the S regions were incorporated into the IgH^a allele. This allowed assessment of class switching of the mutated IgH^a allele relative to that of the wild-type IgH^b allele after the generation of mature B cells. Zarrin *et al.* generated mutations in which one (Sγ1) or both (Sμ and Sγ1) S regions were each replaced by two nearby I-SceI endonuclease cleavage sites. When mouse splenic B cells or B cell hybridomas (B cells engineered to grow indefinitely) expressed the I-SceI endonuclease, IgG1^a production was observed at ~10 to 20% the level observed in cells with wild-type S regions. Because B cell hybridomas do not express detectable AID, Zarrin *et al.* could bypass the requirement for both the deaminase and S regions by artificially generating DNA double-strand breaks.

Two other notable results were obtained. Although deletions between two nearby I-SceI cleavage sites—reminiscent of intra–S region recombination—occurred more frequently than class switching involving distant cleavage sites, the frequency of these short-range deletions (up to ~0.5 kb) was only ~10 times that of the long-range deletions (~100 kb) that occurred during class switching. Moreover, S-region transcription could be dispensed with.

These striking results raise several interesting questions about the role of both S regions and AID in class switch recombination. The frequency of class switching in the Zarrin *et al*. system is much higher than has been seen for joining two double-strand DNA breaks on heterologous chromosomes (*11*). Does some unknown component of the IgH locus provide sites for synapsis that promote DNA joining during recombination, or is the joining of two distant breaks on a single chromosome more frequent than might have been expected? If the latter, perhaps joining is promoted by components of the double-strand break response pathway such as 53BP1 and γH2AX, which may spread a megabase from the break sites (*12*). Although the requirement for S-region transcription is bypassed in the system used by Zarrin *et al*. (at least at Sγ1), is class switching still dependent on activation of other B cell–specific elements involved in gene expression?

B cells orchestrate a complex series of events for class switch recombination, rather than simply providing site-specific endonucleases (like I-SceI) to cleave DNA that lies upstream of constant regions. It may be that involving a specific deaminase and controlling its access to DNA by transcription provide the necessary level of regulation for choosing which of six downstream possible S regions to use. Moreover, cleavage by the yeast endonuclease did not result in normal levels of class switching. Perhaps the multiple DNA lesions throughout the long S regions provide the necessary amount of damage to promote normal levels of class switch recombination. Finally, it may be that AID and/or S regions do have a role in synapsis in the context of normal class switch recombination, and that in the absence of these agents, a high proportion of double-strand breaks are channeled into DNA translocations. The approach designed by Zarrin *et al.* will now allow these questions to be addressed.

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NEUROSCIENCE

Is More Neurogenesis Always Better?

The clinical relevance of increasing neurogenesis in the adult mammalian brain is being questioned as increasing the number of new neurons has positive effects on some brain functions but not others.

Helen E. Scharfman and Rene Hen

For decades, it was believed that the adult mammalian brain could not generate new neurons, but during the 1990s, that concept changed. Evidence of the birth of new neurons in adult mammals, including humans, raised expectations for improved treatment for patients with central nervous system injury or illness. But this enthusiasm has been tempered since then, as more recent studies indicate that excess adult neurogenesis can be as detrimental as a deficit. In some cases, the clinical relevance of increasing neurogenesis may need to be reconsidered.

Neurogenesis in the normal adult mammalian brain is primarily limited to three areas: the subventricular zone, hippocampal dentate gyrus, and olfactory bulb (*1*). The identification that this is true in humans, at least in the hippocampus (*2*), together with the findings that neurogenesis can be increased in laboratory animals by learning, exercise, and antidepressants and decreased by stress and aging (*1*), reinforced the expectation that neurogenesis might be clinically beneficial. Moreover, additional sites in the adult brain—the cortex and hypothalamus—demonstrate ongoing neurogenesis (*3*, *4*), although this remains controversial (*5*). However, we now know that neurogenesis in the adult brain occurs at a very low rate after maturity, and many of the new neurons do not survive for long (*6*). Thus, new neurons born in the adult brain may support plasticity on an acute time scale because of their increased excitability (*7*) but have limited long-term restorative ability. Such transient existence of new neurons should not necessarily dampen therapeutic potential. Survival of new neurons increases with benign interventions such as learning and enriching the environment (*1*). Dormant stem cells may also exist throughout the brain (*8*). These cells could potentially be stimulated to mature in pathological situations or

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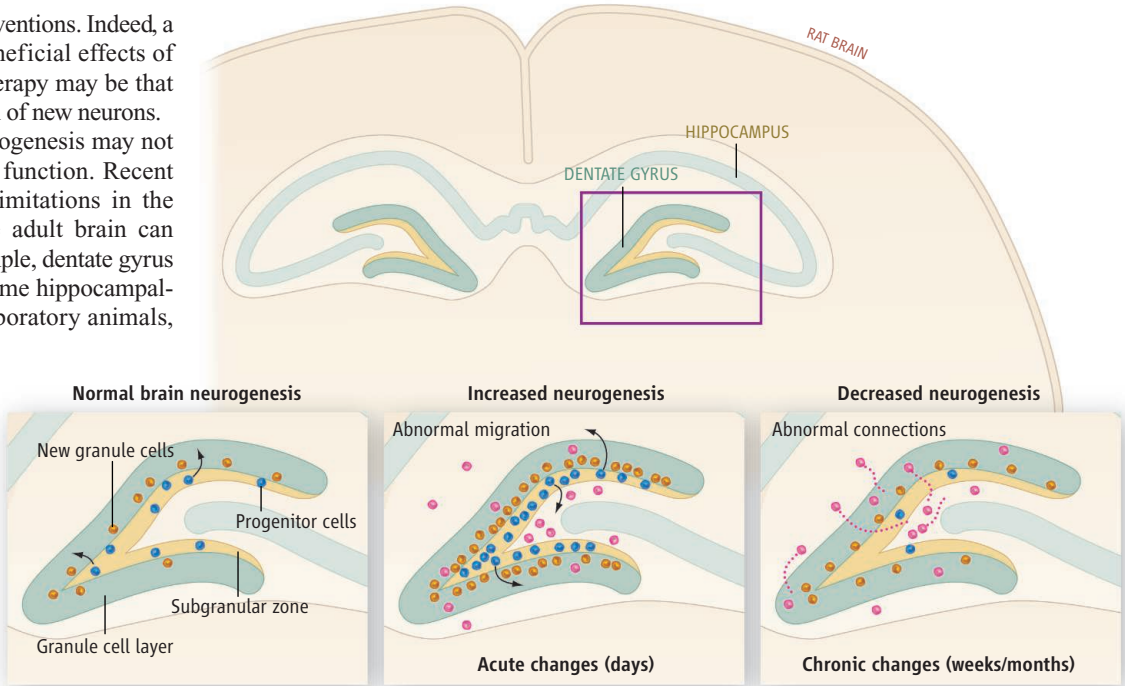
after pharmacological interventions. Indeed, a possible reason for the beneficial effects of rehabilitation or psychotherapy may be that treatment increases survival of new neurons.

But an increase in neurogenesis may not always result in improved function. Recent studies show surprising limitations in the ways new neurons in the adult brain can improve function. For example, dentate gyrus neurogenesis influences some hippocampal-dependent behaviors in laboratory animals, but not others. Specifically, there are positive effects on trace and contextual fear conditioning, but not on spatial learning (*9*–*11*). Animals without new neurons also perform better in certain working memory paradigms (*12*). Specifically, mice that are devoid of neurogenesis due to irradiation or genetic ablation display improved memory in a radial maze, but only when repetitive information is presented. Therefore, manipulations that increase neurogenesis may have positive effects on some behaviors but negative effects on others. In addition, improved function may not always be caused by increased neurogenesis. For example, some of the behavioral effects of enriched environment and antidepressants are independent of their influence on hippocampal neurogenesis (*13*). So despite increasing experimental support for an influence of neurogenesis on specific behaviors, it is not yet clear how these effects may translate into clinical benefits.



Adult hippocampal neurogenesis. Acute and chronic changes in rat brain neurogenesis after severe seizures parallel changes observed in temporal lobe epilepsy. **(Left)** Most progenitor cells typically become granule cells that migrate to the granule cell layer. **(Center)** Seizures rapidly and transiently increase the rate of neurogenesis and expression of growth factors that influence neurogenesis. **(Right)** Ectopic migration of new neurons may result in abnormal neuronal connections. Neurogenesis in laboratory animals and humans may decline at later times, but some of the neurons that were born in the acute period persist. Reduced neurogenesis and growth factor levels, together with abnormal new circuitry, may contribute to the chronic condition.

Neurogenesis under pathological conditions also indicates limits to the utility of new neurons in improving brain function. A common theme is that neurogenesis increases after injury to the central nervous system (*14*). This could be considered restorative, and findings such as the migration of new neurons to the site of damage, at least in animal models of stroke (*15*, *16*), support this view. Because pathological conditions also increase the production of factors that promote neurogenesis (brain-derived neurotrophic factor, vascular endothelial growth factor, insulin-like growth factor, fibroblast growth factor 2, and neuropeptide Y), there may be a rapid response of the brain to damage that reflects a recapitulation of developmental programs. However, the acute increase in neurogenesis and associated growth-related changes are often transient, limiting their influence. Indeed, after an acute increase in neurogenesis, there may be a protracted decline in the rate of neurogenesis (see the figure), and this could contribute to what is often an intractable clinical condition.

Drugs that increase hippocampal neurogenesis
Antidepressants (*19*, *20*, *22*)
Tricyclic antidepressants
Selective serotonin reuptake inhibitors
Mood stabilizers (*22*)
Lithium
Valproic acid
Cognitive enhancers (*23*)
Galantamine
Memantine
Anesthetics (*24*)
Ketamine
Steroids (*1*, *22*)
Estradiol
Dehydroepiandrosterone
Other (*22*)
Rolipram
Statins
Sildenafil (Viagra)

Increasing neurogenesis may not always be beneficial in the context of pathology. New neurons may not develop, migrate, or integrate correctly, as in animal models of temporal lobe epilepsy. In such models, severe prolonged seizures (status epilepticus) are followed not only by robust increases in numbers of new granule neurons in the dentate gyrus, but also by inappropriate migration, differentiation, and integration of many of these new neurons (see the figure) (*17*). This may contribute to persistent seizures in animals, and a similar process may occur in some patients with intractable temporal lobe epilepsy (*18*).

Some commonly prescribed drugs have robust effects on neurogenesis. These include antidepressants and mood stabilizers (see the Table). Indeed, some of these treatments may ameliorate symptoms because of their effects on neurogenesis, as suggested by studies in animal models (*19*, *20*). Specifically, the behavioral effects of selective serotonin reuptake inhibitors and tricyclic antidepressants were blocked in two rodent models of anxiety/depression by radiological and genetic ablation of neurogenesis in the dentate gyrus (*19*). How do changes in hippocampal function, presumably caused by neurogenesis, affect mood or anxiety? Although the answer to this question is not clear, ablation of the ventral hippocampus can alter mood, presumably because of its connectivity with limbic structures such as the amygdala, the prefrontal cortex, and the nucleus accumbens (*21*).

Although neurogenesis occurs throughout life, its clinical potential remains unclear in

some cases. While there is some evidence that strategies to increase neurogenesis may lead to the development of new therapeutics such as antidepressants, decreasing neurogenesis may be beneficial in other cases, such as epilepsy.

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GEOCHEMISTRY

Fuel for Plate Tectonics

Nathalie Bolfan-Casanova

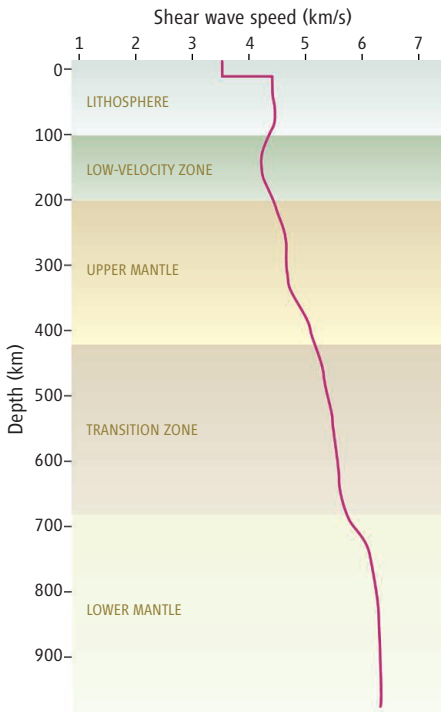
Water storage in Earth's mantle causes seismic waves to slow down when passing through Earth's interior.

Our understanding of plate tectonics relies on the concept of relatively rigid rocky plates moving on a more ductile shallow mantle called the asthenosphere (*1*). The word asthenosphere comes from the Greek "a-sthenos" meaning "without strength." This lack of strength especially affects seismic waves, which slow down when entering the asthenosphere (see the figure). For decades, Earth scientists have tried to understand the reason for this seismic wave deceleration. On page 364 of this issue, Mierdel *et al*. (*2*) report new experimental findings on the maximum amount of water that can be stored by the shallow mantle. These results may solve a number of riddles, including the cause of the seismic slowdown.

Why is water important? Water not only is essential to life but also controls the dynamics of Earth's interior (*3*). Since the 1990s, geologists have recognized with increasing certainty that mantle minerals can hold substantial amounts of water. This implies that the oceans may no longer be the main water reservoir of Earth. But water does not necessarily have to be fluid to be stored in the deep Earth. Rather, it dissolves as hydroxyl (OH^-) in anhydrous minerals (such as olivine, pyroxenes, garnet, and their high-pressure forms) as a result of the association of a proton (H^+) with oxygen of the mineral lattice. This creates a defect in the lattice and thereby speeds up the kinetics of physical properties that depend on the concentration of defects. Even at very low concentrations—lower than 1% by weight—the presence of water has many consequences for mantle properties such as creep and electrical conductivity (*4*, *5*). When present in minerals as a defect, water will enhance the deformation of rocks and make them more ductile. Dissolved as H^+ in minerals, water will also increase the electrical conductivity of the mantle by adding mobile charges. Water also lowers the melting point of mantle rocks and allows melting at greater depths than in the absence of water.

To understand how water affects mantle properties, we need to know how much water can be stored in mantle minerals and how this storage capacity varies with increasing depth. Researchers have firmly established that the solubility of water in minerals increases with pressure and water partial pressure (*6*). The water storage capacity of Earth's upper mantle (extending from the base of the crust down to the transition zone at 410 km depth) was thought to increase monotonically with depth. Moreover, in a mantle consisting of 60% by volume of olivine, this mineral was believed to be the one that dictates the water budget.

The results of Mierdel *et al*. completely change the picture: Water storage capacity in Earth's shallow mantle is controlled by orthopyroxene, a less abundant phase than olivine, because water solubility in this phase is more than two orders of magnitude higher than in olivine. The reason for this is composition. The enhanced affinity of pyroxenes for water is indeed aided by aluminum through the coupled substitution of $2Al^{3+} + 2H^+$ for $2Mg^{2+} + Si^{4+}$, which is a very efficient way to store up to 1 weight % water in $MgSiO_3$ orthopyroxene.



Seismic speed bumps. Schematic shear wave speed profile across Earth's mantle.

Mierdel *et al*. also show that the curve of water saturation versus depth has a pronounced minimum between 100 and 200 km. Indeed, the water storage capacity of pyroxene with substituted aluminum is dependent on the acceptance of the large aluminum cation into the small tetrahedral site of silicon, the

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