based was proposed as a possible biophysically plausible implementation of a normalization operation (Carandini and Heeger, 1994), such as the one in Busse et al.

What biophysical mechanisms may be responsible for divisive gain control? Different studies have addressed this question. One candidate mechanism is short-term synaptic depression (Freeman et al., 2002). Widely tuned, visually evoked cortical shunting inhibition may also contribute to contrast normalization. However, intracellular recording studies in vivo of inhibitory tuning curve profiles and changes in evoked conductance in response to plaid stimuli (Priebe and Ferster, 2008) found no support for this view.

Divisive gain control might support higher-level aspects of visual processing beyond the responses of V1 neurons to relatively simple stimuli. Some studies debate the role of normalization in redundancy reduction and efficient coding (Schwartz and Simoncelli, 2001; Shi et al., 2006), while others suggest that changes in visual processing (sensitivity, gain, etc.) induced by shifts in attention may be explained by a modulation of the input signal by an attentional filter followed by normalization (Reynolds and Heeger, 2009).

Clearly, the functional implications of contrast gain control for downstream visual areas and the contribution of different biophysical mechanisms to its implementation are still open questions. Hopefully, further research and analysis of how large populations process complex stimuli may shed light on these issues.

REFERENCES

Albrecht, D.G., and Geisler, W.S. (1991). Vis. Neurosci. *7*, 531–546.

Busse, L., Wade, A.R., and Carandini, M. (2009). Neuron *64*, this issue, 931–942.

Carandini, M., and Heeger, D.J. (1994). Science *264*, 1333–1336.

Ferster, D., and Miller, K.D. (2000). Annu. Rev. Neurosci. *23*, 441–471.

Freeman, T.C.B., Durand, S., Kiper, D.C., and Carandini, M. (2002). Neuron *35*, 759–771.

Grinvald, A., and Hildesheim, R. (2004). Nat. Rev. Neurosci. *5*, 874–885.

Grinvald, A., Lieke, E.E., Frostig, R.D., and Hildesheim, R. (1994). J. Neurosci. *14*, 2545–2568.

Heeger, D.J. (1992). Vis. Neurosci. *9*, 181–197.

Hubel, D.H., and Wiesel, T.N. (1962). J. Physiol. *160*, 106–154.

Priebe, N.J., and Ferster, D. (2006). Nat. Neurosci. *9*, 552–561.

Priebe, N.J., and Ferster, D. (2008). Neuron *57*, 482–497.

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

Schwartz, O., and Simoncelli, E.P. (2001). Nat. Neurosci. *4*, 819–825.

Sclar, G., and Freeman, R.D. (1982). Exp. Brain Res. *46*, 457–461.

Shi, J., Wielaard, J., and Sajda, P. (2006). Conf. Proc. IEEE Eng. Med. Biol. Soc. *1*, 4991–4994.

Sit, Y.F., Chen, Y., Geisler, W.S., Miikkulainen, R., and Seidmann, E. (2009). Neuron *64*, this issue, 943–956.

Discreet Charm of the GABAergic Bourgeoisie: Superconnected Cells Conduct Developmental Symphonies

Marianne Case[1,*] and Ivan Soltesz[1,*]
[1]Department of Anatomy and Neurobiology, University of California, Irvine, Irvine, CA 92697, USA
*Correspondence: marianne.case@uci.edu (M.C.), isoltesz@hs.uci.edu (I.S.)
DOI 10.1016/j.neuron.2009.12.013

In an exciting study in the December 4th issue of *Science*, Bonifazi and colleagues demonstrated the existence and importance of exceedingly rare but unusually richly connected cells in the developing hippocampus. Manipulating the activity of single GABAergic hub cells modulated network activity patterns, demonstrating their importance for coordinating synchronous activity.

Much to the chagrin of our latte-drinking, sushi-eating, Volvo-driving liberal friends all over, networks in the real world are decidedly not egalitarian but rather aristocratic in nature. Indeed, the disproportionate influence of rare superconnected hubs is well-known in technological, biological, and social networks, including aviation grids (such as LAX and JFK), biochemical reaction pathways (such as pyruvate and ATP), and the proverbial old boys' networks. For neuroscience in particular, hub-like connectors are considered to be of great potential significance because networks with such aristocratic flavor have been predicted by theoretical studies to represent a clever compromise between fast computation, economy of wiring, and robustness against random deletions (Buzsáki et al., 2004; Bullmore and Sporns, 2009). However, while we have thoroughly defined neuronal networks lacking superconnected neurons (such as that of

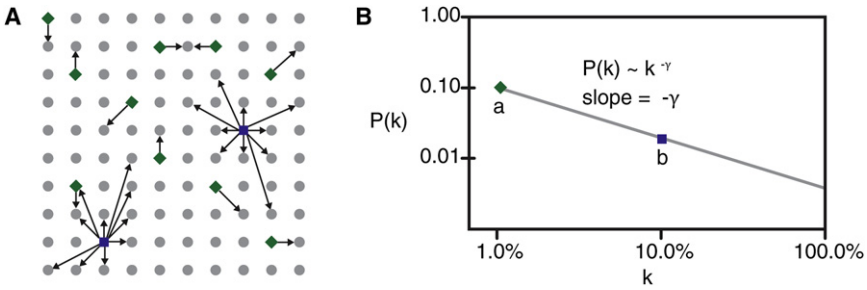

Figure 1. Power-Law Distribution

(A) In a hypothetical scale-free network with 100 nodes, the 10 nodes with 1 output connection each are shown as diamonds and the 2 nodes with 10 output connections each are shown as squares. The connections of the other nodes with varying degrees of connectivity are not elaborated for simplicity.

(B) The probability *P(k)* of a node in a scale-free network having *k* connections is given by a power-law equation of the form $P(k) \sim k^{-\gamma}$. On a log-log graph, the function appears linear. Because the distribution is independent of scale, this same equation could describe a 100 node network or a 100,000 node network. Points *a* and *b* on the graph correspond to the diamond and square nodes in the hypothetical 100-node network of (A). Scale-free topologies are found in networks as diverse as the world wide web and social groups. In most scale-free networks, gamma falls between 2 and 3, but gamma is closer to 1 in the neural networks studied by Bonifazi and colleagues, indicating more connections in the network. This equation describes only the output connections and gives the degree of connectivity as a percent of the possible connections in the manner of Bonifazi and colleagues.

C. elegans), hard evidence is elusive for neuronal networks that display a large disparity in connectivity due to the presence of hub-like cells (Yu et al., 2008; Song et al., 2005). It is the latter gap in our knowledge that the work of Bonifazi and colleagues from Rosa Cossart's lab has now filled by demonstrating, using a combination of cutting-edge network imaging techniques and single-cell electrophysiology (Crépel et al., 2007), that the developing mammalian hippocampus contains GABAergic neurons with unusually high functional connectivity whose activation can have profound impacts on network dynamics (Bonifazi et al., 2009).

Searching for hub cells in the neuronal hay would have been surely doomed to failure because their rarity guarantees their absence from most small samples. However, the innovative method used by the authors allows a sample size sufficiently large to contain at least some rare hub cells. Additionally, the CA3 region in the developing hippocampus offers a number of advantages on which the authors capitalized in their search for hubs. First, the early postnatal hippocampus conveniently displays robust, spontaneous, synchronized network activity in the form of giant depolarizing potentials (GDPs) (Ben-Ari, 2001), and, second, the CA3 region has a network structure dominated by local connections that remain intact in brain slices (Bonifazi et al., 2009). Therefore, a seemingly straightforward general strategy for finding hub cells is to monitor the rhythmic spontaneous GDP activity in a large neuronal assembly in the developing CA3 and identify neurons that appear to play key functional roles in synchronization by focusing on those rare single cells that consistently fire just before GDPs occur in the rest of the population. This strategy is akin to finding the conductor in an orchestra by monitoring every participating musician's movements and finding the person whose movements predictably precede everybody else's. However, there is an extra requirement that makes the task suddenly much more daunting. Namely, in addition to showing that the conductor always begins to move slightly before all others, it is critical to demonstrate the conductor's commanding authority by showing that the orchestra blindly follows the conductor's commands even when the conductor changes the musical script suddenly from Bach to The Beatles. This unequivocal demonstration of the causal influence of hub cells on network-wide activity dynamics requires identification of the rare leader cells using analysis of temporal correlations, followed by manipulation of the activity of those putative hub cells to show their effect on the network.

Because post hoc analysis precludes such a feat, Bonifazi and colleagues analyzed the functional connectivity lightning fast, while the activity was still ongoing. They employed multibeam two-photon microscopy, which allows relatively high spatial and temporal resolution by splitting a laser into multiple beams that scan different points in the sample almost simultaneously (Nielsen et al., 2001; Crépel et al., 2007). With this powerful tool, the authors recorded the intracellular calcium signals that occur during GDPs in hundreds of CA3 neurons. If activity in neuron A consistently preceded activity in neuron B, a functional connection from A to B was assumed, and a network-wide functional connectivity map was constructed by performing such pair-wise analysis for all recorded cells. To test whether functional connectivity faithfully represented effective connectivity, the authors stimulated neurons with varying degrees of connectivity and observed whether a calcium response occurred in other neurons, finding that the two types of connectivity maps overlapped by 53% for hub cells. The functional connectivity analysis revealed the existence of very rare cells that possessed a disproportionate number of connections. Remarkably, the distribution of such output links was best fitted with a so-called power-law function, characteristic of a scale-free network as described in Figure 1 (Barabási and Albert, 1999). The authors' ingenious approach of analyzing the activity of a large number of neurons and constructing such functional connectivity maps while still "online" enabled them to target these richly connected neurons for recording using single-cell electrophysiology techniques. By manipulating the firing of such neurons of interest, the authors could directly study single-cell/network interactions and assess the functional effect of "conductor cells" using a number of metrics. One such metric was the expected versus observed frequency of occurrence of GDPs after delivery of suprathreshold depolarizations to the putative single hub cells. Astonishingly enough, changes in hub cell firing caused predictable alterations in GDP dynamics, establishing the functional influence of these heavily connected but rare neurons.

So who are these Herbert von Karajans of the developing hippocampus? The

authors used genetically modified mice expressing the green fluorescence protein (GFP) specifically in GABAergic neurons to determine whether the hub cells were GABAergic. All of the hub neurons were indeed GABAergic cells, and subsequent morphological reconstructions revealed that many of these cells had extensive, long-range axonal arborizations. Furthermore, the hub cells not only appeared to possess a high number of outgoing connections, they also received more spontaneous excitatory synaptic inputs and showed a more hyperpolarized action potential threshold, all consistent with predicted requirements for efficient hub-like behavior.

This elegant study poses a number of additional questions that must be addressed in future experiments. In particular, the effect on GDPs varied among hub neurons; while stimulation of several hubs resulted in an increase in GDP frequency, other hub neurons effected a decrease in GDP frequency, and the reason for the difference remains to be elucidated. Second, it is interesting that the architecture of such aristocratic, hub-containing networks characterized by power-law connectivity distribution can be most easily constructed using a simple preferential attachment rule, where newly added nodes form connections preferentially with nodes that are already well-connected. While it is not yet known whether GABAergic hub cells are formed in the developing hippocampus according to such unseemly "rich-get-richer" schemes, the wide axonal arborization and the low action potential threshold are certainly consistent with the advanced maturation stage that would be expected of an established hub neuron. Third, it will be important to establish whether hub cells exist in the adult networks as well, and whether only GABAergic neurons can serve as hub cells. Indeed, long-range GABAergic neurons certainly exist in the adult hippocampus, connecting distant parts of the hippocampus and related structures such as the septum (Klausberger and Somogyi, 2008), but it cannot be excluded that non-GABAergic cells may also serve as hubs in certain neuronal circuits. Finally, it will be of critical importance to determine if, as predicted by computational simulations, the number of hub cells increases in neurological diseases including epilepsy, and whether it is specifically the adult-generated, newly born cells that give rise to the added hub cells in pathological conditions (Morgan and Soltesz, 2008). Thus, be forewarned, members of the neuronal bourgeoisie, we are coming for you!

REFERENCES

Barabási, A.-L., and Albert, R. (1999). Science *286*, 509–512.

Ben-Ari, Y. (2001). Trends Neurosci. *24*, 353–360.

Bonifazi, P., Goldin, M., Picardo, M.A., Jorquera, I., Cattani, A., Bianconi, G., Represa, A., Ben-Ari, Y., and Cossart, R. (2009). Science *326*, 1419–1424.

Bullmore, E., and Sporns, O. (2009). Nat. Rev. Neurosci. *10*, 186–198.

Buzsáki, G., Geisler, C., Henze, D.A., and Wang, X.J. (2004). Trends Neurosci. *27*, 186–193.

Crépel, V., Aronov, D., Jorquera, I., Represa, A., Ben-Ari, Y., and Cossart, R. (2007). Neuron *54*, 105–120.

Klausberger, T., and Somogyi, P. (2008). Science *321*, 53–57.

Morgan, R.J., and Soltesz, I. (2008). Proc. Natl. Acad. Sci. USA *105*, 6179–6184.

Nielsen, T., Fricke, M., Hellweg, D., and Andresen, P. (2001). J. Microsc. *201*, 368–376.

Song, S., Sjöström, P.J., Reigl, M., Nelson, S., and Chklovskii, D.B. (2005). PLoS Biol. *3*, e68.

Yu, S., Huang, D., Singer, W., and Nikolic, D. (2008). Cereb. Cortex *18*, 2891–2901.