et al.'s series of tests. If the deficit depended on the need to learn from identity prediction errors, behavior should now be impervious to cholinergic interventions in the pDMS, since all three manipulations would involve value as well as identity prediction errors. If, on the other hand, the problem was one of retrieval, then the rats' responding should still reflect the erroneous association of both levers with both outcomes, with response rates postreversal evidencing similar predictions for both levers. Of course, single unit recordings would still be useful for understanding the relationship between either of these roles and the precise firing patterns of the neurons, as well as the dynamics of learning in the striatal network that gives rise to these functions (and associated deficits). However, it is always inspiring to see well-controlled behavioral designs reveal underlying neural processes, even absent electrodes.

ACKNOWLEDGMENTS

The authors' work was funded by the NIDA Intramural Research Program (G.S. and T.A.S.) and the Human Frontiers Science Program (Y.N.).

REFERENCES

Apicella, P. (2007). Trends Neurosci. *30*, 299–306.

Bertran-Gonzalez, J., Chieng, B.C., Laurent, V., Valjent, E., and Balleine, B.W. (2012). PLoS ONE *7*, e53195.

Bradfield, L.A., Bertran-Gonzalez, J., Chieng, B., and Balleine, B.W. (2013). Neuron *79*, this issue, 153–166.

Dickinson, A., and Balleine, B.W. (1994). Anim. Learn. Behav. *22*, 1–18.

Gershman, S.J., and Niv, Y. (2010). Curr. Opin. Neurobiol. *20*, 251–256.

Gershman, S.J., Blei, D.M., and Niv, Y. (2010). Psychol. Rev. *117*, 197–209.

Morris, G., Arkadir, D., Nevet, A., Vaadia, E., and Bergman, H. (2004). Neuron *43*, 133–143.

Yin, H.H., Ostlund, S.B., Knowlton, B.J., and Balleine, B.W. (2005). Eur. J. Neurosci. *22*, 513–523.

Zhou, F.M., Wilson, C.J., and Dani, J.A. (2002). J. Neurobiol. *53*, 590–605.

Pursuing the Link between Neurons and Behavior

Douglas A. Ruff[1] **and Marlene R. Cohen**[1,*]
[1]Department of Neuroscience and Center for the Neural Basis of Cognition, University of Pittsburgh, Pittsburgh, PA 15260, USA
*Correspondence: cohenm@pitt.edu
http://dx.doi.org/10.1016/j.neuron.2013.06.045

Hohl et al. (2013) found that fluctuations in neuronal responses in the middle temporal area (MT) are correlated with variability in smooth pursuit eye movements. The pattern of neuron-behavior correlations constrains models of how sensory neurons guide behavior and establishes pursuit as an attractive model system for studying how sensory neurons guide behavior.

The way humans and animals respond to any sensory stimulus is unreliable. For example, an animal being pursued by a predator might sometimes run away and might other times lie still and hide. Some of this behavioral variability might come from variability in the way sensory stimuli are encoded in the brain. Neuronal responses are also variable: a given neuron in visual cortex, for example, will respond differently each time an animal views the same visual stimulus.

Over the past two decades, experimenters have capitalized on this variability to establish a link between the activity of neurons in different brain areas and specific behaviors. The earliest such study measured the relationship between motion-direction-selective neurons in the middle temporal area (MT) and monkeys' decisions in a motion-direction discrimination task that required the animals to determine in which of two opposite directions a random dot stimulus was moving (Britten et al., 1996). On repeated presentations of an identical stimulus, fluctuations in the activity of single MT neurons were weakly but consistently correlated with the monkeys' decisions. On trials in which a neuron tuned for upward motion fired more than its average, the monkey was more likely to report seeing upward than downward motion.

Since that initial study, correlations between the fluctuations in the responses of individual neurons and behavior (typically called choice probability for discrimination tasks or detect probability for detection tasks) have been observed in a variety of sensory areas and behavioral tasks (for review, see Nienborg et al., 2012; Parker and Newsome, 1998). The existence of such neuron-behavior correlations, when combined with data from more causal experimental methods like pharmacology, lesions, or electrical stimulation, can provide evidence that those neurons are part of the neural mechanisms underlying specific percepts or behaviors (Parker and Newsome, 1998).

Using neuron-behavior correlations (or other experimental methods) to infer the computation that downstream areas perform to decode sensory information from areas like MT has been much more difficult, however. This difficulty has at least three sources. (1) The relationship between any one neuron's activity and behavior is typically weak and noisy. This is expected because a large number of

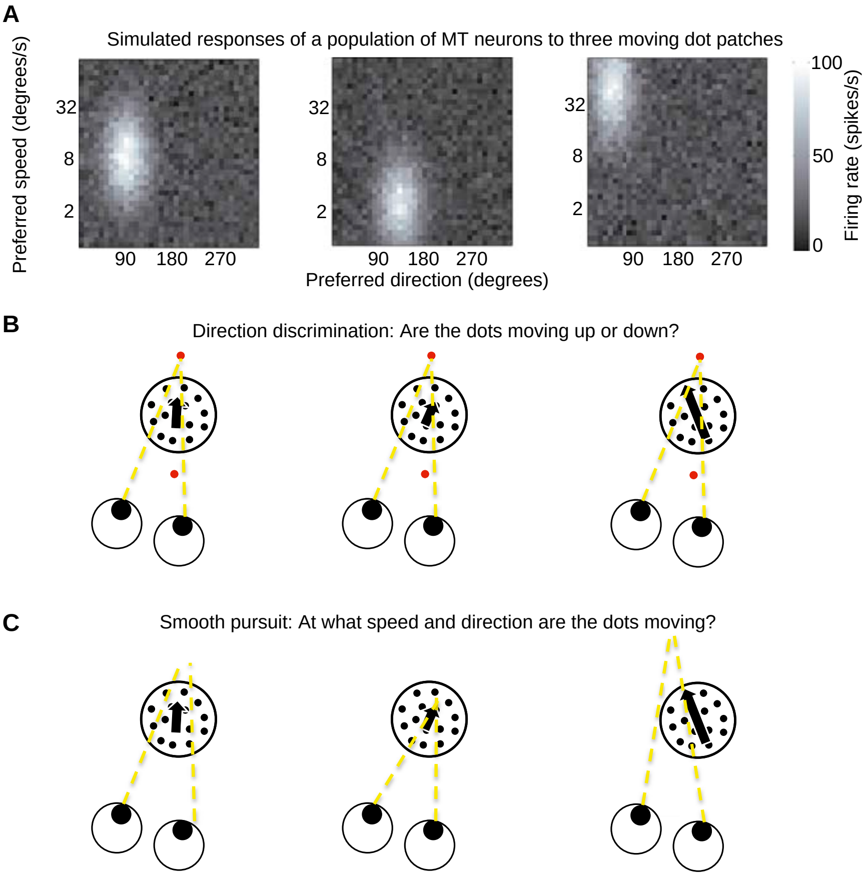

Figure 1. Smooth Pursuit Eye Movements, Unlike Responses in Discrimination, Differentiate between Similar Visual Stimuli

(A) Simulated responses of a population of MT neurons to stimuli moving upward at medium speed (left panel), slightly to the right of upward at low speed (middle panel), or slightly to the left of upward at high speed (right panel).

(B) In the direction discrimination task of Britten and colleagues (1996), behavioral responses to all three stimuli would be identical upward eye movements.

(C) In the smooth pursuit task of Hohl et al. (2013), behavioral responses differentiate between the stimuli, providing richer behavioral measurements with which to compare MT responses.

neurons in multiple brain areas likely contribute to any behavior, but it makes neuron-behavior correlations difficult to measure and interpret. (2) Neuron-behavior correlations are highly influenced by, and in some cases arise solely because of, variability that is shared among groups of neurons (Nienborg and Cumming, 2010). If the firing rates of many neurons rise and fall together, the responses of any one neuron will be correlated with behavior because its fluctuations reflect the activity of a large population. (Such shared variability is typically quantified as correlations between the trial-by-trial fluctuations between pairs of neurons and referred to as spike count correlation or noise correlation.) This shared variability makes it possible to observe neuron-behavior correlations, but it can also make such correlations arise artifactually: a neuron's response may be correlated with behavior even if it is not involved in the underlying computation if its variability is shared with neurons that contribute to the behavior. (3) Neuron-behavior correlations are influenced by variability in external factors such as the visual stimuli used, the difficulty of the task, or aspects of the animal's cognitive state such as its motivation level. Because neuron-behavior correlations are typically measured in one neuron per experimental session, day-to-day variability in these factors might cloud the dependence of these measurements on factors such as the neuron's tuning.

These problems can be mitigated by using an experimental system for which the stimuli, psychophysical task, sensory responses, motor system, and behavioral output have been well characterized. Decision-making in the direction-discrimination task of Britten, Newsome, and colleagues fits many of these criteria (Parker and Newsome, 1998). Even so, neuron-behavior correlations in this and other discrimination and detection tasks have had limited utility for understanding the algorithm by which information is read out from sensory areas.

The limitation arises in part because, although neuronal responses vary over a large range, the behavioral output in these tasks is very reduced. MT neurons, for example, carry information about the motion direction, speed, binocular disparity, size, and location of visual stimuli (Born and Bradley, 2005), but subjects in the direction-discrimination task must simply report whether they saw upward or downward motion. Because the space of possible responses to a moving stimulus is reduced to only two options, many algorithms for reading out information from MT would yield identical performance on the direction-discrimination task and identical patterns of neuron-behavior correlations.

Considering how populations of MT neurons respond to slightly different visual stimuli can reveal how difficult it is to infer readout algorithms from tasks with a binary behavioral output. The left panel of Figure 1A shows responses of a simulated population of MT neurons to a stimulus moving upward at about 8 deg/s. When performing the direction-discrimination task of Britten and colleagues (1996), one could correctly conclude that the motion was more upward than downward using many different algorithms to read out the population of MT neurons. These potential algorithms include determining the direction tuning of the most active cells, comparing the average responses of all neurons tuned for upward motion with all neurons tuned for downward motion regardless of preferred speed, comparing the responses of the upward- and downward-preferring neurons with preferred speeds of 8 deg/s, or using a number of other algorithms. Each of these algorithms would lead to identical upward choices in the direction discrimination task for many other stimuli, including a stimulus moving slightly to the right of up at a low speed (Figure 1A, middle panel) or a stimulus moving slightly to the left of upward at high speed (Figure 1A, right).

These algorithms would also lead to qualitatively indistinguishable neuron-behavior correlations in a discrimination task because in MT (and throughout visual cortex), neurons with similar tuning typically have more shared variability than neurons with dissimilar tuning (Cohen and Kohn, 2011; Huang and Lisberger, 2009). Under all of the algorithms, the monkey would report upward motion when some subset of neurons with near-upward preferred directions fired more than a subset of downward-preferring neurons. On average, neurons with near-upward preferred directions share more variability with each other than with downward-preferring neurons, regardless of whether they actually contribute to the decision. Therefore, upward choices would be associated with high firing rates from upward-preferring neurons and low firing rates from downward-preferring neurons under all of those readout algorithms (see also Nienborg et al., 2012; Shadlen et al., 1996), making it impossible to differentiate between them.

Hohl et al. (2013), in this issue of *Neuron*, realized that these problems using neuron-behavior correlations to infer a readout algorithm would be mitigated in a task with a richer behavioral output. They trained monkeys to perform a step-ramp pursuit task that required the animals to estimate the direction and speed of a moving stimulus and match it with their eye velocity. This task therefore requires subjects to identify, rather than categorize, the direction and speed of a moving stimulus. Indeed, the monkeys' eye speed and direction would differentiate between the three stimuli whose responses are simulated in Figure 1C.

In addition to having a behavioral output that reflects a continuous estimate of two aspects of visual motion (speed and direction), the smooth-pursuit system has the advantage that its neural substrates in both the sensory and motor domains are particularly well understood. In particular, the areas involved in planning and executing pursuit eye movements have been well studied by this group and others (for review, see Krauzlis, 2004; Lisberger, 2010). Their previous work suggests that very little behavioral variability originates in the motor system and suggests that the primary sources of behavioral variability are errors in encoding motion information, which probably occurs in MT (Osborne et al., 2005).

By measuring the correlation between fluctuations in the responses of MT neurons with different tuning properties and fluctuations in the velocity of the monkeys' eyes during smooth pursuit, the authors verified that variability in eye velocity is correlated with variability in MT. They went on to test the hypothesis that the pattern of neuron-behavior correlations would provide information about the algorithm by which motion information is read out from MT. They used known patterns of shared variability within MT (Huang and Lisberger, 2009) and their own data to simulate the patterns of neuron-behavior correlations under several different readout algorithms.

These methods allowed the authors to differentiate between potential models of the readout process. For example, maximum-likelihood or vector-averaging models predicted qualitatively different patterns of neuron-behavior correlations than normalization or optimal linear decoding models. Unlike in discrimination tasks, comparing neuron-behavior correlations among neurons whose tuning differed continuously along two dimensions (speed and direction) caused different models to make qualitatively different predictions.

Because the authors combined careful analysis with an experimental system that provided a rich data set against which to test different potential readout algorithms, the challenges faced by the authors reveal the areas in which other experimental and theoretical methods can complement this approach. As the authors point out, the models they tested perform computations based on simple equations, not with neural responses. In particular, there is good reason to think that divisive normalization (comparing a neuron's response to the summed response of a larger population; Carandini and Heeger, 2012) plays an important role in calculating velocity to guide pursuit. However, the neuronal mechanism underlying normalization and the way normalization affects response variability are unknown. An important difficulty of using neuron-behavior correlations (which are a measure of neuronal and behavioral variability) to infer readout mechanisms is that the potential mechanisms describe mean rates and ignore response variability. It is not clear how an arithmetic operation like division would affect variability when computed with spiking neurons.

Recent theoretical and experimental advances may allow future studies to build on the work of Hohl et al. (2013). For example, it would be interesting to see how circuit models predict computations like normalization will affect neuron-behavior (or neuron-neuron) correlations. Incorporating neuron-to-neuron variability into these models will also be important: recent work has shown that variability in something as simple as peak firing rate can dramatically change the effect of shared variability on the amount of information a group of neurons encodes (Ecker et al., 2011). Most circuit models predict different roles for excitatory and inhibitory neurons, and experimental advances like optogenetics might make it possible to measure neuron-behavior correlations for different cell types. Because neuron-behavior correlations depend so critically on the extent to which response variability is shared among neurons (Nienborg and Cumming, 2010; Shadlen et al., 1996), measuring shared variability among different cell types and between the brain areas known to be involved in sensing motion and planning and generating eye movements will also be important for inferring readout algorithms.

By using what is currently the experimental system best suited for this type of analysis, the study by Hohl et al. (2013) reveals the strengths and also the limitations of using variability to establish a link between neurons and behavior. Besides advancing our specific understanding of the relationship between MT neurons and pursuit eye movements, the authors have made important testable predictions that will guide future work. The recent explosion of new experimental techniques makes it possible to address questions about the relationship between sensory neurons and behavior in new ways, but it has also highlighted the need for an established psychophysical and neuronal system in which to do so. The study by Hohl et al. (2013) makes a compelling case for using their experimental system to pursue these questions.

REFERENCES

Born, R.T., and Bradley, D.C. (2005). Annu. Rev. Neurosci. *28*, 157–189.

Britten, K.H., Newsome, W.T., Shadlen, M.N., Celebrini, S., and Movshon, J.A. (1996). Vis. Neurosci. *13*, 87–100.

Carandini, M., and Heeger, D.J. (2012). Nat. Rev. Neurosci. *13*, 51–62.

Cohen, M.R., and Kohn, A. (2011). Nat. Neurosci. *14*, 811–819.

Ecker, A.S., Berens, P., Tolias, A.S., and Bethge, M. (2011). J. Neurosci. *31*, 14272–14283.

Hohl, S.S., Chaisanguanthum, K.S., and Lisberger, S.G. (2013). Neuron *79*, this issue, 167–179.

Huang, X., and Lisberger, S.G. (2009). J. Neurophysiol. *101*, 3012–3030.

Krauzlis, R.J. (2004). J. Neurophysiol. *91*, 591–603.

Lisberger, S.G. (2010). Neuron *66*, 477–491.

Nienborg, H., and Cumming, B.G. (2010). Curr. Opin. Neurobiol. *20*, 376–381.

Nienborg, H., Cohen, M.R., and Cumming, B.G. (2012). Annu. Rev. Neurosci. *35*, 463–483.

Osborne, L.C., Lisberger, S.G., and Bialek, W. (2005). Nature *437*, 412–416.

Parker, A.J., and Newsome, W.T. (1998). Annu. Rev. Neurosci. *21*, 227–277.

Shadlen, M.N., Britten, K.H., Newsome, W.T., and Movshon, J.A. (1996). J. Neurosci. *16*, 1486–1510.

Not So Uncertain at Last: Locus Coeruleus and Decision Making

Emrah Duzel[1,2,3,*] **and Marc Guitart-Masip**[4]
[1]Institute of Cognitive Neuroscience, University College London, London, WC1N 3AR, UK
[2]Institute of Cognitive Neurology and Dementia Research, Otto-von-Guericke-University Magdeburg, Leipziger Strasse 44, 39120 Magdeburg, Germany
[3]German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Leipziger Strasse 44, 39120 Magdeburg, Germany
[4]Aging Research Center, Karolinska Institute, Stockholm 171 77, Sweden
*Correspondence: emrah.duezel@dzne.de
http://dx.doi.org/10.1016/j.neuron.2013.06.023

A report by Payzan-LeNestour et al. (2013) in this issue of *Neuron* shows that the human locus coeruleus, a brain stem nucleus containing cell bodies of noradrenergic neurons, dynamically tracks the level of uncertainty about knowledge of the environment while making decisions.

Our forecasts about the consequences of our decisions are often uncertain. In many instances, this uncertainty cannot be eliminated. A typical example is the weather forecast, where our mathematical models are inherently inaccurate. Nevertheless, because we know how bad our models are, we can adequately adapt and take sensible decisions by embracing this form of uncertainty. Such known, or “expected,” uncertainties shape our beliefs about the regularities in our natural and social environment.

A more challenging scenario occurs when rules in our environment unexpectedly change. One daunting source for such unexpected uncertainty is global climate change. It is clear that at some unpredictable and hence unexpected time in the not-so-distant future our current models will become quite inadequate and our forecasts more uncertain than they are now. When this occurs, we will need to rapidly recognize this state of increased uncertainty and learn new models that allow more reliable predictions. It is intuitively evident that the challenge for our brain is remarkable; it needs to distinguish whether the uncertainty is caused because our environment has changed or because we have not yet obtained enough samples (or observations) in an otherwise stable environment.

We don’t need to exhaust examples of natural disaster to understand that being able to rapidly adapt to “unknown unknowns“ or “unexpected uncertainties” is a key cognitive feat which expands to all aspects of decision making given the dynamic environment in which we live. A simple example from economic decision making is depicted in Figure 1.

Despite its ubiquitous importance, we know surprisingly little about how the human brain computes unexpected uncertainty and which brain mechanisms are recruited to adapt to it. In this issue of *Neuron*, Payzan-LeNestour et al. (2013) have now taken a big leap to close this gap combining a formal treatment of the different sources of uncertainty (also see Yu and Dayan, 2005) with fMRI. As depicted in Figure 1, expected uncertainty (or risk) is the irreducible entropy in the outcome probabilities of a given option. Another source of uncertainty is estimation uncertainty (or ambiguity) which results from the lack of knowledge about the outcome probabilities, e.g., when the options have not been sampled enough. Finally, unexpected uncertainty results from sudden changes in the outcome probabilities, which calls for a reset in the learning process. Whereas previous neuroimaging studies have delineated the neuronal circuits involved in tracking