system is under partial load, parts of it can be throttled to decrease the power consumption without a reduction of overall performance.

The power consumption and the packet service times can be depicted for different scenarios (see the figure). When smart standby is used, different idle states are usually designed by selectively turning off an increasing number of hardware units. This leads to a reduction of the energy consumption during idle times; however, longer times are needed to wake up all the hardware. Similarly, dynamic frequency scaling hardware support is designed by preselecting a set of operating clock frequencies whose values are submultiple of the maximum one and that provide silicon stability. Dynamic frequency scaling causes a stretching of packet service times, while the sole adoption of smart standby introduces an additional delay in packet service, due to the wake-up times. Finally, the joint adoption of both energy-aware capabilities may not lead to outstanding energy gains because dynamic frequency scaling causes larger packet service times and, consequently, shorter idle periods.

The next generation of network devices will include local control policies (*8*) that will be able to set up and synchronize their energy-aware capabilities. For example, analytical models have been defined to allow designers of green network devices to calculate in advance the temperature statistics of a device and decrease it when possible (*11*). Reduction of the average temperature allows designers to reduce the hardware size and the size of passive and active cooling systems and thus reduce energy consumption.

New algorithms for network-wide control, both distributed and centralized, are starting to take green metrics into account. For example, a possible distributed solution currently builds upon link-state protocols and puts links in an Internet protocol–based network into sleep mode at appropriate times (*12*). This method allows limiting the amount of shared information, avoiding explicit coordination among nodes, and reducing the problem complexity. Thus, the switch-off decision takes the current load of links and the history of past decisions into account.

With such practices spreading into industry, large companies are now building energy-efficient data centers for minimizing data-center power costs (*13*). Moreover, measurement of servers in a production data center from both power and performance reveal that most servers are underused and have similar activity patterns across the days of the week (*14*).

The fundamental problem of greening the Internet is to strike a fine balance between the demands of performance and the limitations of energy usage. New research initiatives in energy optimization have revealed several aspects of the Internet that can be streamlined. Addressing the issues of energy efficiency will allow us to draw deeper conclusions on how new network systems can be smarter and more effective.

References

1. C. Bianco, F. Cucchietti, G. Griffa, Proceedings of the 29th International Telecommunications Energy Conference INTELEC 2007, Rome, Italy, September 2007, pp. 737–742.
2. www.telecomitalia.com/tit/en/sustainability.html
3. www.datacenterdynamics.com /focus/archive/2011/09/global-data-center-energy-use-grow-19-2012
4. C. Belady, *Electron. Cool.* **13**, 1 (2007).
5. www.econet-project.eu (2010).
6. www.fp7-trend.eu (2010).
7. www.greentouch.org (2011).
8. A. Lombardo, C. Panarello, D. Reforgiato, G. Schembra, Globecom, Anaheim, CA, 3 to 7 December 2012, pp. 3086–3091.
9. S. Nedevschi, L. Popa, G. Iannacone, D. Wetherall, S. Ratnasamy, Proceedings of the 5th USENIX Symposium on Networked Systems Design and Implementation, San Francisco, CA, 2008, pp. 323–336.
10. R. Bolla, R. Bruschi, F. Davoli, F. Cucchietti, *IEEE Comm. Tutorials* **13**, 223 (2011).
11. A. Lombardo, D. Reforgiato, V. Riccobene, G. Schembra, Conf. on Sustainable Internet and ICT for Sustainability Pisa, Italy, 4 to 5 October 2012, pp. 1–9.
12. A. P. Bianzino, L. Chiaraviglio, M. Mellia, J.-L. Rougier, *J. Comp. Telecom. Network.* **56**, 3219 (2012).
13. S. Govindan, A. Sivasubramaniam, B. Urgaonkar, Proceedings of the 38th International Symposium on Computer Architecture, San Jose, CA, 4 to 8 June 2011, pp. 341–352.
14. A. Vasan, A. Sivasubramaniam, V. Shimpi, T. Sivabalan, R. Subbiah, International Symposium on High Performance Computer Architecture Bangalore, India, 9 to 14 January 2010, pp. 1–10.

10.1126/science.1235623

NEUROSCIENCE

Neural Stem Cells, Excited

Electrical activity in the adult mammalian brain triggers neurogenesis.

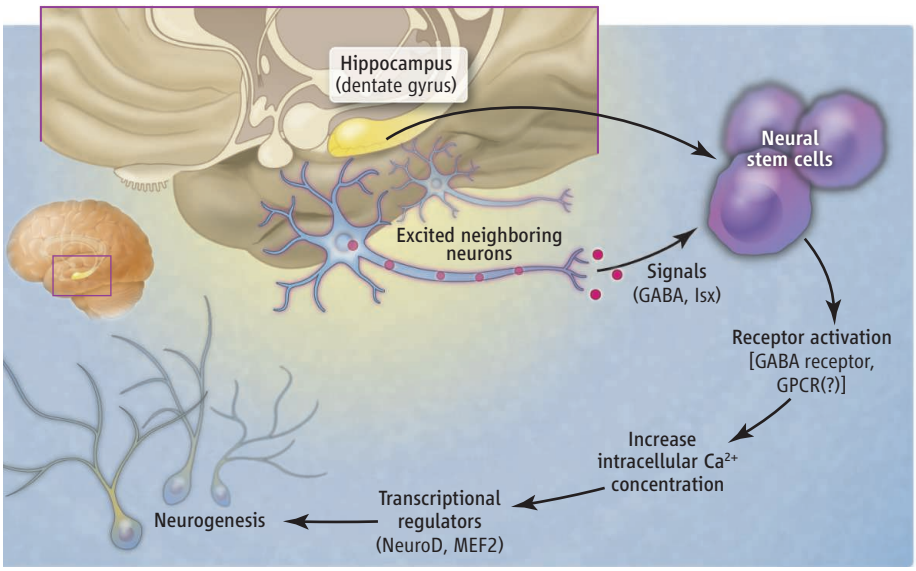
Jenny Hsieh[1] and Jay W. Schneider[2]

Although the brain is generally considered a terminally differentiated organ, new nerve cells are made every day through a process called "adult neurogenesis," which occurs in specialized regions like the hippocampal dentate gyrus (*1*). Stem cells in the brain sample electrical signals (activity) from neighboring neurons, deciding which genes to express and which signaling pathways to launch toward developing their own neuronal identity. Why would stem cells be able to respond to exogenous neuronal electrical activity, which can be considered a highly specialized function? Indeed, it seems counterintuitive insofar as one of the defining functions of all stem cells is to actively maintain the undifferentiated state.

The central feature of brain function is the transmission of electrical signals from neuron to neuron in complex networks and circuits. How neurons "listen and talk" to each other is determined by cell identity—that is, which genes (e.g., encoding receptor systems or neurotransmitter biosynthesis pathways) are expressed by an individual neuron and which are not. The complexity of this information exchange is staggering because billions of neurons, falling into distinct molecular and cellular phenotypes based on their gene expression patterns, are communicating with each other at the same time.

Cultured neural stem/progenitor cells isolated from rodent hippocampus can respond to external neural activity and differentiate into neurons (*2*). This activity-dependent neurogenesis requires Ca^{2+} channels and receptors for the neurotransmitter *N*-methyl-D-aspartate (NMDA) on proliferating stem/progenitor cells, and hence is called "excitation-neurogenesis coupling." In vivo, type 2 stem/progenitor cells [expressing nestin, a protein marker for neural stem/progenitor cells; they also morphologically lack projections (dendrites and axons) from the cell body] express receptors for γ-aminobutyric acid (GABA) and can be activated by this chemical when released by nearby active neurons (*3*, *4*). A possible mechanism for excitation-neurogenesis coupling is GABA-mediated depolarization (*4*), previously

[1]Department of Molecular Biology, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA. [2]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA. E-mail: jenny.hsieh@utsouthwestern.edu; jay.schneider@utsouthwestern.edu



Exciting development. The differentiation of stem/progenitor cells of the hippocampus can be influenced by the electrical activity of surrounding mature neurons. The pathways are only beginning to be elucidated. Isx, isoxazole; GPCR, G protein–coupled receptor.

described in mouse embryonic neuronal progenitor cells (*5*). Depolarization causes an increase in intracellular Ca^{2+} concentration similar to that evoked in cultured neural stem/progenitor cells (*2*). This excitation signal is relayed to the genome wherein the transcription factor NeuroD is rapidly activated to promote neurogenesis (*2*, *4*). Once proliferating stem/progenitor cells differentiate into slightly later stages of neuroblasts and immature neurons, excitation signaling in the form of GABA is also necessary to drive the functional integration of newborn neurons (*6*, *7*).

These early studies highlight the importance of excitation-neurogenesis coupling in the stepwise differentiation and maturation of adult neural stem/progenitor cells in the mammalian brain. They do not, however, address whether all types of neural stem cells in the brain have this response to activity. For example, neural stem cells in the brain called type 1 or radial glial-like (RGL) cells can respond to neural activity. RGLs maintain the adult neural stem cell pool in the hippocampus by remaining quiescent; the maintenance and activation of RGLs is dynamically controlled by experience and aging (*8*, *9*). Nestin-expressing RGLs can be activated by GABA (*10*). The absence of functional $GABA_A$ receptors results in rapid exit from quiescence and increased production of RGLs. Cells in the stem cell niche required to maintain RGLs are interneurons (expressing the Ca^{2+}-binding protein parvalbumin), a source of GABA. Modulation of GABA signaling affects the generation of more RGLs or causes them to remain quiescent, but not to differentiate. Thus, these particular neural stem cells are sensitive to activity, but have a different behavior. Many open questions remain, including the identity of other cell types that work in concert with parvalbumin-expressing interneurons and RGLs, and whether other possible niche components exist for neural stem cell excitation.

One limitation of assessing the specific function of endogenous chemicals, such as amino acids, peptides, and monoamines, on excitation-neurogenesis coupling is that classical neurotransmitters do not appear to distinguish between stem cells and mature neurons. Theoretically, stem cell–selective chemicals could provide a tool to probe and explore mechanistic pathways of excitation-neurogenesis coupling. Among the small molecules found to activate gene expression exclusively in neural stem/progenitor cells were 3,5-disubstituted isoxazoles (*11*). This compound class triggered differentiation of cultured neural stem/progenitors and promoted hippocampal adult neurogenesis when administered to mice systemically (*12*–*14*). Moreover, isoxazole-9 improved hippocampal-dependent memory formation in adult mice (*14*). This small molecule causes an increase in intracellular Ca^{2+} concentration through both classical neurotransmitter signaling pathways such as that controlled by the NMDA receptor, and pathways activated by G protein–coupled receptors. The receptor responsible for isoxazole-9's neural progenitor selectivity has not yet been identified, but the compound elicits the expression of differentiation genes that are also turned on in response to the electrical activity of other neurons. This includes the gene encoding myocyte-specific enhancer factor 2 (MEF2) (see the figure) (*12*, *14*). MEF2 is a critical regulator of muscle development in all muscle lineages, including the heart (*15*). Studies of excitation-neurogenesis may potentially guide a better understanding of how electrical stimulation and stretch of developing cardiac precursor cells promotes myocyte differentiation and contractile function, especially in the context of cardiac tissue engineering (*16*).

Generally, stem cells deflect or reject environmental signals (e.g., through drug efflux pumps) that might trigger differentiation and the loss of stemness. In adult tissues and organs, like the brain, stem cells already possess sophisticated receptor systems to immediately sense environmental changes. However, instead of initiating cellular specialization, which would possibly irreversibly deplete the stem cell pool, these receptor systems help stem cells decide how many (or how few) progeny cells to produce. It may be that the neurogenesis response of stem/progenitor cells to activity is an adaptive mechanism to maintain regional homeostasis: increasing stem cell production when local circuitry activity levels are low, and restoring quiescence when activity levels are high.

It is not entirely surprising that the adult brain continues to develop under the influence of electrical activity, such that similar to mechanical stretch regulation of muscle growth, behavior and circuit activity control adult neurogenesis. A potential "cost" of excitable stem cells is inappropriate activation after pathological forms of activity, such as seizures. Understanding how electrical activity controls adult neural stem cell properties and neurogenesis is likely to provide mechanistic insight into neural circuit function and new tools for mapping human brain connections.

References

1. C. Zhao, W. Deng, F. H. Gage, *Cell* **132**, 645 (2008).
2. K. Deisseroth *et al.*, *Neuron* **42**, 535 (2004).
3. L. P. Wang, G. Kempermann, H. Kettenmann, *Mol. Cell. Neurosci.* **29**, 181 (2005).
4. Y. Tozuka, S. Fukuda, T. Namba, T. Seki, T. Hisatsune, *Neuron* **47**, 803 (2005).
5. D. F. Owens, A. R. Kriegstein, *Nat. Rev. Neurosci.* **3**, 715 (2002).
6. S. Ge *et al.*, *Nature* **439**, 589 (2006).
7. L. Overstreet Wadiche, D. A. Bromberg, A. L. Bensen, G. L. Westbrook, *J. Neurophysiol.* **94**, 4528 (2005).
8. A. Dranovsky *et al.*, *Neuron* **70**, 908 (2011).
9. J. M. Encinas *et al.*, *Cell Stem Cell* **8**, 566 (2011).
10. J. Song *et al.*, *Nature* **489**, 150 (2012).
11. H. Sadek *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **105**, 6063 (2008).
12. J. W. Schneider *et al.*, *Nat. Chem. Biol.* **4**, 408 (2008).
13. J. W. Schneider *et al.*, *ACS Chem. Neurosci.* **3**, 557 (2012).
14. D. Petrik *et al.*, *FASEB J.* **26**, 3148 (2012).
15. B. L. Black, E. N. Olson, *Annu. Rev. Cell Dev. Biol.* **14**, 167 (1998).
16. W. H. Zimmermann *et al.*, *Circ. Res.* **90**, 223 (2002).

10.1126/science.1237576

Neural Stem Cells, Excited

Jenny Hsieh and Jay W. Schneider (March 28, 2013)

Science **339** (6127), 1534-1535. [doi: 10.1126/science.1237576]