memory content stored in the cortex (Teyler and DiScenna, 1986). According to this account, memories expressed via activation of hippocampal indices or, artificially, via direct activation of cortical engram cells should not differ in quality. That is, the same content is being accessed, albeit via different routes. Alternatively, others argue that, along with containing an index, the information in the hippocampus necessarily includes at least some content that is not present in the cortex (for example, contextually dense or highly spatial details) (Winocur and Moscovitch, 2011). Therefore, according to this account, whether or not the hippocampus contributes to expression does make a difference in the quality of the retrieved memory. A fear memory expressed via activation of hippocampal indices should retain its contextually rich and detailed nature. In contrast, direct activation of cortical engram cells will lead to expression of a fear memory that is necessarily less detailed and more gist-like in quality. In fear conditioning studies, memory quality has most often been assessed by comparing freezing levels in trained versus similar contexts. However, since the artificial recall is already assessed in a neutral context in the Cowansage et al. (2014) study, these types of context generalization experiments are not possible here. This particular debate is destined to continue, and it is our hope that the creative application of new tools will also shed light on this question.

REFERENCES

Cowansage, K.K., Shuman, T., Dillingham, B.C., Chang, A., Golshani, P., and Mayford, M. (2014). Neuron *84*, this issue, 432–441.

Denny, C.A., Kheirbek, M.A., Alba, E.L., Tanaka, K.F., Brachman, R.A., Laughman, K.B., Tomm, N.K., Turi, G.F., Losonczy, A., and Hen, R. (2014). Neuron *83*, 189–201.

Eichenbaum, H. (2000). Nat. Rev. Neurosci. *1*, 41–50.

Frankland, P.W., and Bontempi, B. (2005). Nat. Rev. Neurosci. *6*, 119–130.

Liu, X., Ramirez, S., Pang, P.T., Puryear, C.B., Govindarajan, A., Deisseroth, K., and Tonegawa, S. (2012). Nature *484*, 381–385.

Squire, L.R., Stark, C.E., and Clark, R.E. (2004). Annu. Rev. Neurosci. *27*, 279–306.

Tanaka, K.Z., Pevzner, A., Hamidi, A.B., Nakazawa, Y., Graham, Y., and Wiltgen, B.J. (2014). Neuron *84*, this issue, 347–354.

Teyler, T.J., and DiScenna, P. (1986). Behav. Neurosci. *100*, 147–154.

Wheeler, A.L., Teixeira, C.M., Wang, A.H., Xiong, X., Kovacevic, N., Lerch, J.P., McIntosh, A.R., Parkinson, J., and Frankland, P.W. (2013). PLoS Comput. Biol. *9*, e1002853.

Winocur, G., and Moscovitch, M. (2011). J. Int. Neuropsychol. Soc. *17*, 766–780.

Keeping an Eye on Cortical States

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Membrane potential recordings in awake mice have correlated cortical state with locomotion and whisker movements. In this issue of *Neuron*, Reimer et al. (2014) now reveal that pupil dilation in stationary mice equally signals a change in cortical state and an enhancement of visual processing.

Sensory processing and perception are not simply a passive detection of stimuli by the nervous system; in animals that are awake and behaving, it is an active process and a highly integrative one. The peripheries of our sensory systems are constantly engaged, whether we realize it or not: eyes scan, hands manipulate, noses sniff, tongues roll. Although we rarely use them, we even have muscles to move our ears—maybe the vestige of some ancient mechanism to reposition them and capture more sound. When sensory input reaches the CNS, it is integrated with sensory signals of other modalities and a wide range of internally generated signals including copies of motor commands, memories, arousal, and attention. Understanding where, how, and why sensory integration occurs in the brain is a grand challenge for neuroscience.

Nowhere is the integration of external and internal neural signals more apparent than in the mammalian neocortex. The very first electroencephalogram (EEG) recordings of electrical activity from awake animals and the human brain revealed patterns of spontaneous activity that correlated to different behavioral states but seemed unrelated to direct sensory input. This suggested that the neocortex would be a good place to study changes in brain states and their relation to sensory integration, in the hope of finding cellular correlates possibly in identified populations of neurons. This was theoretically possible, but anesthesia was typically used to immobilize the animal. It was a dilemma if you were interested in waking brain states.

The head-restrained mouse preparation came to the rescue and is now in widespread use. This provides the stability

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necessary to make whole-cell membrane potential recordings and functional imaging from cortical neurons while the mice are awake and behaving. These recordings have revealed that cortical activity is dynamically regulated as mice engage in different types of behavior. Large-amplitude, low-frequency fluctuations represent a resting or synchronized state and dominate the membrane potential in stationary mice. But their amplitude is reduced during movement (an active or desynchronized state). Similar correlations between movement and membrane potential have been recorded in primary somatosensory, auditory, and visual cortical areas (Bennett et al., 2013; Polack et al., 2013; Poulet and Petersen, 2008; Schneider et al., 2014). Recently, Harris and Thiele (2011) proposed that changes in cortical state during wakefulness may reflect more than general cortical arousal: they may also be involved with modes of cortical processing underlying selective attention. Changes of pupil size are a classic means of measuring visual attention in primates. In the present issue of *Neuron*, Reimer et al. (2014) show that pupil size in mice correlates to a change in the state of visual cortex, even in resting mice.

Reimer et al. (2014) combined whole-cell, membrane potential recordings from primary visual (V1) and somatosensory (S1) cortical layer 2/3 neurons with filming of awake mice on a trackball. This led to the key observation that their pupils dilate during running, and this correlates to an active cortical state. Intriguingly, even in periods without overt body or whisker movement, the pupil size continued to fluctuate, undergoing smaller changes in diameter. These minute movements correlated to a switch from resting to active cortical states.

What generates these rapid changes in state? The simplest explanation might be that when pupils dilate, more information comes streaming in through the eyes, activating cortical neurons. This hypothesis could be tested in a strain of mice with degenerated retinal ganglion cells and reduced visual responsiveness. If light were the cause, such mice should not exhibit any correlation between change in pupil size and cortical state. However, recordings in mutant mice told the same story, the correlation remained. These results reflect findings in the mouse whisker system, where changes in cortical state persist even in the absence of somatosensory input from the whiskers (Poulet and Petersen, 2008; Poulet et al., 2012).

Thus, cortical states in mice are not simply responses to sensory stimuli but can be generated internally within the brain. Recent years have seen rapid progress in unraveling the cell-specific mechanisms and networks involved in generating the activated cortical state in awake mice. Particular roles are played by the thalamus, neuromodulatory systems, the brain stem reticular formation, and motor cortex (Bennett et al., 2014; Pinto et al., 2013; Polack et al., 2013; Poulet et al., 2012; Schneider et al., 2014; Zagha et al., 2013). What remains to be done is to piece these circuits together and link them to the control of pupil dilation.

Primary sensory cortical circuits are composed of different excitatory glutamatergic and inhibitory GABAergic cell types arranged into six layers. Reimer et al. (2014) focused on supragranular layer 2/3, and asked, how similar is state change during pupil dilation between different layer 2/3 cell types? Reimer et al. (2014) used in vivo two-photon microscopy to target their recordings to two types of layer 2/3 inhibitory neurons, the vasoactive intestinal peptide (VIP), and somatostatin (SOM)-expressing GABAergic interneurons. VIP-expressing neurons were depolarized during running, while the majority of SOM-expressing neurons were hyperpolarized. Both types of cells followed a similar pattern of response during fast pupil dilatations, when the mice were not running. Future studies will, literally, delve deeper into the cortex and characterize cortical states across different cell types in granular and infragranular layers. These data will provide essential blocks to help build our understanding of cortical state change. This will be aided by visually targeted whole-cell recordings from deep layer cortical neurons, which will soon be possible thanks to improvements in the depth resolution of two-photon microscopy.

Cortical sensory responses are strongly correlated with the state of the cortex across different sensory systems, but the relationship is not simple. In the somatosensory and auditory system, sensory responses are reduced in amplitude and show less adaptation during active states as compared to resting states (Castro-Alamancos, 2004; Otazu et al., 2009; Schneider et al., 2014; Zhou et al., 2014). In contrast, in the visual cortex, sensory responses are enhanced during active states (Niell and Stryker, 2010; Bennett et al., 2013; Polack et al., 2013). There are several possible reasons for these discrepancies: active cortical states may influence different sensory modalities in different ways, they may also be associated with distinct subcortical processing; differences may also derive from stimulus design and the ongoing behavior. Reimer et al. (2014) used functional Ca^{2+} imaging of layer 2/3 neurons to measure the impact of the activated state during pupil dilation on visual sensory processing. About one-third of the neurons they recorded were tuned to a specific, "preferred" direction of a drifting, oriented-grating stimulus. During running, tuned cells showed an increase in the sensory response amplitude to all directions of visual stimulation. Sensory responses during dilation in stationary mice, however, were only enhanced to stimuli of a neuron's preferred direction. Moreover, sensory responses during pupil dilation were more reliable and less correlated than during pupil constriction. Similar changes were seen to more natural visual stimuli. Sensory processing was therefore enhanced during pupil dilation in resting mice.

This intriguing finding implies that there may be different forms of the activated state with distinct effects on sensory processing. It raises the questions: just how similar are the activated states during pupil dilation in resting compared to moving mice? Are they driven by different circuit mechanisms? Given the possibility of multiple forms of activated state, a critical issue that needs addressing is the definition of the term "state" itself. It suggests that some feature of cortical activity, like the spike timing across nearby neurons or the low-frequency power of the local field potential, shows a distinct distribution between different behavioral states. One intracellular recording study in awake rats, however, has demonstrated how widely cortical states vary between animals (Okun et al., 2010). Neuromodulatory, subcortical, and cortical inputs to cortical neurons are mixed in many ways, producing what might be a continuum of states that are likely influenced by changes in movement, what has motivated the behavior, and expectation

about the outcome of the behavior. Cortical states in mice could also be far more anatomically restricted than we currently appreciate. At a broad level, neuromodulators or thalamic input might set the tone for global changes in cortical state, hence the active states in S1 and V1 during pupil dilation. On top of this, subcircuits might be locally activated through the activity of corticocortical and/or thalamocortical connections. Activation could therefore be targeted to subcircuits processing features of the environment that are relevant to behavior—a situation that would again closely resemble models of selective attention (Harris and Thiele, 2011). A full description of waking cortical states in mice will require a deeper analysis of multiregion recordings in combination with high-resolution monitoring of multiple limbs and sense organs.

The correlation of activated cortical states with pupil dilation in the absence of movement is an important observation, but what is its role in visual perception? Two recent studies have shown that visual perception is improved in running mice (Bennett et al., 2013) and during activated states induced by optogenetic stimulation of cholinergic axons in visual cortex (Pinto et al., 2013). It will now be exciting to examine visual perception during pupil dilation in stationary and running mice. The combination of high-resolution behavioral monitoring with neuronal recordings and manipulations in awake, head-restrained mice is opening a window onto a bigger vista—an understanding of the roles of specific types of cortical neurons in the internal control of sensory processing and perception.

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REFERENCES

Bennett, C., Arroyo, S., and Hestrin, S. (2013). Neuron *80*, 350–357.

Bennett, C., Arroyo, S., and Hestrin, S. (2014). Neuron *83*, 260–261.

Castro-Alamancos, M.A. (2004). Neuron *41*, 455–464.

Harris, K.D., and Thiele, A. (2011). Nat. Rev. Neurosci. *12*, 509–523.

Niell, C.M., and Stryker, M.P. (2010). Neuron *65*, 472–479.

Okun, M., Naim, A., and Lampl, I. (2010). J. Neurosci. *30*, 4440–4448.

Otazu, G.H., Tai, L.-H., Yang, Y., and Zador, A.M. (2009). Nat. Neurosci. *12*, 646–654.

Pinto, L., Goard, M.J., Estandian, D., Xu, M., Kwan, A.C., Lee, S.-H., Harrison, T.C., Feng, G., and Dan, Y. (2013). Nat. Neurosci. *16*, 1857–1863.

Polack, P.-O., Friedman, J., and Golshani, P. (2013). Nat. Neurosci. *16*, 1331–1339.

Poulet, J.F.A., and Petersen, C.C.H. (2008). Nature *454*, 881–885.

Poulet, J.F.A., Fernandez, L.M.J., Crochet, S., and Petersen, C.C.H. (2012). Nat. Neurosci. *15*, 370–372.

Reimer, J., Froudarakis, E., Cadwell, C.R., Yatsenko, D., Denfield, G.H., and Tolias, A.S. (2014). Neuron *84*, this issue, 355–362.

Schneider, D.M., Nelson, A., and Mooney, R. (2014). Nature *513*, 189–194.

Zagha, E., Casale, A.E., Sachdev, R.N.S., McGinley, M.J., and McCormick, D.A. (2013). Neuron *79*, 567–578.

Zhou, M., Liang, F., Xiong, X.R., Li, L., Li, H., Xiao, Z., Tao, H.W., and Zhang, L.I. (2014). Nat. Neurosci. *17*, 841–850.

Concept Cells through Associative Learning of High-Level Representations

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In this issue of *Neuron*, Quian Quiroga et al. (2014) show that neurons in the human medial temporal lobe (MTL) follow subjects' perceptual states rather than the features of the visual input. Patients with MTL damage however have intact perceptual abilities but suffer instead from extreme forgetfulness. Thus, the reported MTL neurons could create new memories of the current perceptual state.

Neurons along the ventral visual pathway respond with varying degrees of specificity to subjects' perceptual decisions. In situations where the visual input and the subjective percept can be experimentally dissociated, most neurons in early visual areas respond to low-level stimulus properties, whereas approximately 90% of neurons in higher-level inferotemporal (IT) cortex are modulated by the subjects' perceptual report (Logothetis, 1998). Neurons from area TE of IT feed into medial temporal lobe (MTL) structures that include the hippocampal formation and the entorhinal, perirhinal, and parahippocampal cortices (Suzuki and Eichenbaum, 2000). A new study in this issue of *Neuron* by Quian Quiroga et al. (2014) shows that "concept cells" in the human MTL closely follow subjective awareness.