. & Haber, S.N. *Neuroscience* **59**, 625–640 (1994).
10. Fiorillo, C.D., Yun, S.R. & Song, M.R. *J. Neurosci.* **33**, 4693–4709 (2013).
11. Lammel, S., Ion, D.I., Roeper, J. & Malenka, R.C. *Neuron* **70**, 855–862 (2011).
12. Matsumoto, M. & Hikosaka, O. *Nature* **459**, 837–841 (2009).
13. Brozoski, T.J., Brown, R.M., Rosvold, H.E. & Goldman, P.S. *Science* **205**, 929–932 (1979).
14. Stopper, C.M., Tse, M.T.L., Montes, D.R., Wiedman, C.R. & Floresco, S.B. *Neuron* **84**, 177–189 (2014).
15. Hamid, A.A. *et al. Nat. Neurosci.* **19**, 117–126 (2016).

Schizophrenia and brain volume genetic covariation



Schizophrenia is a heterogeneous group of disorders at the level of genetic etiology and clinical presentation. Disentangling the relationship between genotype and phenotype will help determine which patient features are a cause or consequence of disease. On page 420, Franke *et al.* took advantage of large-scale genome-wide association studies of schizophrenia and of subcortical brain volumes to examine the relationship between the two.

There was no genetic overlap between the overall common variants influencing both sets of traits (see picture for genetic overlap between schizophrenia and hippocampal volume), nor did they share any single risk gene. Thus, even though meta-analyses find subcortical volumetric differences in schizophrenia patients, it is unlikely these are due to genetic risk factors driving the disease. The authors also found that the effect sizes of variants influencing disease risk were similar to those influencing brain volumes. This is in line with previous evidence that brain measures are not genetically simpler but rather are just as complex as behavioral measures such as psychiatric diagnosis.

Large-scale studies of additional structural and functional imaging measures in patients and controls are needed to determine, *in vivo*, the brain circuits and processes mediating the effect of genetic risk for schizophrenia.

Corrected after print 23 February 2016

P. Alexander Arguello

Erratum: Schizophrenia and brain volume genetic covariation

P Alexander Arguello

Nat. Neurosci. **19, 419 (2016); published online 23 February 2016; corrected after print 23 February 2016**

In the version of this article initially published, the page number for the cross-referenced article was given as 414 instead of 420 and the author name was misspelled Frank instead of Franke. The errors have been corrected in the HTML and PDF versions of the article.