Matters of Size

Charles Kopec and Roberto Malinow

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NEUROSCIENCE

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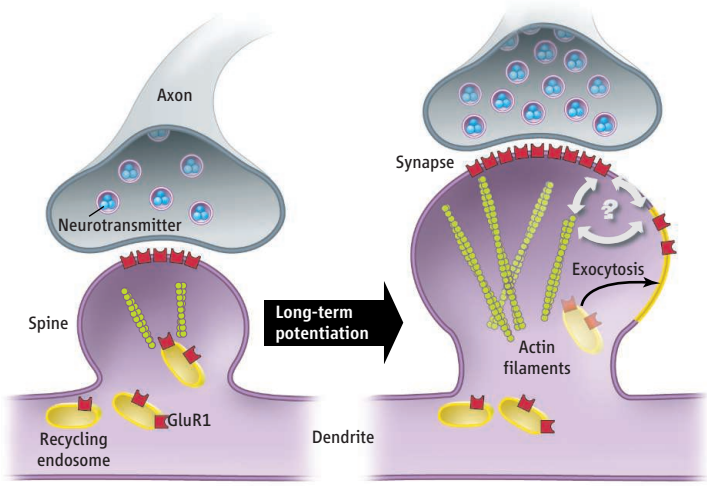
Bigger dendritic spines are associated with stronger neural connections. Now underlying mechanisms for this association are being revealed.

From the overall body plan of an organism to the intricate three-dimensional fold of proteins, structure is a key determinant of function. Neurons, the fundamental cells of the nervous system, are no exception. The architecture of their dendritic and axonal arbors—the cellular extensions that receive and transmit information—determines which neurons they can connect to, whereas the diameter of these extensions determines the speed and filtering of electrical signals that travel down them. Tiny femtoliter (10^{-15} liter)–sized protrusions from neuronal dendrites, called spines, receive a functional connection from another neuron's axon at a specialized area of contact known as a synapse. A study by Park *et al*. in a recent issue of *Neuron* (*1*) marks a large step forward in our understanding of how spine size and synaptic strength are balanced.



Balancing act. Long-term potentiation drives exocytosis of recycling endosomes, providing dendritic spines with more membrane and receptors (GluR1). Actin polymerization provides structural support. These processes are somehow balanced to regulate the size of spines and the strength of synaptic connections.

A neuron can have up to 100,000 spines, each generally forming a single synapse. Spines function as chemical compartments for signaling molecules that become activated by specific patterns of synaptic transmission (*2*–*4*). This organization provides each synapse with a miniature caldron in which to concoct a chemical brew to effect changes in connections between neurons (*5*).

Interestingly, large spines contain strong synapses (robust transmission) and small spines have weak synapses (*6*, *7*). A spine is at least an order of magnitude larger than a synapse, and thus there is no physical requirement for this correlation. The reason for this correlation between structure and function remains elusive, but an abundance of circumstantial evidence points to its importance. Stimuli that cause stable changes in synaptic strength lead to corresponding stable changes in spine volume (*8*, *9*). Heritable forms of mental retardation can present abnormalities in spine morphology as well as synaptic function (*10*). Furthermore, Alzheimer's disease may involve a loss of spines that is fundamentally linked to a decrease in the number of neurotransmitter receptors at the synapse (*11*). Therefore, understanding how and why this correlation between synapse strength and spine size exists will not only expand our understanding of how synapses work, but may have clinical relevance as well.

Park *et al*. elegantly combine serial section electron microscopy and live cell fluorescence microscopy to afford us a view of the inner workings of spines. The authors stimulated cultured mammalian neurons to generate a stable increase in synaptic strength known as long-term potentiation (LTP), and confirmed that the rapid increase in synaptic strength is accompanied by a matched increase in spine volume. They then probed the molecular and cellular mechanisms behind this correlation.

Park *et al*. focused on the role of the recycling endosome, an intracellular membrane-bound compartment that is part of the system that transports membrane-bound proteins onto and off the cell surface. Previous work by this group showed that the protein GluR1 is delivered to the neuronal surface from the recycling endosome through exocytosis, the cell's secretory process (*12*). GluR1 is a glutamate receptor subunit that is inserted into synapses during LTP and plays an important role in mediating the increase in synaptic strength (*13*). Blocking this delivery by expressing mutant proteins that specifically inhibit this exocytosis prevented the stable increase in synaptic strength.

In the present work, Park *et al*. provide tantalizing evidence that the lipids delivered to the neuron's surface from the vesicles carrying GluR1 are the raw materials that allow the spine to enlarge (see the figure). The recycling endosome appears to be situated in the right place, just below or even within some spines, and is of sufficient size to influence spine volume. LTP-inducing stimuli mobilize these endosomes from dendrites into spines, positioning the endosome perfectly to fuse with the spine surface. Blocking exocytosis from this compartment prevents spines from enlarging, strongly suggesting that the recycling endosome is a source of structural plasticity. Furthermore, the amount of surface area lost in the endosomal system equals the amount gained by the spines, hinting at a direct transfer of material. Park *et al.* also directly visualize exocytosis with a pH-sensitive fluorescence indicator that translates the pH change experienced during exocytosis (the pH inside the recycling endosome is acidic, whereas in the extracellular space it is mildly alkaline) into a large change in fluorescence. By monitoring events simultaneously, these experiments reveal that exocytosis takes place directly in spines and that the amount of exocytosis correlates extremely well with the increase in spine volume.

Although this study elucidates how spine size and synaptic strength are kept in check, it is not the whole story. Several groups have investigated the role of the actin cytoskeleton in determining spine morphology (*14*, *15*). Indeed, LTP causes an increase in the amount of filamentous actin in spines (*16*, *17*), and preventing the formation of filamentous actin blocks structural (*16*) and functional (*18*, *19*) changes during LTP. It is difficult to imagine how lipids that are added to the spine membrane could be sufficient to make a larger spine, rather than simply flow off into the membrane of the dendrite. It is thus likely a combination of actin polymerization and the exocytosis of recycling endosomes that mediate spine enlargement during LTP. Filamentous actin acts as a skeleton to support a larger spine, whereas more lipids are the raw material to increase the spine's surface area.

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But if these two processes are required for structural and functional plasticity, how are they balanced? That is, how are the distinct molecular cascades underlying exocytosis and actin cytoskeletal reorganization coordinated? Perhaps evolution has perfectly balanced their rates, or maybe there is a physical link between the two systems. For instance, receptors delivered to the synapse from the recycling endosomes could stabilize the actin cytoskeleton and thereby provide a simple accounting process to balance changes in synaptic strength and spine size. Maybe when we fully understand how spine size and synapse strength are coordinated will we be poised to comprehend why spine size matters.

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EVOLUTION

The Puzzle of Human Sociality

Human cooperation may have evolved as a consequence of genetic relatedness, culture, or language within groups.

Robert Boyd

The scale and complexity of human societies present an important evolutionary puzzle. In every human society, people cooperate with many unrelated individuals. Division of labor, trade, and large-scale conflict are common. The sick, hungry, and disabled are cared for, and social life is regulated by commonly held moral systems that are enforced, albeit imperfectly, by third-party sanctions. In contrast, in other primate species, cooperation is limited to relatives and small groups of reciprocators. There is little division of labor or trade, and no large-scale conflict. No one cares for the sick, or feeds the hungry or disabled. The strong take from the weak without fear of sanctions by third parties. On page 1569 of this issue, Bowles (*1*) provides one explanation for the commonness of costly, prosocial behavior in human societies.

The behavior of other primates is easy to understand. Natural selection only favors individually costly, prosocial behavior when the beneficiaries of the behavior are disproportionately likely to share the genes that are associated with the behavior. Selection can favor altruism toward close relatives because recent common descent provides a cue of genetic similarity. The small size of primate families limits the size and complexity of the groups that can be formed through this process. Thus, standard evolutionary theory provides a perfectly good explanation for the behavior of other primates, but not humans.

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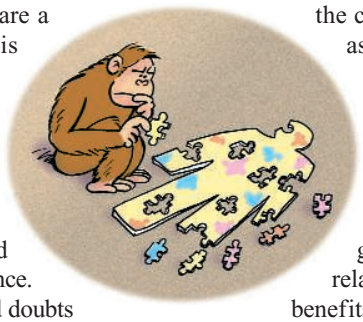
Bowles proposes that competition between genetically differentiated groups led to the evolution of our prosocial psychology. Limited migration between groups can lead to the buildup of genetic relatedness (which measures how much the possession of a particular gene in one individual predicts the presence of the same gene in a second individual) among group members. This means that group membership can also be a cue that allows assortative interaction—genes that cause you to help members of your group can be favored because other group members are disproportionately likely to carry the same genes, even though you do not share a recent common ancestor. This is an old idea. A version appears in *The Descent of Man* (*2*) and has reappeared many times since then. It has never gained much traction, however, because there have been good reasons to doubt its importance. First, theoretical work raised doubts about levels of genetic relatedness being high enough to favor prosocial behavior toward group members (*3*). Second, limited migration generates more competition within groups than between groups. This means that helping others in your own group reduces your own relative fitness and the fitness of your descendants. In some plausible models of the evolution of altruism when migration is limited, this effect exactly balances increases in relatedness, eliminating selection for altruism toward group members (*4*). Finally, the benefits of success in intergroup competition seems too small and the costs too large to allow cooperation to evolve. After all, other primates live in similar groups, but show little evidence of group-level cooperation.



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Bowles meets these objections with a combination of data and theory. First, he has assembled data on the amount of genetic differentiation among human hunter-gatherer groups (or put another way, the level of relatedness within such groups). These data show that the level of relatedness within such groups is substantially higher than previously supposed, a bit below that of cousins. This means that the cooperation will be favored as long as the benefits to individuals are about 10 times the cost. Second, because competition occurs between groups and successful groups are able to colonize the territories of extinct groups, competition among relatives does not attenuate the benefits derived from cooperation. Third, intergroup competition is common in small-scale societies, so the benefits derived from collective efforts to compete with other groups are plausibly substantial. Finally, Bowles notes that human foraging groups typically have culturally transmitted norms and practices, including food sharing and socially imposed monogamy, which reduce fitness differences within groups. He makes the original and interesting argument that such "leveling mechanisms" act like redistributive taxes to reduce the disadvantage of engaging in costly