scenario is correct, then the fine and coarse components should be the same age. If they are not the same age, as is the case here, then the most likely explanation is that the filler is not inert. Instead, it carries a signal similar to, but older than, that sinking from the overlying waters.

In this case, some aspects of the fine material at a location cannot be interpreted as a time history of events at the sea surface directly above that location. It is contaminated by displaced records of events at a different place with different characteristics. Support for this interpretation comes from Benthien and Müller (*5*), who showed that modern bottom sediments in the Argentine Basin record temperatures that are 2° to 6°C colder than the sea surface. Strong bottom currents transport material from the south into this region (*6*).

Most sediment drifts lie under deep boundary currents downstream from a major source of sediment (*7*). In contrast, Bermuda Rise, a mud-covered plateau at 4000 to 4500 m depth, is separated from the adjacent continent by a 5500-m-deep abyssal plain that is not a regular current-controlled sediment transport pathway.

Because of its midocean setting, Bermuda Rise might have been thought free of the signal contamination associated with resuspension and transport on continental margins. The sediment cover is derived from pelagic fallout, turbidity-current material from the Laurentian Fan swept over the rise by deep currents (*8*), and resuspended sediment from the Grand Banks and United States/Canada margins entrained in the deep circulation (see the figure). On the basis of expected pelagic sedimentation rates, the latter two components must dominate by a factor of at least 5, although it remains unclear which of them is more important (*8–10*).

Ohkouchi *et al.* show that the thick sediment on Bermuda Rise is more likely to come from resuspension of relatively young (a few thousand years) sediment on continental margins than from wholesale mixing of material accumulated over several hundred thousand years, as would be typical of turbidity currents (*9*). This argues against the turbidity current model of Laine and Hollister (*8*) as the only transport path.

Bermuda Rise is an important location from which key palaeoclimatic results have emerged. What is true for one millennial-scale oscillation—the Little Ice Age—may well be true for other such oscillations 30,000 to 60,000 years ago.

For example, Sachs and Lehman (*11*) have argued that alkenone-based SSTs matched temperature variations in the Greenland ice cores. They established their sediment core's age by correlating variations in sediment lightness with the calcium carbonate variations in a nearby sediment core previously dated by radiocarbon and oxygen isotopic stages. They noted that "this method produced ages for the SST events that were 2000 to 5000 years older than their apparent counterparts in Greenland paleotemperature ... records" (p. 758).

They attributed this surprising (for believers in the second scenario) result to radiocarbon dating errors and uncertainties in the oxygen isotopic age scale. They therefore devised a new age scale that maximized the correlation between Bermuda Rise SSTs and oxygen-isotope variations in the Greenland ice core. This approach, of course, produced a close relation between temperature at Bermuda and Greenland. It looks as though their earlier interpretation may have been strikingly, but perhaps less interestingly, correct.

The report by Ohkouchi *et al.* illustrates that the size dependence of sediment transport processes must be considered carefully in sediment core interpretations. Age models should not be based on highly mobile material. This stricture could also apply to sediment color, which is dominated by the highly mobile fine particle fraction. (In a single transport system, color may still be useful.) Alkenones provide excellent records of SSTs, but sediment records will be most credible when the second scenario is fulfilled.

Continental margins, with high resuspension and lateral sediment supply from diverse sources, are particularly prone to problems associated with sediment core interpretation. One way of checking for the potential error is to date foraminifera and fine-grained cocolith carbonate from the same core level. These dates should be the same [after checking that the fine carbonate is not limestone ground up by glaciers (*12*)]. The Grail may not always be poisoned, but one should not drink from it indiscriminately.

References and Notes

1. N. Ohkouchi *et al.*, *Science* **298**, 1224 (2002).
2. W. L. Balsam, F. W. McCoy, *Paleoceanography* **2**, 531 (1987).
3. In all of these cases, there is an important difference in behavior between the foraminifera used for analysis (generally >250 μm diameter), whose sinking speed of >1 cm s^{-1} requires currents of more than ~25 cm s^{-1} for suspension, and the silt- and clay-sized material, whose sedimentation rate of <0.2 cm s^{-1} (and mostly <0.01 cm s^{-1}) requires currents of only 1 to 2 cm s^{-1} to maintain suspension. This fine-grained material has long residence times and is susceptible to long-distance transport (*13*).
4. L. Keigwin, *Science* **274**, 1503 (1996).
5. A. Benthien, P. J. Müller, *Deep-Sea Res. I* **47**, 2369 (2000).
6. M. T. Ledbetter, *Nature* **321**, 423 (1986).
7. I. N. McCave, B. E. Tucholke, in *The Geology of North America*, vol. M, *The Western North Atlantic Region*, P. R. Vogt, B. E. Tucholke, Eds. (Geological Society of America, Boulder, CO, 1986), pp. 451–468.
8. E. P. Laine, C. D. Hollister, *Mar. Geol.* **39**, 277 (1981).
9. P. P. E. Weaver, *Sedimentology* **41**, 1025 (1994)
10. R. F. Anderson *et al.*, *Deep-Sea Res. II* **41**, 669 (1994).
11. J. P. Sachs, S. J. Lehman, *Science* **286**, 756 (1999).
12. W. L. Balsam, D. Williams, *Mar. Geol.* **112**, 23 (1993).
13. I. N. McCave, *Spec. Publ. Geol. Soc. London* **15**, 35 (1984).
14. W. J. Schmitz, M. S. McCartney, *Rev. Geophys.* **31**, 29 (1993).

PERSPECTIVES: NEUROSCIENCE

Freeing the Brain from the Perineuronal Net

Kevin Fox and Bruce Caterson

You can't teach an old dog new tricks, or can you? On page 1248 of this issue, Pizzorusso *et al.* (*1*) provide new data indicating that the brain of an adult animal can be persuaded to respond like a young brain to changes in visual experience. They use an enzyme known as chondroitinase ABC to alter the biochemical composition of the perineuronal net that surrounds neurons in the visual cortex. Degrading the glycosaminoglycan components of this perineuronal net restores the ability of cortical neurons to alter their synaptic connections. Normally, neurons in the visual cortex of rats only retain their plasticity for 4 to 5 weeks after birth, before the perineuronal net matures. Remarkably, injecting chondroitinase ABC into the visual cortex of adult rats restores this plasticity.

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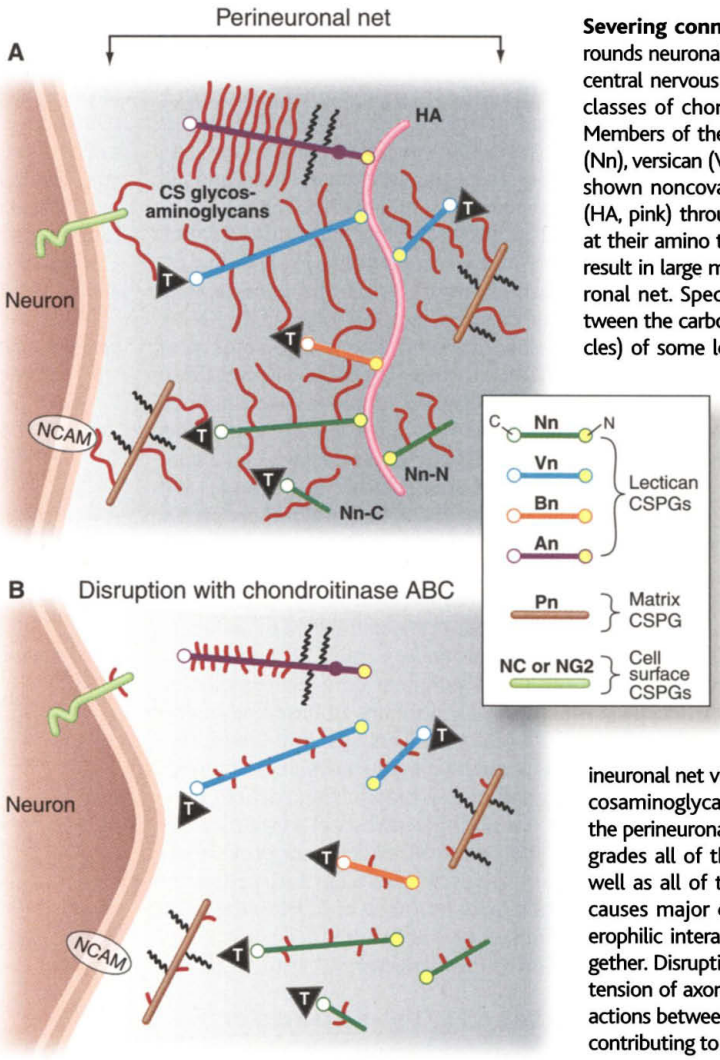
The visual cortex receives two images of the world, one from each eye. The images are combined in the binocular zone of the cortex, which makes up most of the visual cortex in humans and a smaller component in rats because their eyes lie on either side of the head. But if one eye is forcibly closed early in development (monocular deprivation), the open eye takes over control of the binocular zone (*2*). At the cellular level, this means that neurons that would have developed connections to both eyes lose synaptic input

The authors are in the Neuroscience Research Group and the Connective Tissue Biology Labs, Cardiff School of Biosciences, Cardiff University, Cardiff CF10 3US, UK. E-mail: foxkd@cardiff.ac.uk

from the closed eye and gain synaptic input from the open eye, a process called ocular dominance plasticity.

Losing vision in one eye during the critical period can have serious consequences because once the critical period of development has ended, the synaptic inputs to the neurons are set. Consequently, neurons that do not respond to the closed eye will not regain connections from the closed eye if it is reopened, and the individual remains blind in that eye. In humans, the critical period for vision is about 7 to 8 years, although some visual problems such as astigmatism can lead to permanent deficits in vision if not corrected by 2 years of age (*3*). Clearly, a procedure that could reestablish the plasticity of brain neurons at later ages would hold great therapeutic promise and would also yield further insights into the molecular mechanisms responsible for brain plasticity.



Severing connections. (**A**) The perineuronal net surrounds neuronal cell bodies and proximal dendrites in the central nervous system and is composed of several subclasses of chondroitin sulfate proteoglycans (CSPGs). Members of the lectican subfamily of CSPGs—neurocan (Nn), versican (Vn), brevican (Bn), and aggrecan (An)—are shown noncovalently associated with matrix hyaluron (HA, pink) through globular hyaluronan-binding domains at their amino termini (yellow circles). These associations result in large macromolecular aggregates in the perineuronal net. Specific noncovalent associations occur between the carboxyl-terminal globular domains (white circles) of some lecticans (such as neurocan and versican) and the matrix glycoprotein tenascin (T, triangles). Tenascin, in turn, binds to CS glycosaminoglycans (red lines) on phosphacan (Pn) and other lecticans, as well as to cell surface CSPGs such as neuroglycan C (NC) and NG2. Phosphacan can also bind to cell surface receptors such as neural cell adhesion molecule (NCAM) through its CS glycosaminoglycan chains. Two splice variants of versican are depicted, as well as intact neurocan and its two proteolytic cleavage isoforms: neurocan-N (Nn-N) bound to HA, and neurocan-C (Nn-C) bound in the perineuronal net via interactions with tenascin and a CS glycosaminoglycan. (**B**) Chondroitinase ABC treatment of the perineuronal net associated with cortical neurons degrades all of the CS glycosaminoglycans (red lines) as well as all of the matrix hyaluronan (pink line), which causes major disruptions to the macromolecular heterophilic interactions that hold the perineuronal net together. Disruption of the perineuronal net may allow extension of axons into the vacated space and closer interactions between the membranes of neighboring neurons, contributing to a restoration of neuronal plasticity (*1*).

Pizzorusso *et al.* (*1*) restore plasticity by dissolving part of the perineuronal net that surrounds neuronal cell bodies and their extensions (proximal dendrites) in the brain. The perineuronal net is composed of a diverse set of macromolecules (*4*). Many of these are chondroitin sulfate proteoglycans (CSPGs) that broadly fall into three classes: (i) the lecticans or hyalectans (*5*), which include aggrecan, versican, neurocan, and brevican; (ii) matrix-associated proteoglycans such as phosphacan; and (iii) cell surface proteoglycans such as neuroglycan C, NG2, and a receptor protein tyrosine phosphatase isoform related to phosphacan. CSPGs undergo heterophilic interactions with other matrix molecules to link the net in various ways (see the figure). Matrix glycoproteins such as tenascins link CSPGs to each other and to cell surface molecules via the CSPG chondroitin sulfate side chains. Hyaluronan, an important matrix component, can also link some CSPGs (the lecticans) to one another via their globular hyaluronan-binding domains at their amino termini. The CSPG side chains are phenomenally hydrated because they are composed of polyanionic polysaccharides (glycosaminoglycans) and they therefore keep the phospholipid membranes of neurons apart and occupy large amounts of extracellular space at the same time.

Much of the perineuronal net structure is blown away by the bacterial enzyme chondroitinase ABC, which attacks the CS glycosaminoglycan side chains, preventing CSPG–matrix glycoprotein interactions. However, chondroitinase ABC also degrades hyaluronan, thus destroying the macromolecular aggregation of the lectican CSPGs via their globular amino-terminal domains. Consequently, after chondroitinase ABC digestion of the perineuronal net, neurons should be able to interact with one another more freely in the absence of the extracellular matrix, and neuronal processes such as axons and dendrites should be able to grow more freely into the extracellular space. Dendritic spines are small protrusions on the dendrites of neurons that are known to grow and retract even in adults (*6*) and are the principal sites where excitatory synapses form. It is plausible that spine turnover is facilitated in the absence of a perineuronal net. In this environment, new synapses could form and old synapses break, resulting in a reestablishment of neuronal plasticity. Two pieces of evidence support this idea. First, spine motility is increased when sensory inputs are manipulated to induce plastic changes in the cortex. Second, extracellular matrix molecules gradually increase in extent and complexity during development, and several key components correlate with the end of the critical period of neuronal plasticity (*1, 7*).

It is less clear how the Pizzorusso *et al.* study fits in with other attempts to restore the critical period. More than a decade ago, Muller and Best restored plasticity in the adult cat visual cortex by injecting immature astrocytes (a type of glial cell) into cat brain (*8*). It would be of interest to know whether this treatment affected the extracellular matrix of the cortex. Some components of the perineuronal net are manufactured by glial cells, for example, NG2, phosphacan, versican, and glycosylphos-

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phatidylinositol (GPI)–linked brevican. Interestingly, immature glial cells elaborate larger extracellular matrices than do mature glial cells (*9*). The extracellular matrix in the developing brain is more permissive for growth, but it is not known whether the injected immature astrocytes (*8*) altered the extracellular matrix to a growth-permissive form in the adult cat. If they did, it would help to explain how injecting immature astrocytes restored plasticity.

Future experiments are likely to explore the nature of the perineuronal net and examine its properties in more detail. A number of useful enzymes already exist to do this, including that used by Pizzorusso *et al.* For example, whereas chondroitinase ABC removes CS side chains of CSPGs and degrades hyaluronan, the enzyme streptomyces hyaluronidase could be used to specifically degrade hyaluronan alone. This would only affect the macromolecular aggregation of lecticans in the perineuronal net, leaving the CS side-chain interactions via tenascin intact. Unfortunately, all of the chondroitinases that degrade CS also degrade hyaluronan (*10*). But some specificity could be achieved with keratanases, which degrade keratan sulfate glycosaminoglycans on phosphacan and aggrecan in the perineuronal net without affecting hyaluronan. Experimenting with different enzyme combinations will enable exploration of the properties of the perineuronal net that permit and restrict plasticity.

From a therapeutic viewpoint, it will be important to elucidate whether chondroitinase treatment facilitates invasion of the cerebral cortex by glial tumor cells, a possible detrimental side effect of restoring plasticity. It has been shown that catabolism of a brevican CSPG (called BEHAB) in the brain facilitates glial tumor invasion of cortical tissues (*11*). The time course over which chondroitinase treatment affects the perineuronal net also will be a critical factor in attempts to increase plasticity. It takes at least 8 weeks for the perineuronal net to reestablish itself after a single chondroitinase injection (*12*), which might be a useful time period during which to restore plasticity. Clearly, the road to a useful therapy for enhancing neuronal plasticity in the brain is long, but Pizzorusso and colleagues are among those who have taken the first crucial step.

References

1. T. Pizzorusso *et al.*, *Science* **298**, 1248 (2002).
2. T. N. Wiesel, D. H. Hubel, *J. Neurophysiol.* **26**, 1003 (1963).
3. N. W. Daw, *Visual Development* (Plenum, New York, 1995), chap. 9.
4. A. Oohira *et al.*, *Arch. Biochem. Biophys.* **374**, 24 (2000).
5. R. V. Iozzo, *Annu. Rev. Biochem.* **67**, 609 (1998).
6. B. Lendvai, E. A. Stern, B. Chen, K. Svoboda, *Nature* **404**, 876 (2000).
7. S. Hockfield, R. G. Kalb, S. Zaremba, H. Fryer, *Cold Spring Harbor Symp. Quant. Biol.* **55**, 505 (1990).
8. C. M. Muller, J. Best, *Nature* **342**, 427 (1989).
9. M. Maleski, S. Hockfield, *Glia* **20**, 193 (1997).
10. See http://www.acciusa.com/seikagaku/products/product.asp?catalog=100740-1.
11. C. L. Nutt *et al.*, *Neuroscientist* **7**, 113 (2001).
12. G. Bruckner *et al.*, *Exp. Brain Res.* **121**, 300 (1998).

PERSPECTIVES: SIGNAL TRANSDUCTION

Decoding NF-κB Signaling

Alice Y. Ting and Drew Endy

Pressing a piano key causes a hammer to hit a string. Until the resulting oscillation of the string dampens of its own accord, an audible tone is produced for as long as the key is depressed. A pianist can modify this tone by depressing foot pedals that indirectly control how hard the string is hit and whether or not string vibration is sustained after the key is released. Similarly, signal transduction pathways in living systems are activated by information in the environment; by encoding and transmitting this information, they produce "music" that is interpreted by cells and results in direct changes to cellular behavior. On page 1241 of this issue, Hoffmann *et al.* (*1*) use a combination of experiments and computer modeling to make sense of a particular signal transduction pathway, and they illustrate how the pathway can be manipulated to switch on different target genes.

Hoffmann *et al.* chose to study the NF-κB/IκB signaling pathway. NF-κB (nuclear factor κB) is a transcription factor that helps to govern the expression of genes involved in both the innate and adaptive immune response (*2, 3*). The ability of NF-κB to regulate gene expression is controlled by chemical modifications such as the addition of phosphate groups, and by interactions with other proteins notably members of the IκB family (inhibitors of NF-κB). The binding of NF-κB to IκB helps to localize NF-κB in the cytoplasm. Upon activation of the NF-κB signaling pathway by tumor necrosis factor (TNF), IκB kinases target IκBs for degradation. This allows NF-κB to accumulate in the nucleus, where it binds to DNA, resulting in the expression of target genes. One of the genes activated by NF-κB is that encoding IκBα. Newly synthesized IκBα binds to NF-κB and attenuates the pathway response to TNF, thereby creating a negative feedback loop within the NF-κB/IκB signaling pathway (see the figure). The new work explores two unanswered questions. First, why are there different isoforms of IκB (for example, IκBα, IκBβ, and IκBε)? Second, how does NF-κB control the expression of different genes, or classes of genes, each of which might be required at different times depending on the needs of the cell?

Hoffmann and colleagues start with experimental observations that show how NF-κB activity varies dynamically in response to sustained pathway activation [e.g., (*1, 4*)]. Given knowledge about how IκBα is regulated, they use an abstract linear model of a simple system containing negative feedback to explore how such a system might produce time-dependent oscillations. For a broad range of model parameters, "self-regulation" of model variables results in dampened oscillatory behavior. Hoffmann *et al.* posit that the NF-κB/IκB signaling pathway could produce dampened oscillations of NF-κB activity through the combined action of different IκB isoforms. To examine the individual contributions of each of the IκBs, Hoffmann *et al.* created and characterized knockout cell lines (or "genetically reduced" systems) that each contained only one of the three IκB isoforms. Their surprising observation was that IκBα cells (lacking both β and ε isoforms) behaved quite differently from cells containing only IκBβ or IκBε. The IκBα cells displayed prominent undampened oscillations in nuclear NF-κB upon pathway activation by TNF, whereas IκBβ and IκBε cells produced a monotonic increase in nuclear NF-κB (see the figure).

To better understand the observed differences in the regulation of NF-κB, Hoffmann *et al.* constructed a quantitative model for both the wild-type and knockout cells. According to the model, TNF treatment of IκBα cells causes IκBα degradation, which results in NF-κB translocation to the nucleus (first peak, see the figure, panel A). NF-κB replenishes the level of IκBα, promoting a re-inhibition of NF-κB (first dip, see the figure, panel A). Continued cycles of IκBα degradation and synthesis give rise to oscillations in nuclear NF-κB activity. In the wild-type model

A. Y. Ting is in the Department of Chemistry and D. Endy is in the Division of Biological Engineering and Department of Biology, Massachusetts Institute of Technology, Cambridge, MA 02139, USA. E-mail: endy@mit.edu