synaptic strength lowers the number of spikes needed to reach a given level, effectively lowering the threshold. This model has growing experimental support. First, it is clear that cortico-stratial projections are involved in decision making (Znamenskiy and Zador, 2013). Second, human neuroimaging experiments have shown that the effective connectivity between cortex and striatum is correlated with decision-making thresholds (Green et al., 2012). This model is particularly intriguing given the known role of dopamine in modulating cortico-striatal connections and the growing understanding of dopamine's role in attention (Noudoost and Moore, 2011).

Finally, Luo and Maunsell's results highlight the advantage of building more complete models of behavior in order to understand the many facets of a task (Luo and Maunsell, 2015). In this case, signal detection theory led to a more complete understanding of the behavior and, thus, a more complete understanding of the neural correlates of attention. Similarly, exhaustive behavioral models have recently provided novel insights into the underlying neural mechanisms of decision making (Brunton et al., 2013). The brain exists to produce behavior and, therefore, understanding the brain should begin with complete descriptions of behavior.

REFERENCES

Brunton, B.W., Botvinick, M.M., and Brody, C.D. (2013). Science *340*, 95–98.

Carrasco, M. (2011). Vision Res. *51*, 1484–1525.

Cohen, M.R., and Maunsell, J.H.R. (2009). Nat. Neurosci. *12*, 1594–1600.

Fries, P., Reynolds, J.H., Rorie, A.E., and Desimone, R. (2001). Science *291*, 1560–1563.

Green, N., Biele, G.P., and Heekeren, H.R. (2012). J. Neurosci. *32*, 14942–14950.

Kinchla, R.A. (1992). Annu. Rev. Psychol. *43*, 711–742.

Lee, J., and Maunsell, J.H.R. (2010). J. Neurophysiol. *104*, 960–971.

Lo, C.-C., and Wang, X.-J. (2006). Nat. Neurosci. *9*, 956–963.

Luo, T.Z., and Maunsell, J.H.R. (2015). Neuron *86*, this issue, 1182–1188.

Miller, E.K., and Buschman, T.J. (2013). Curr. Opin. Neurobiol. *23*, 216–222.

Noudoost, B., and Moore, T. (2011). Trends Cogn. Sci. *15*, 585–591.

Posner, M.I., Snyder, C.R., and Davidson, B.J. (1980). J. Exp. Psychol. *109*, 160–174.

Reynolds, J.H., and Heeger, D.J. (2009). Neuron *61*, 168–185.

Reynolds, J.H., Pasternak, T., and Desimone, R. (2000). Neuron *26*, 703–714.

Znamenskiy, P., and Zador, A.M. (2013). Nature *497*, 482–485.

Cortical Cliques: A Few Plastic Neurons Get All the Action

Tania A. Seabrook[1] **and Andrew D. Huberman**[1,2,3,4,*]
[1]Department of Neurosciences, School of Medicine
[2]Neurobiology Section in the Division of Biological Sciences
[3]Department of Ophthalmology, School of Medicine
University of California, San Diego, La Jolla, CA 92093, USA
[4]Salk Institute for Biological Studies, La Jolla, CA 92037, USA
*Correspondence: ahuberman@ucsd.edu
http://dx.doi.org/10.1016/j.neuron.2015.05.039

Adjustments in neural activity can drive cortical plasticity, but the underlying circuit components remain unclear. In this issue of *Neuron*, Barnes et al. (2015) show that visual deprivation-induced homeostatic plasticity invokes specific changes among select categories of V1 neurons.

The brain has evolved extensive mechanisms to maintain stable activity levels in the face of fluctuating synaptic drive. Indeed, when these mechanisms fail, devastating consequences can occur such as runaway excitation and epilepsy. At the same time, there are a number of instances in which neural circuits need to greatly increase their levels of activation, such as during sensory plasticity. How does the brain reconcile these seemingly contradictory needs? One way is through homeostatic plasticity or the ability to fine tune the excitability of specific neuronal networks (Turrigiano, 2012). In this issue of *Neuron*, Barnes et al. (2015) addressed whether homeostatic recovery of cortical activity in response to visual deprivation reflects the involvement of specific subsets of neurons and how those cells contribute to the plasticity of the larger circuits in which they are embedded.

Classic paradigms for manipulating sensory drive and cortical plasticity, such as eye-lid suture, dark rearing, or retinal lesions, have been shown to trigger homeostatic regulation of firing rate in the developing (Desai et al., 2002; Hengen et al., 2013) and in the mature (Keck et al.,

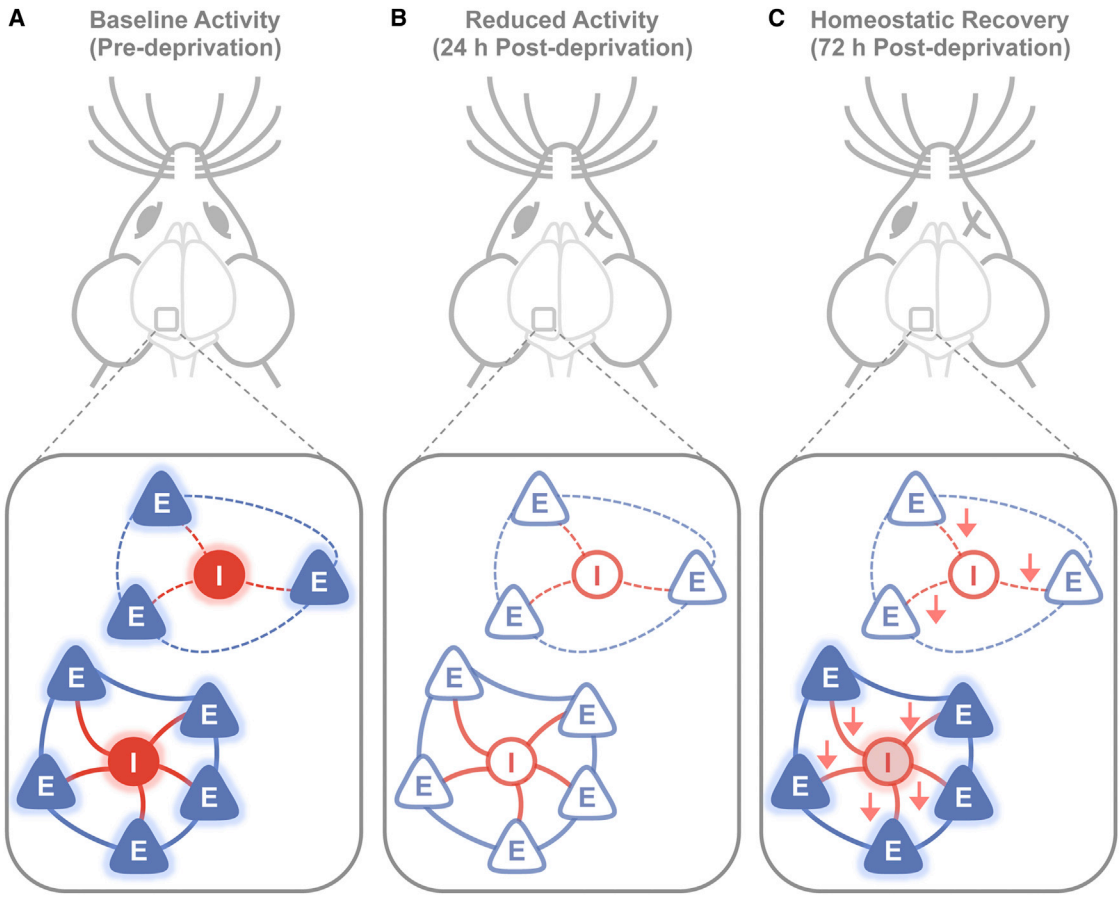

Figure 1. Correlated Activity of Neuronal Subnetworks and Reduced Synaptic Inhibition Drive Homeostatic Recovery after Sensory Deprivation

Schematic of subnetworks of excitatory (E, blue) and inhibitory (I, red) neurons in layer 2/3 of visual cortex (A) before, (B) 24 hr after, and (C) 72 hr after monocular enucleation. Solid triangles and circles represent active neurons. Open triangles and circles indicate neurons rendered inactive by visual deprivation. Lines indicate correlations for recovering (solid lines) and inactive (dashed lines) subnetworks. Arrows indicate a decrease in synaptic inhibition.

2013) neocortex. While there is general agreement that both excitatory and inhibitory mechanisms are at play, until recently it was challenging to tackle the cell-type-specific dynamics of homeostatic plasticity in the intact brain—in large part because such events occur over a period of several days or longer. However, due to recent advances in optical and other neuronal recording techniques, it is now possible to monitor the activity of large populations of identified cells in intact, awake behaving animals and to correlate the observed changes with molecular, connectivity, or structural analysis post hoc (e.g., Bock et al., 2011; Ko et al., 2013).

In this issue of *Neuron*, Barnes et al. (2015) used a powerful combination of in vivo and ex vivo approaches to explore the cell-type-specific changes that underlie sensory-driven homeostatic plasticity in the visual system. The authors imaged the activity of mouse primary visual cortex (V1) neurons expressing the genetically encoded calcium indicator GCaMP5 in awake behaving mice while the mice viewed patterned stimuli. Using this approach they were able to chronically measure the activity of the same individual neurons located in layer 2/3 both before and after monocular enucleation. They noted that prior to any visual deprivation, V1 cells displayed heterogeneous profiles of calcium transient kinetics—some were very slow and some were fast—and they hypothesized that those differences represent excitatory versus inhibitory neurons, respectively. Indeed, by staining V1 for the inhibitory transmitter GABA after the conclusion of the imaging experiments, they were able to confirm that it was the inhibitory V1 neurons that had faster calcium kinetics. This gave them a nice handle on the ability to monitor these two general categories of cell types in vivo and thereby address the relative roles and timescales over which inhibitory and excitatory neurons contribute to homeostatic plasticity, as well as how those two forces interact.

Barnes et al. (2015) found that soon after monocular enucleation, the overall activity of cells in the region of V1 corresponding to the deprived-eye pathway initially plummeted but then recovered after 48–72 hr (summarized in Figures 1A–1C). By analyzing the activity profiles of individual neurons, however, they discovered that only a subset of layer 2/3 cells actually undergoes homeostatic recovery (Figure 1C). Many inhibitory neurons in V1 became and stayed inactive after deprivation, whereas others reduced

and then partially recovered their output but never back to their pre-deprivation levels. Thus, unlike the scenario in developing V1 (Hengen et al., 2013), inhibitory neurons in adult V1 do not undergo homeostatic recovery. These findings indicate that sensory deprivation in adulthood results in lower overall levels of inhibition. Barnes et al. (2015) confirmed this by performing whole-cell patch-clamp recordings of the inputs onto V1 excitatory neurons in acute slices. They found a reduction in the frequency of miniature inhibitory postsynaptic currents indicating that, indeed, there are fewer inhibitory synapses following monocular enucleation as compared to pre-deprivation.

Not surprisingly, Barnes et al. (2015) also observed that visual deprivation shifted the excitatory/inhibitory (E/I) balance toward excitation. In several deprivation-induced plasticity paradigms, reduced synaptic inhibition has been shown to precede excitatory changes (Chen et al., 2011; Keck et al., 2011; van Versendaal et al., 2012), thus Barnes et al. (2015) next explored the changes that excitatory V1 neurons underwent. They observed that ~50% of the excitatory neurons they imaged became inactive *and stayed inactive*, long after deprivation—i.e., they never recovered (Figures 1A–1C). However, other excitatory neurons recovered within ~72 hr after eye removal (Figure 1C). Barnes et al. (2015) referred to these neurons as "recovering cells." To separately examine the homeostatic mechanisms in recovering cells versus those that became and stayed inactive, they combined intracellular dye-filling of electrophysiologically recorded V1 neurons with immunolabeling for the activity marker c-Fos. They found that the presence of c-Fos expression in a neuron closely reflected the level of activity that cell displayed in vivo and thus was a good readout of highly active versus less active cells. Some V1 neurons were highly active after deprivation and expressed c-Fos, whereas most of the inactive V1 neurons did not express c-Fos. Interestingly, synaptic inhibition was reduced onto both the c-Fos-expressing and the c-Fos-negative groups of neurons. This suggests that diminished synaptic inhibition alone cannot explain the fact that some excitatory cells recover and others do not. This is a particularly novel finding given the large body of work pointing to inhibition as a major driving force for plasticity. Thus, Barnes et al. (2015) discovered that homeostatic recovery of activity in response to visual deprivation does not occur equally between excitatory versus inhibitory neurons, nor does it impact all excitatory neurons in the same way.

Why did some excitatory cells recover and others did not? In recent years, several groups have unveiled "subnetworks" of highly interconnected cortical neurons that are activated by common stimuli and/or input pathways (Ko et al., 2011; Miller et al., 2014; Yoshimura et al., 2005). Are cortical subnetworks also activated during adult homeostatic plasticity? Barnes et al. (2015) measured the correlation of GCaMP5 signals in V1 cells prior to enucleation and found that certain groups of these neurons tended to display synchronous activity. Remarkably, the subsets of excitatory neurons that they observed undergoing homeostatic recovery tended to be the same ones that participated in highly correlated networks at the outset of the experiment. In a similar and equally interesting vein, the excitatory neurons that *failed* to recover after deprivation tended to exhibit activity that, at the outset of the experiment (pre-deprivation), was correlated to other non-recovering cells (Figures 1A and 1C). These results were surprising given that, normally, sensory-driven cortical ensembles are highly dynamic—recruiting new cells and synaptic interactions depending on stimulus conditions (Miller et al., 2014). The findings of Barnes et al. (2015) argue that sensory deprivation-induced plasticity invokes relatively fixed groups of strongly correlated cells and interactions among them.

Barnes et al. (2015) also examined the correlations that existed between the excitatory and inhibitory groups of neurons and found that groups that were highly correlated prior to deprivation tended to remain so even after plasticity, albeit with the reduced levels of inhibition that exist compared to non-deprived conditions (Figure 1C). As a consequence of this, the subnetworks of excitatory neurons that recovered activity tended to be correlated with inhibitory neurons that managed to maintain some level of activity after deprivation (Figure 1C).

Barnes et al. (2015) also explored for evidence that other mechanisms such as synaptic scaling are involved in driving homeostatic recovery. They found no changes in miniature excitatory postsynaptic potential frequency or amplitude, spine size or density, or intrinsic excitability of V1 cells. That, coupled with the changes they did observe in select groups of highly correlated neurons (Figures 1A–1C), led them to the conclusion that local network activity plays a key role in the homeostatic recovery to sensory deprivation in adult V1. A critical next step for the field is to understand whether this network activity is not just reflective of, but necessary for, homeostatic plasticity and if so what feature(s) of the subnetworks are crucial. New techniques that allow for the selective activation and silencing of neurons based on their activity profiles (Guenthner et al., 2013; Packer et al., 2015) may be useful in this context by allowing replay or inhibition of the relevant members of highly active cortical subnetworks. Barnes et al. (2015) suggest that the interconnections between cells in a subnetwork or the common inputs they share might influence whether they can recover after deprivation. Therefore, it will also be important to identify differences among the sources of synaptic input to the recovering versus non-recovering cells. Furthermore, understanding how local subnetwork activity influences homeostatic synaptic plasticity may prove important for developing new therapeutic approaches to help re-establish broken neural circuits and treat neurological conditions and disorders.

REFERENCES

Barnes, S.J., Sammons, R.P., Jacobsen, R.I., Mackie, J., Keller, G.B., and Keck, T. (2015). Neuron *86*, this issue, 1290–1303.

Bock, D.D., Lee, W.C., Kerlin, A.M., Andermann, M.L., Hood, G., Wetzel, A.W., Yurgenson, S., Soucy, E.R., Kim, H.S., and Reid, R.C. (2011). Nature *471*, 177–182.

Chen, J.L., Lin, W.C., Cha, J.W., So, P.T., Kubota, Y., and Nedivi, E. (2011). Nat. Neurosci. *14*, 587–594.

Desai, N.S., Cudmore, R.H., Nelson, S.B., and Turrigiano, G.G. (2002). Nat. Neurosci. *5*, 783–789.

Guenthner, C.J., Miyamichi, K., Yang, H.H., Heller, H.C., and Luo, L. (2013). Neuron *78*, 773–784.

Hengen, K.B., Lambo, M.E., Van Hooser, S.D., Katz, D.B., and Turrigiano, G.G. (2013). Neuron *80*, 335–342.

Keck, T., Scheuss, V., Jacobsen, R.I., Wierenga, C.J., Eysel, U.T., Bonhoeffer, T., and Hübener, M. (2011). Neuron *71*, 869–882.

Keck, T., Keller, G.B., Jacobsen, R.I., Eysel, U.T., Bonhoeffer, T., and Hübener, M. (2013). Neuron *80*, 327–334.

Ko, H., Hofer, S.B., Pichler, B., Buchanan, K.A., Sjöström, P.J., and Mrsic-Flogel, T.D. (2011). Nature *473*, 87–91.

Ko, H., Cossell, L., Baragli, C., Antolik, J., Clopath, C., Hofer, S.B., and Mrsic-Flogel, T.D. (2013). Nature *496*, 96–100.

Miller, J.E., Ayzenshtat, I., Carrillo-Reid, L., and Yuste, R. (2014). Proc. Natl. Acad. Sci. USA *111*, E4053–E4061.

Packer, A.M., Russell, L.E., Dalgleish, H.W., and Häusser, M. (2015). Nat. Methods *12*, 140–146.

Turrigiano, G. (2012). Cold Spring Harb. Perspect. Biol. *4*, a005736.

van Versendaal, D., Rajendran, R., Saiepour, M.H., Klooster, J., Smit-Rigter, L., Sommeijer, J.P., De Zeeuw, C.I., Hofer, S.B., Heimel, J.A., and Levelt, C.N. (2012). Neuron *74*, 374–383.

Yoshimura, Y., Dantzker, J.L., and Callaway, E.M. (2005). Nature *433*, 868–873.

Cortical Sensorimotor Reverberations

Sylvain Crochet[1,*] and Carl C.H. Petersen[1,*]
[1]Laboratory of Sensory Processing, Brain Mind Institute, Faculty of Life Sciences, École Polytechnique Fédérale de Lausanne (EPFL), Lausanne 1015, Switzerland
*Correspondence: sylvain.crochet@epfl.ch (S.C.), carl.petersen@epfl.ch (C.C.H.P.)
http://dx.doi.org/10.1016/j.neuron.2015.05.030

In this issue of *Neuron*, Manita et al. (2015) report that reciprocal excitatory interactions between higher-order frontal motor cortex and primary sensorimotor cortex might play a key role in hindlimb sensory perception in mice.

Sensory percepts are not out there in the world around us; rather, they are internal constructs, actively generated by neurons in the brain. Sensory perception can be viewed as an active process in which motor commands move sensors to selectively acquire sensory information as neurons actively construct subjective sensory percepts based on that information. For instance, humans actively initiate eye movements to foveate on specific parts of the visual world around us and palpate objects with hands and fingers to sense the texture and shape of objects. These internal motor commands control important aspects about what sensory information the brain will receive. This incoming sensory information is processed in a highly experience-dependent and context-dependent manner to give rise to our subjective reality. Subjective percepts are based not only on the current incoming sensory information, but also on expectations, current behavioral goals, and previous experiences in the near or distant past. Sensory percepts might operationally be considered as learned, context-dependent associations arising from sensorimotor interactions with our immediate environment. Thus, sensory perception, which at first glance seems intuitively simple, is in fact a very complex phenomenon. In order to understand sensory perception, we need to look closely at learning, context, and sensorimotor interactions. Given this complexity, one might suspect that interactions between many different brain areas, including at least sensory and motor cortices, might be of fundamental importance for sensory perception. In this issue of *Neuron*, Manita et al. (2015) find that interactions between higher-order frontal cortex and primary sensorimotor cortex appear to be necessary for accurate hindpaw tactile sensory perception in mice.

Manita et al. (2015) use voltage-sensitive dye imaging of dorsal mouse cortex (Ferezou et al., 2007) to localize a region (M2) in frontal cortex activated by hindpaw stimulation in a manner dependent upon activity in hindpaw S1/M1 (hindpaw S1 and M1 are thought to be largely colocalized in rodents) (Figure 1A). Adeno-associated virus expressing GFP for anterograde tracing revealed direct excitatory projections from hindpaw S1/M1 to M2, which could mediate the sensory response in M2. However, in contrast to the ~6 ms delay between activity in sensory and motor cortex upon whisker stimulation, consistent with a monosynaptic relay (Ferezou et al., 2007; Matyas et al., 2010), the delay of the M2 response observed by Manita et al. (2015) was much longer (~30 ms in voltage-sensitive dye imaging and ~50 ms in electrophysiological recordings of action potential firing) (Figure 1B). The circuits functionally connecting hindpaw S1/M1 and M2 may therefore be more complex than monosynaptic excitation.

Having localized hindpaw M2, Manita et al. (2015) investigated the role of M2 in top-down control of sensory processing in S1/M1, with which it is reciprocally connected through long-range excitatory glutamatergic projections. The early activity evoked by hindlimb stimulation in S1/M1 was followed by a second late excitatory component, which could be suppressed by pharmacological inactivation of M2. The sequence of hindlimb-evoked activity therefore appears to consist of at least three parts: (i) thalamocortical excitation of S1/M1, (ii) S1/M1-dependent excitation of M2, and (iii)