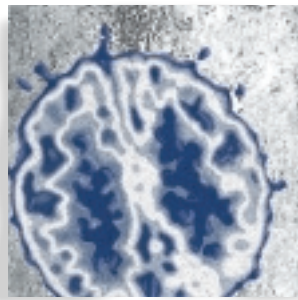


Structural plasticity of the adult brain

Fred H. Gage, PhD



The adult brain has long been considered stable and unchanging, except for the inevitable decline that occurs with aging. This view is now being challenged with clear evidence that structural changes occur in the brain throughout life, including the generation of new neurons and other brain cells, and connections between and among neurons. What is as remarkable is that the changes that occur in the adult brain are influenced by the behaviors an individual engages in, as well as the environment in which an individual lives, works, and plays. Learning how behavior and environment regulate brain structure and function will lead to strategies to live more effective lives and perhaps protect from, or repair, brain damage and brain disease.

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Those of us who study the nervous system believe that the brain is the organ that controls our behavior. Therefore, what we think and what we do, while obviously influenced by the experience, are results of the brain's processing of information and directing our subsequent actions. Given this basic assumption, it is no wonder that the most common model or analogy of how the brain operates is that of a computer. While this analogy may have some heuristic value, it is likely wrong or at least very limiting. The brain is an organ, like the liver, heart, and kidney, and is made of chemicals, cells, and tissue.

Communication between brain cells is mediated through neurons with long processes (axons) that connect many cells at once and release small batches of chemical information (neurotransmitters) to a network of other neurons. The neurons receive the signals on their antennae, called dendrites, which protrude, in many cases, quite elaborately from the cell body. The specific site where the chemical signal from one cell makes contact with another cell is called a synapse, which is made up of signaling cells (presynaptic boutons) and receiving cells (postsynaptic spines). The synapse is the structural unit that transmits the majority of information between neurons. Each neuron can have thousands of these synapses on its dendrites and cell body. The real trick for the neuron is to calculate (interpret) the temporal and spatially transmitted information it receives and to send that interpreted message onto the next neurons in a circuit. The aggregation of this information passing and processing results in thought and behavior.

Adult neural stability

One of the main reasons for viewing the brain as a stable machine or computer is because this analogy helps explain how we can remember from one instant to the next. If the underlying structure was changing all the

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time, how could we do that? For that matter, if the brain is the seat of consciousness, as proposed by Francis Crick,¹ how would we maintain a self identity if the brain were not stable? Well, the dirty little secret is coming out: the brain is not stable and that is a good thing. The structural changes seen in the brain may be required to provide the extra capacity we need for dealing with complexity. It may also provide the underpinning for the adaptability and flexibility, or “plasticity” as neuroscientists refer to it, that is required for dealing with the variety of challenges that we face throughout life.

In addition, and in some ways even more importantly, structural plasticity provides the mechanism for the brain to repair itself. All organs of the body have some capacity to repair themselves following minor injury. Skin, liver, heart, kidney, lung, and blood have some level of repair capacity, and most have the capacity to generate new cells to replace damaged ones, at least to a small extent.

Until recently, the brain was considered unique in its lack of ability to repair itself once it had matured to adulthood. Researchers were convinced that “*Once development was ended, the founts of growth and regeneration of the axons and dendrites dried up irrevocably. In the adult center the nerve paths are something fixed and immutable, nothing may be regenerated*” (S. Ramon y Cajal, 1928).² This dogma even influenced clinical research and the accepted methods for treating brain damage. In general, the therapeutic strategy clinicians would suggest could be summed up as “try not to damage your brain, because there is no way to fix it.” The dominant strategy for repairing a broken, injured, or damaged brain was to replace the lost neurotransmitters (for example, providing L-dopa for Parkinson’s disease [PD], which works pretty well for a while) or, more experimentally, to replace the missing or dead neurons (as in neural transplantation for treating PD, Huntington’s disease [HD], Alzheimer’s disease, amyotrophic lateral sclerosis, or spinal cord injury). The replacement of dead cells by transplantation of externally derived cells continues both experimentally and clinically and, with the new hope provided by the availability (albeit limited) of the pluripotent human embryonic stem cells, optimism for transplantation therapy has been renewed. The previously accepted dogma of adult neural stability is now being called into question. Pioneering studies by Raisman,³ Bjorklund,⁴ and Aguayo⁵ and their colleagues in the 1960s and 1970s revealed that damaged axons could grow under some extraordinary circumstances. These studies have led to a recent stampede of very

promising work that could lead to the regeneration of cut or damaged axons due to spinal cord injury.⁶ A deeper blow to the dogma of adult neural stability has been the recent acceptance of the ability of certain areas of the adult brain to generate new neurons throughout life, known as adult neurogenesis. Early evidence of this ability was generated by Altman and colleagues in the 1960s and 1970s,⁷ and was beautifully extended to birds by Goldman and Nottebohm in the 1980s,⁸ and later to nonhuman primates and humans in the 1990s.⁹ During this same period, it was discovered that adult neurogenesis itself was not stable and predictable, but was, in fact, highly regulated by experience, with stress and aging decreasing neurogenesis and environmental enrichment and exercise increasing neurogenesis.

Stem cells in the adult brain

The surprising observation that neurogenesis continues in the adult nervous system has led to the discovery that there are stem cells in the adult brain that generate the new neurons. A stem cell is an uncommitted cell that, when it divides, can give rise to itself (self-renewal) and can also give rise to any or all of the three main cell lineages of the brain: neurons, astrocytes, and oligodendrocytes. Using a variety of methods, it is now possible to isolate these stem cells from the adult brain and use specific growth factors, like fibroblast growth factor (FGF) and epidermal growth factor (EGF), to induce them to divide indefinitely in culture dishes in the laboratory. Most of the studies that have determined that the cells from the brain are stem cells have done so by studying the cells in vitro; the demonstration of “stemness” in vivo in the adult brain is difficult. However, the numbers of adult stem cells can be greatly expanded and they can be genetically marked in culture and then transplanted back to the adult nervous system.¹⁰ In these studies, the cells survived well and differentiated or matured into authentic neurons in the two areas of the brain where neurogenesis normally occurs, the hippocampus and the olfactory bulb. However, the adult stem cells did not readily differentiate into neurons in any other areas. Interestingly, they did differentiate into astrocytes and oligodendrocytes in other areas.

This behavior of adult stem cells that were expanded in culture and transplanted back to the adult brain contrasts with the behavior of fresh tissue derived from the fetal brain that has not been extensively expanded in

culture. Freshly dissociated cells from the fetal brain, if taken at the appropriate time and from the appropriate location, survive and differentiate quite readily into the types of neurons and glial cells from which they were obtained. In fact, the fetal cells have already matured somewhat and have committed themselves to a particular neuronal type; given minimal local environmental signals, they proceed toward their predetermined fates. These properties of fetal tissue make it more amenable to therapeutic applications. For example, in experimental treatments for PD, committed dopamine cells are being taken from fetal substantia nigra for transplantation; in HD treatment, fetal cells are being taken from fetal basal ganglia and transplanted into patients.

The irony then is that fetal tissue grafts are more mature than adult stem cells that have been isolated and expanded in culture. The problem with the adult brain is that, outside of the limited number of stem cells, the adult cells are too mature and will not withstand the isolation and transplantation procedures; they have lost the youthfulness to survive and integrate into the adult brain. Part of the problem with fetal tissue is that there are so few cells available that are at just the right age and in just the right location, which means that either many fetuses must be used for each transplantation or the cells must be put in culture to expand their number. However, once placed in culture, only the primitive fetal stem cells will divide extensively, and, as was seen with adult stem cells, these fetal stem cells are so immature that, unless the adult brain has all the necessary signals to direct them to a particular neural type, ie, a hippocampal neuron, then the cells will either die or become glial cells or merely persist as stem cells.

The way to make both fetal and adult stem cells more useful for therapeutic transplantation applications is to determine what the signals are in development that induce the stem cells to become a particular neuronal type, and then induce the stem cells toward that lineage in a culture dish just far enough so that, once they are subsequently transplanted to a particular part of the brain, they will continue toward that cell type and eventually integrate and replace the missing function.

At this juncture of stem cell biology and adult neurogenesis, the concept of neural self-repair emerged. The question was posed: if the adult brain has pockets of stem cells that can become neurons, astroglial cells (which play a crucial role in generating and maintaining the health of neurons), and oligodendrocytes (a third type of cell in the

brain that insulates the neuronal axons so that they can transmit their information efficiently), then why can't the brain repair itself after injury or disease? The answer seemed to be that the brain is capable of repairing itself and that it already does, to a limited extent. The current strategy is, therefore, to try to understand how, and perhaps to what end, adult neurogenesis normally occurs, in order to find ways whereby we can enhance it, direct it, and more generally harness the residual elements of neural plasticity that are inherent to neural self-repair as a treatment for brain disorders. Surprisingly, we may not be too far away from this goal. Let's first summarize what we know about the process of adult neurogenesis.

What is adult neurogenesis/cell genesis?

As it turns out, the birth of new brain cells or neurogenesis is not an all-or-nothing event. The multipotent stem cell divides periodically in the brain, giving rise to another stem cell (self-renewal) and some progeny that may grow up to be working cells, but the fate is not guaranteed. The progeny must move away from the influence of the mother stem cell into an area that is permissive for maturation. On average, about 50% of these newborn cells never make it and instead die and disappear. Those that do survive may become a neuron or glial cell, depending on where they end up and what type of activity is going on in that brain area at that time. Even so, it takes over a month from the time the new cell is born until it is functionally integrated in the brain, receiving and sending information. Thus, neurogenesis is a process, not an event, and one that—as I said earlier and will emphasize repeatedly—is highly regulated. The factors that regulate neurogenesis are being intensely investigated and new factors that modulate different components of neurogenesis are being discovered on a regular basis. For example, factors known to be important in development of the nervous system, like Sonic hedgehog¹¹ (which was first discovered in fly brain and called hedgehog), have been shown to regulate the proliferation; BMPs (bone morphogenetic proteins) and Notch¹² (which were also first discovered in fly brain) appear to be regulators of whether the newborn cells decide to become glia; and molecules associated with the glial cells that surround the stem cells instruct the newborn cells to become neurons. Once the cells are committed to becoming a neuron or glial cell, other growth factors like brain-derived neurotrophic factor (BDNF)¹³ and insulin-like growth factor (IGF)¹⁴ play important roles in keeping the cells alive and encouraging

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the young cells to mature and become functional. It is the understanding of how these growth factors and cellular environments control neurogenesis in the normal setting that will lead to development of therapies aimed at enhancing and directing neurogenesis in disease states.

Where does adult neurogenesis/ cell genesis occur?

Neurogenesis, the process of generating new neurons, does not occur spontaneously in every part of the brain. In fact, it only occurs robustly in two areas of the brain, while cell division or cell genesis appears, surprisingly, to occur everywhere in the brain and spinal cord.^{15,16} In most areas of the brain, cell genesis results in the birth of new glial cells that are likely participating in the microrepair process. Reports that new neurons are born outside of the two well-documented areas of neurogenesis, eg, the frontal cortex, have not been substantiated.¹⁷ It is most likely that the complexity of the methods used to prove neurogenesis have led to these anomalous observations, though with new and more sensitive methods, low levels of neurogenesis may be detected in more regions of the adult brain and spinal cord. Certainly, as we learn more about the molecular mechanism that controls neurogenesis, as well as the environmental stimuli that regulate neurogenesis, we anticipate that we will be able to direct neurogenesis anywhere in the brain.¹⁰ The most robust cell proliferation occurs in the ventricles of the forebrain, where large numbers of cells migrate forward to the olfactory bulb, a brain structure involved in smell, where the cells differentiate into a variety of different kinds of neurons. We are just now learning about how the olfactory bulb functions normally, and do not have a clear picture as to what role these new cells may play in the function of this brain structure.^{18,19} The second brain area—and the only structure where neurogenesis has been confirmed in all adult mammals from mice to man—is the hippocampus, or more precisely the dentate gyrus of the hippocampus.¹⁹ The stem cells of the hippocampus reside in the interior of the densely packed granule cells. Once the stem cells divide and progeny are born, they migrate into the densely packed area and over the next month either die or survive and contribute to the function of the critical brain area. The hippocampus is critical to the formation of new memories, and thus any theory for the functional significance of neurogenesis will likely interpret the value of new neurons in terms of providing flexibility and

adaptability to the processing of new information. Since it takes a month from the time the new cells are born until they are integrated into the functional circuits of the brain, the role that the new neurons play in behavior has likely less to do with birth of the cells and more to do with the properties of the newly born functioning neuron.²⁰ Thus, future studies are focusing in part on determining whether the spines and synapses of the newly born neurons have properties that give them advantages over neurons that have been in the circuit for the whole life of an animal. One of the most striking aspects of neurogenesis in the hippocampus is the number of events, experiences, and factors that can regulate either the rate of cell division, the survival of the newly born neurons, or their integration into the neural circuitry. First and foremost, there is a clear genetic underpinning to neurogenesis, with a correlation in mice showing that those strains of mice with higher rates of neurogenesis learn more quickly.^{21,22} However, as with most things, it is not nature or nurture, but more correctly an interaction or cooperation between the two. For example, movement of adult and even old mice from a rather sterile simplified cage into a large enriched environment with significant complexity and diversity will result in a significant increase in new neurons by decreasing the number of cells that die. This increase in new neurons correlates with increased functioning of the hippocampus, as well as a significant improvement in learning and memory. In an attempt in my laboratory to tease out the elements of the enriched environment that are critical for the increased neurogenesis, van Praag discovered that running on a running wheel alone was sufficient to nearly double the number of dividing cells, resulting in robust increases in new neurons.^{23,24} In addition to the positive effects of exercise and environmental enrichment, the process of neurogenesis is also negatively regulated by events in the environment, such as stress, injury, and disease. Understanding how neurogenesis is normally regulated will be the key to developing strategies to counteract the misregulations of neurogenesis.

How does the process of neurogenesis respond in the damaged, injured, or diseased brain?

In the last 5 years, a striking number of neurological diseases and conditions have been shown to affect neurogenesis, especially in the hippocampus. For example, most forms of experimental epilepsy^{25,26} result in a robust

increase in the proliferation of stem cells within the hippocampus. Many of these new cells die, but some survive and, as a result of the epileptic state, these new cells migrate to the wrong place in the hippocampus and appear to differentiate incorrectly. These incorrectly generated new neurons have been speculated to play a role in the persistence of certain types of abnormal behavior and pathology that result from the epileptiform activity. By understanding how neurogenesis normally occurs to generate healthy neurons, it is hoped that this aberrant neurogenesis could be blocked or perhaps the aberrantly generated cells could be trained to wire up correctly (even at a later point in time), given the remarkable structural plasticity of these new brain cells.

Cerebral stroke also results in a striking increase in the proliferation of new cells in the hippocampus, but most of these cells die soon thereafter. In addition, in certain types of stroke (like ischemia), there is loss of cells in areas of the brain that do not normally give rise to new neurons, and thus offer little hope for repair.^{27,28} Quite remarkably, more recent studies have revealed that, in fact, the brain is inducing repair by bringing new cells in from areas of the brain that do have stem cells and directing them to the sites of damage. While with severe strokes, this microrepair is not enough to reverse the damage, it is likely that this microrepair system is adequate to protect, prevent, and repair the brain after small, often-unrecognized strokes. Some of this repair is likely to be behind the often-observed remarkable though quite variable recovery that occurs after many strokes. Growth factors like EGF and FGF are now being used to try to enhance the intrinsic repair process, and with encouraging results.²⁹

One of the most striking correlations between disease and neurogenesis is in depression. As mentioned above, stress reduces the process of neurogenesis leading to fewer newborn cells in the dentate gyrus, and chronic stress is believed to be the most important causal factor in depression aside from genetic predisposition.³⁰⁻³² Antidepressants (tricyclic antidepressants, selective serotonin reuptake inhibitors, tianeptine, and lithium) augment neurogenesis in the dentate gyrus of experimental animals and, interestingly, the time required to observe therapeutic effects of these drugs corresponds to the time course for neurogenesis. This has led to a hypothesis that depression is in part caused by a decrease in neurogenesis in the dentate gyrus and thus antidepressant therapy and physical therapy (ie, running and exercise)

reverse depression by activating neurogenesis in the dentate gyrus. While this is currently only a working hypothesis, there is converging evidence to support this view, which is leading to the examination of other factors that affect adult neurogenesis and the determination of their effects on depression.

Harnessing the endogenous capacity for self-repair that exists in the adult brain

We now know that the brain does indeed have a pool of residual cells that can divide making new cells that can roam around the brain and spinal cord and, under special conditions, differentiate into new functioning cells. We are also beginning to understand some of the cellular and molecular factors, as well as environment events, that regulate the process of neurogenesis. Importantly, there is a consistent correlation between improved function and increases in neurogenesis. This is particularly the case for hippocampus-associated behaviors and functions; moreover, several neural diseases have been associated with changes in neurogenesis. Now the principle strategy is to learn enough about the factors that regulate each of the components of neurogenesis in order to control cell proliferation (making more cells), migration (getting the cells to places where they are needed), and differentiation (turning the cells into the type of cell that is needed). For diseases of the brain and spinal cord, this will require more knowledge about which cells are affected in a disease, as well as knowing more about the factors that regulate the components of neurogenesis:

- For depression, epilepsy, and stroke, which are diseases that involve the hippocampus (a structure where neurogenesis does occur), the most straightforward strategy would be to induce more neurogenesis or reroute neurogenesis.
- In diseases like HD and PD, where very specific cell types die to cause the symptoms, the best strategy would be to induce the local dividing cells to proliferate and then differentiate in small spine neurons, in the case of HD, and dopamine neurons, in the case of PD.
- In diseases like spinal cord injury or multiple sclerosis, the strategy may not be to make endogenous cells become neurons, but rather to ensheath oligodendrocytes. Since the endogenous cells already have the capacity to make these cells at low frequency in the intact spinal cord, the task will be to enhance the endogenous capacity.

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Conclusion

The task ahead—to realize the goals of these strategies—is not an easy one, but it is the knowledge that this is a realistic and approachable strategy that heralds a remarkable change in how we even think about brain disease, damage, and repair. I imagine a time when selective drugs will be available to stimulate components of neurogenesis, and

this treatment will be combined with very specific physical therapy directed at activating specific brain areas to accept and integrate the new cells in that brain area. The implication of this knowledge is that we will be able to conduct our lives in such a way as to limit brain disease and enhance the natural repair process. □

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Plasticidad estructural del cerebro adulto

Por largo tiempo el cerebro adulto se ha considerado estable e inmodificable, excepto por la declinación inevitable que ocurre con el envejecimiento. Este punto de vista actualmente se cuestiona debido a claras evidencias acerca de cambios estructurales en el cerebro a lo largo de la vida, incluyendo la generación de nuevas neuronas y otras células cerebrales, como también de conexiones entre las neuronas. Es destacable el hecho que los cambios que ocurren en el cerebro adulto son influenciados por las conductas que el individuo adopta, como también por el ambiente en que vive, trabaja y se desenvuelve. El conocer cómo la conducta y el ambiente regulan la estructura y función cerebral conducirá a adoptar modos de vida más efectivos y tal vez ayudará a protegerse de, o a tratar daños y enfermedades cerebrales.

Plasticité structurale du cerveau adulte

Le cerveau adulte a longtemps été considéré comme stable et immuable, sauf en ce qui concerne l'inévitable déclin survenant avec le vieillissement. Ce point de vue est maintenant remis en question par des arguments manifestes en faveur de changements structuraux apparaissant dans le cerveau au cours de la vie, dont la création de nouveaux neurones et autres cellules cérébrales et de connexions parmi les neurones et entre eux. Le fait remarquable est que les changements apparaissant dans le cerveau adulte sont influencés par les comportements qu'un individu adopte ainsi que par l'environnement dans lequel celui-ci vit, travaille et agit. Apprendre comment le comportement et l'environnement régulent la structure et la fonction cérébrales conduira à adopter des modes de vie plus efficaces et peut-être se prémunir contre des lésions et pathologies cérébrales, ou les traiter.

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