The results of Kuzmiski *et al.*[4] are important because they link basic synaptic plasticity mechanisms to whole-organism physiology processes that we may experience in our daily life. Although the idea is well accepted that experience-dependent plasticity of NMDAR is central to the dynamic control of synaptic functions[6], there still is a big gap between the elucidation of the versatile mechanisms mediating synaptic plasticity *in vitro* and the realization that these mechanisms may participate in a physiological behavioral response. For example, Kuzmiski *et al.*[4] show that although stress-induced priming involves the long-term depression of postsynaptic NMDARs, the STP that it unmasks is instead expressed presynaptically and is mediated, at least in part, by multivesicular glutamate release (**Fig. 1**). Although multivesicular release has been increasingly observed in short- and long-term potentiation (see ref. 11), this is the first report, to the best of our knowledge, that this atypical phenomenon occurs in a physiological context. Similarly, this report provides a new physiological context for postsynaptic vesicular release, a phenomenon that was shown to participate in hippocampal long-term plasticity over a decade ago[12]. By showing that NMDAR-dependent exocytosis represses synaptic gain independently of AMPAR trafficking and desensitization in naive PVN, Kuzmiski *et al.*[4] expand the functions of activity-dependent vesicular release beyond classical views and bring retrograde signaling back into the spotlight[10].

Because it occurs in the PVN, the output structure of the HPA, environment-regulated synaptic priming has the potential to affect the entire functional repertoire of the HPA axis, assuming that the majority of the excitatory synapses on parvocellular neurons are under the control of the mysterious retrograde messenger (**Fig. 1**). Alternatively, if only a subset of glutamate afferents is sensitive to retrograde plasticity, then one expects stress-induced priming to displace the balance toward a particular set of neuroendocrine, synaptic and behavioral responses. Resolving these issues will first necessitate drawing a clear picture of the specific sources of the glutamatergic innervation of PVN parvocellular neurons (such as the dorso-medial hypothalamic nucleus and the bed nucleus of the stria terminalis)[1–3,5]. A related issue in need of further investigation is the modulation of synaptic priming in the PVN by other stress mediators, such as monoamines, neuropeptides and steroids. These other mediators can potentially modulate synaptic plasticity, and precise interactions among them are necessary to achieve the appropriate stress response[2]. The advent of optogenetic approaches allowing targeted stimulation of precise neuronal networks in specific brain areas may help clarify the exact circuitry at work.

Finally, it is important to remember that stress comes in two different colors. Hans Selye, who first put stress in a physiological context, coined the terms 'distress' for negative stress (such as punishment, danger) and 'eustress' for positive stress (reward)[13]. Kuzmiski *et al.*[4] reveal that two different forms of distress can trigger priming. It is now important to determine whether eustress triggers similar or different synaptic adaptations. Indeed, deciphering the protracted adaptive regulation of the stress response is crucial to understanding the role of stress in the etiology of major stress-related neuropsychiatric diseases such as drug addiction[14], depression and post-traumatic stress disorder[1,3,15]. Multiple neuronal circuits and stress mediators orchestrate the 'neurosymphony of stress'[2], and by introducing new players to the band, Kuzmiski *et al.*[4] substantially extends the repertoire of the orchestra.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

1. Armario, A., Escorihuela, R.M. & Nadal, R. *Neurosci. Biobehav. Rev.* **32**, 1121–1135 (2008).
2. Joëls, M. & Baram, T.Z. *Nat. Rev. Neurosci.* **10**, 459–466 (2009).
3. Lupien, S.J., McEwen, B.S., Gunnar, M.R. & Heim, C. *Nat. Rev. Neurosci.* **10**, 434–445 (2009).
4. Kuzmiski, J.B., Marty, V., Baimhoukhametova, D.V. & Bains, J.S. *Nat. Neurosci.* **13**, 1257–1267 (2010).
5. Ulrich-Lai, Y.M. & Herman, J.P. *Nat. Rev. Neurosci.* **10**, 397–409 (2009).
6. Lau, C.G. & Zukin, R.S. *Nat. Rev. Neurosci.* **8**, 413–426 (2007).
7. Schierloh, A., Deussing, J., Wurst, W., Zieglgansberger, W. & Rammes, G. *Neurosci. Lett.* **416**, 82–86 (2007).
8. Sheng, H. *et al. Endocrinology* **149**, 1389–1398 (2008).
9. Ludwig, M. & Leng, G. *Nat. Rev. Neurosci.* **7**, 126–136 (2006).
10. Regehr, W.G., Carey, M.R. & Best, A.R. *Neuron* **63**, 154–170 (2009).
11. Bender, V.A., Pugh, J.R. & Jahr, C.E. *J. Neurosci.* **29**, 10974–10978 (2009).
12. Lledo, P.M., Zhang, X., Sudhof, T.C., Malenka, R.C. & Nicoll, R.A. *Science* **279**, 399–403 (1998).
13. Selye, H. *Stress Without Distress* (New American Library, New York, 1975).
14. Koob, G.F. *Neuron* **59**, 11–34 (2008).
15. Feder, A., Nestler, E.J. & Charney, D.S. *Nat. Rev. Neurosci.* **10**, 446–457 (2009).

It takes all kinds to make a brain

Rachel I Wilson

Variation in neuronal properties is often thought of as noise that interferes with information processing. A study now suggests that neuronal diversity may actually improve the coding capacity of neural ensembles.

As neuroscientists, we sometimes wish our data looked a bit tidier than it actually does. For example, we tend to report our measurements as a mean plus or minus error, but many of us secretly yearn for small error bars. When we measure the same variable from many neurons of the same type (even when our notion of a 'type' is fuzzy), we suspect this variable should really have a fixed value. In other words, we tend to feel that variation is merely a result of Mother Nature's poor quality control.

However, variation in the nervous system isn't necessarily a bad thing. In an evolving population, variation among the nervous systems of different organisms is part of the diversity that natural selection acts on[1,2]. In a developing organism, variation among neurons competing for territory and survival may help to ensure that the winners are fit[3]. Finally, some variation may simply be neutral. If variable neurons can combine in many ways to produce adequately functional circuits, then there is no disadvantage to this variability[4].

In this issue of *Nature Neuroscience*, Padmanabhan and Urban[5] show us another reason why variation isn't intrinsically bad. Specifically, they found that variation among neurons of the same type increases the coding capacity of neural ensembles (we define neurons of the same type as being neurons that carry approximately the same signal). To get an intuition for why this should be so, consider the following problem. You are trying to learn the plot of a movie you haven't seen based on conversations with several friends. All of the friends saw the same movie (the same signal), but each friend is attuned to something

The author is in the Department of Neurobiology and the Howard Hughes Medical Institute, Harvard Medical School, Boston, Massachusetts, USA.
e-mail: rachel_wilson@hms.harvard.edu

different; some are interested in the kissing scenes, others in the chase scenes. Clearly, your reconstruction will be most accurate if your friends have diverse interests, assuming that their interests as a group are a good match for the plot of the movie.

Although this intuition is simple, it's not trivial to show that the sort of variability exhibited by real neurons can actually expand coding capacity. The first problem is that it's difficult to define a population of neurons that are all of the same type. The very existence of diversity makes classification sometimes feel arbitrary. The second problem is that it's difficult to manipulate the amount of variability in a neural population to test the extent to which this manipulation actually degrades coding capacity.

Padmanabhan and Urban[5] addressed the first problem by choosing a circuit in which the definition of a type is fairly obvious: the mouse olfactory bulb. The bulb is divided into ~1,000 discrete neuropil compartments known as glomeruli (**Fig. 1**). Each glomerulus receives excitatory synaptic input exclusively from all of the olfactory receptor neurons (ORNs) that express a given odorant receptor gene[6,7]. Postsynaptic to each glomerulus are several dozen principal neurons known as mitral cells[8]. There is some evidence that every ORN projects to each and every principal neuron in its target glomerulus[9,10]. Moreover, each mitral cell is postsynaptic to a single glomerulus. Thus, all of the sister mitral cells postsynaptic to the same glomerulus carry approximately the same signal and they may even receive input from completely identical sets of ORNs.

Padmanabhan and Urban[5] found that the intrinsic properties of sister mitral cells are diverse. Recording in olfactory bulb slices, they injected a fluctuating current waveform through the somatic recording pipette into many individual sister cells. Each cell responded with a consistent pattern of spikes to repeated presentations of the identical input current. Notably, the difference between the responses of sister cells was consistently larger than the trial-to-trial variability in the responses of each individual cell.

This study describes these differences by reducing the characteristic properties of each cell to a compact mathematical descriptor: a linear filter. In general terms, a linear filter is the simplest description of the relationship between an input signal and an output signal. For a spiking neuron, the linear filter can be estimated by averaging together all of the input signals that immediately preceded a spike. The result of this procedure (called spike-triggered averaging) is termed the filter and it represents an estimate of the input that optimally drives a spike. Padmanabhan and Urban[5] computed filters in the time domain for each of several sister mitral cells and found that they have different shapes. This means that each cell is optimally driven by a different temporal profile of input current. As a result, each cell is attuned to a slightly different temporal aspect of their shared input.

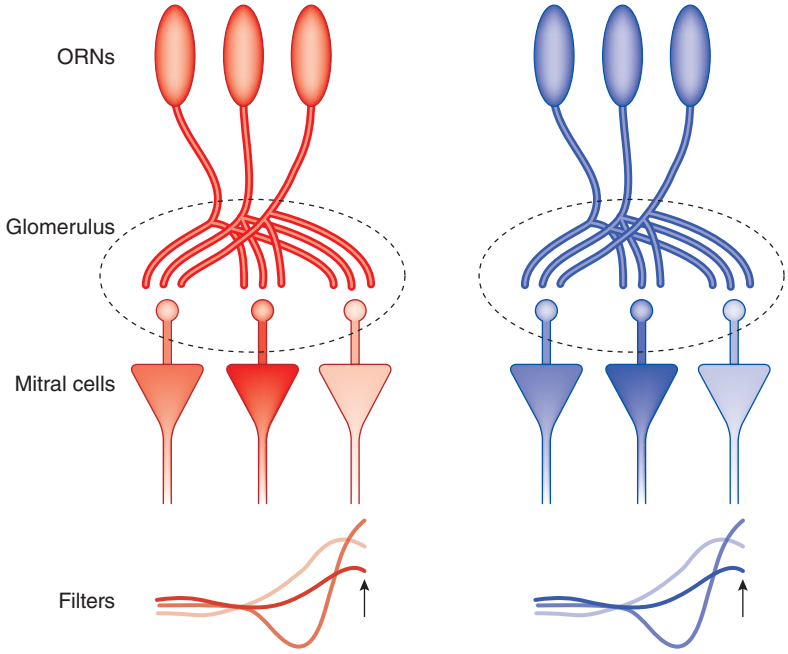


Figure 1 Mitral cell diversity. All of the ORNs that express a given odorant receptor converge on a glomerulus, where they make excitatory synapses with mitral cells. Padmanabhan and Urban[5] found that the mitral cells postsynaptic to the same glomerulus have diverse intrinsic electrophysiological properties. Schematized filters (below) show the temporal pattern of input current that is optimal for driving a spike in each mitral cell. The timing of the spike is indicated by the arrow. This diversity maximizes information transmission by mitral cells.

Next, Padmanabhan and Urban[5] tackled the problem of how to reduce the amount of diversity among mitral cells. They solved this by performing the manipulation in a simulation rather than experimentally. Recorded spike trains were assigned to a simulated population of mitral cells in which either all of the spike trains were recorded from the same neuron or each was recorded from a different (sister) neuron. This emulates either a relatively stereotyped population of sister cells or a more diverse population of sister cells. Compared with the stereotyped population, Padmanabhan and Urban[5] found that the diverse population carried substantially more information about the pattern of input current fluctuations.

These results imply that diversity among the intrinsic properties of mitral cells is useful in maximizing the information that the brain receives about the olfactory world. Each mitral cell should spike in response to a slightly different temporal feature of the ORN input to its glomerulus. Combining these differently filtered signals should yield better olfactory acuity than combining identically filtered signals.

However, the situation *in vivo* may be different from the *in vitro* conditions of this study. Padmanabhan and Urban[5] used somatic current injections that were not meant to closely emulate real patterns of synaptic input from ORNs. To draw an analogy, your ability to reconstruct the movie depended on the fact that your friends' collective interests were a good match for that movie. Similarly, the ability of mitral cells to encode an odor stimulus may depend on how well their filters match the properties of ORN input.

Nevertheless, the fundamental conclusion of this study is likely to be relevant to other circuits. Indeed, there is evidence for a similar phenomenon in the salamander retina, where each functional type of ganglion cell (for example, monophasic-OFF or biphasic-OFF cells) densely covers the retina[11]. When two cells of the same type have highly overlapping spatial receptive fields, we might expect that they should carry essentially the same information. However, the amount of shared information between these pairs seems to be limited to ~25% at most[11]. In other words, these cells evidently carry largely nonredundant information about the same patch of the visual world. It should be noted that we do not know how much of the

nonredundancy in these retinal ganglion cell signals arises from diverse intrinsic properties versus diverse circuit connections. Another caveat in this particular experimental preparation is that the definition of a ganglion cell type is somewhat subjective. One might argue that low shared information between two neurons should mean that, by definition, these cells belong to different types. Indeed, the largest information gain comes from pooling signals from different types (for example, ON versus OFF cells), rather than from cells from the same type[11,12].

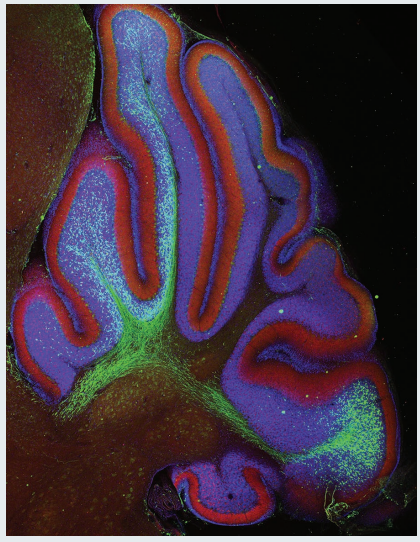
Notably, the broader implications of Padmanabhan and Urban's study[5] do not rely on any particular definition of a neuronal type. First, this study illustrates why it can be inappropriate to model populations of neurons as replicates of the same neuron with fixed intrinsic properties. Instead, it might be more realistic (in some contexts) to model populations of neurons by drawing from distributions of parameters specifying their intrinsic properties[13].

Second, this study suggests that diversity in the intrinsic properties of neurons can be a virtue. Given this, it is tempting to speculate that there might be mechanisms in place to increase diversity. These mechanisms appear to exist at the level of genetic variation. Because mechanisms of genetic replication and repair are variable and heritable, they are themselves subject to natural selection, and variants that increase mutation rates can actually enjoy an advantage[14]. Similarly, it has been postulated that there are mechanisms in place that reduce the lethality associated with genetic variation, thereby increasing the amount of variation that is retained during natural selection[15]. It will be interesting to learn whether analogous mechanisms exist to promote variation in a neural population.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

1. Rakic, P. *Nat. Rev. Neurosci.* **10**, 724–735 (2009).
2. Ryan, T.J. & Grant, S.G. *Nat. Rev. Neurosci.* **10**, 701–712 (2009).
3. Luo, L. & Flanagan, J.G. *Neuron* **56**, 284–300 (2007).
4. Prinz, A.A., Bucher, D. & Marder, E. *Nat. Neurosci.* **7**, 1345–1352 (2004).
5. Padmanabhan, K. & Urban, N. *Nat. Neurosci.* **13**, 1276–1282 (2010).
6. Ressler, K.J., Sullivan, S.L. & Buck, L.B. *Cell* **79**, 1245–1255 (1994).
7. Vassar, R. *et al. Cell* **79**, 981–991 (1994).
8. Shepherd, G.M. & Greer, C.A. in *The Synaptic Organization of the Brain* (ed. Shepherd, G.M.) 159–203 (Oxford University Press, Oxford, 1998).
9. Chen, T.W., Lin, B.J. & Schild, D. *Proc. Natl. Acad. Sci. USA* **106**, 2401–2406 (2009).
10. Kazama, H. & Wilson, R.I. *Nat. Neurosci.* **12**, 1136–1144 (2009).
11. Segev, R., Puchalla, J. & Berry, M.J. II. *J. Neurophysiol.* **95**, 2277–2292 (2006).
12. Warland, D.K., Reinagel, P. & Meister, M. *J. Neurophysiol.* **78**, 2336–2350 (1997).
13. Goldman, M.S., Golowasch, J., Marder, E. & Abbott, L.F. *J. Neurosci.* **21**, 5229–5238 (2001).
14. Drake, J.W., Charlesworth, B., Charlesworth, D. & Crow, J.F. *Genetics* **148**, 1667–1686 (1998).
15. Gerhart, J. & Kirschner, M. *Proc. Natl. Acad. Sci. USA* **104** Suppl 1, 8582–8589 (2007).

Spinal convergence of motor and sensory pathways



Effective motor execution needs to accurately integrate proprioceptive sensory feedback to update the motor command centers about the outcome of the movements. The motor system can also generate an internal prediction of the planned actions to reduce delay. Previous studies have suggested that several cerebellar and cortical sites act as integration centers, where internal motor predictions can be made by converging sensory feedback and cortical corollary pathways. On page 1232 of this issue, Hantman and Jessell find that the convergence of the cortical command pathway and the proprioceptive sensory feedback pathway occurs even earlier, at Clarke's column in the spinal cord.

Clarke's column comprises dorsal spinocerebellar (dSC) tract neurons, which form a nucleus spanning thoracic and lumbar spinal cord and that relay proprioceptive sensory information from the hindlimb. Although dSC tract neurons are known to be active upon electrical stimulation of descending corticospinal tracts, the exact nature of corticospinal input and the interaction between corticospinal efferent activity and spinocerebellar afferent activity were unclear. Hantman and Jessell used genetic and anatomical tracers to map out dSC neurons and their inputs and outputs in the mouse and found that dSC tract neurons in Clarke's column receive both proprioceptive axonal projections from the dorsal root ganglion and descending corticospinal projections. To do this, they identified Clarke's column dSC neurons by their expression of *glial cell-derived neurotrophic factor* (*Gdnf*); this expression pattern distinguishes them from other spinocerebellar projections neurons. The authors then used the *Gdnf* promoter to create inducible mice that selectively expressed the fluorescent protein mGFP in their dSC neurons. Using this elegant genetic technique, the authors found that dSC spinocerebellar projections reach cerebellar lobules I, II, III and VIII (see image; mGFP-positive dSC projections terminating at the cerebellum are shown in green, vGlut1 immunostaining is shown in red and Neurotrace Nissl staining is shown in blue). The authors also measured the electrophysiological responses of dSC neurons on corticospinal or dorsal root ganglion stimulation and found that these neurons receive excitatory inputs from proprioceptive dorsal root ganglion projections and direct excitatory inputs from corticospinal axons and/or indirect cortically-evoked inhibitory inputs.

These findings suggest that dSC neurons in Clarke's column represent a spinal cord–level convergence site where descending motor corollary signals and ascending sensory feedback may be integrated, perhaps serving to fine-tune ascending proprioceptive feedback to the locomotor command center.

Min Cho