In summary, the study by Knafo *et al.*[2] provides a new perspective on the mechanisms leading to AD-associated synaptic depression and the critical role of lipid signaling[15]. It emphasizes that understanding spatial and temporal control of PTEN localization and its dynamic interactions with specific binding partners is required for rational design of a new generation of AD therapies.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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Gaining on reward prediction errors

Nathan F Parker & Ilana B Witten

In this issue of *Nature Neuroscience*, Eshel *et al.* characterize the homogeneity with which individual dopamine neurons encode reward prediction error, a teaching signal that is thought to be crucial for associative learning.

The smell of coffee, the sound of a text notification, the familiar trees and signs of your home street: these are all examples of stimuli that have been associated with rewarding experiences. Dopamine neurons in the ventral tegmental area (VTA) and substantia nigra help form such associations through the encoding of a reward prediction error (RPE), or the difference between received and expected reward[1]. This teaching signal is essential to learning the value of stimuli in the environment[2,3]. Although it is well accepted that at least some dopamine neurons encode RPE, more recent studies have begun to highlight the anatomical, physiological and functional diversity among dopamine neurons[4–7]. Thus, the question of the heterogeneity versus consistency with which individual dopamine neurons encode RPE has become a subject of increasing interest.

In this issue of *Nature Neuroscience*, Eshel *et al.*[8] address this question using electrophysiological recording of activity of identified dopamine neurons in the lateral VTA of mice performing a Pavlovian conditioning task. To identify the recorded neurons as dopaminergic, the authors used a technique termed phototagging, wherein neurons express the light-sensitive protein channelrhodopsin-2 (ChR2) under the control of the dopamine transporter promoter. Because expression of ChR2 is limited to dopaminergic neurons, the experimenters were able to identify extracellularly recorded neurons on the basis of their short-latency optical responses. Of these optically identified dopamine neurons, 40 of 43 were deemed reward responsive, as they responded with a phasic increase in firing rate to unexpected reward. Characterization of RPE encoding in this subset of neurons was the focus of the study.

Toward this end, the mice were trained on a Pavlovian conditioning task with parametrically varying reward sizes and reward expectations. During the recordings, mice received water droplets of varying sizes either unexpectedly or following the presentation of a predictive odor cue. This allowed an assessment of the effect of reward size as well as of reward expectation on neural responses. The authors then asked how similar this response function was between neurons.

In response to increasing reward size, all dopamine neurons that responded to unexpected reward displayed a monotonically increasing and saturating response to increasing reward size (**Fig. 1a**,**b**). The authors fit this response function with a Hill function. Notably, they found that the only aspect of the function that varied substantially between the neurons was the gain of the function, which the authors term α. This indicates that different dopamine neurons are not specialized to respond to specific reward sizes, nor do they have different thresholds in their unexpected reward response function.

An essential feature of RPE encoding is the suppression of reward responses by reward-predicting stimuli (reward expectation). To investigate how similar or different the effect of reward expectation is on individual dopamine neurons, the authors presented reward-predicting odor cues before reward delivery. Across all recorded dopamine neurons, the reward predictive cue reduced the response to reward in a subtractive manner (**Fig. 1c**). Interestingly, the amount of subtraction was linearly related to the strength of the neuron's response to unexpected reward (α). The slope of this correlation between response to unexpected reward and subtraction by reward expectation, which the authors denote as β, represents the degree to which reward expectation reduces the firing rate of the recorded population of dopamine neurons.

Together, these results demonstrate an impressive degree of uniformity in RPE encoding across this population of dopamine neurons. Only two free parameters, α and β, were sufficient to describe reward prediction error encoding across the population. Although the gain parameter α was neuron specific, β was a function of the level of expectation and other task parameters. When the authors varied expectation, they found that the value of β changed, and yet the two parameters remained sufficient to explain RPE encoding throughout the population.

Some of the reward-responsive dopamine neurons had very weak reward responses (small α). The authors went on to ask whether these neurons simply have lower excitability or whether they instead respond more strongly to another stimulus; for example, an aversive one. The latter possibility would contradict the assertion that the neurons encoded RPE in a similar manner. To address this question, they compared responses to three forms of aversive stimuli—reward omission, air puff and a cue-predicting air puff—with reward responses in the population of dopamine neurons. Notably, there was a correlation between the strength of reward responses and the extent of suppression in response to aversive stimuli. This is consistent with the idea that the entire population of neurons encodes RPE in a similar fashion.

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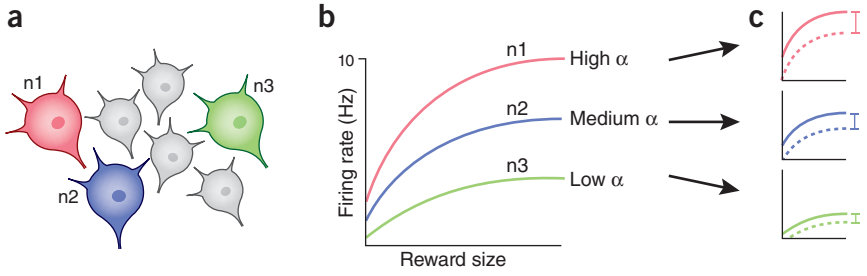

Figure 1 Responses of individual dopamine neurons to varying levels of expected and unexpected reward. (**a**) Recorded population of neurons in the lateral VTA. Reward-responsive dopamine neurons are colored. (**b**) Response of three dopamine neurons to unexpected rewards of varying sizes. As reward 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.

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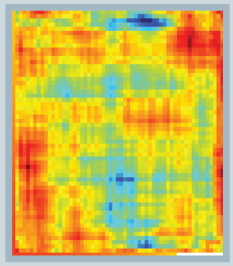
Schizophrenia and brain volume genetic covariation



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 414, Frank *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.

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