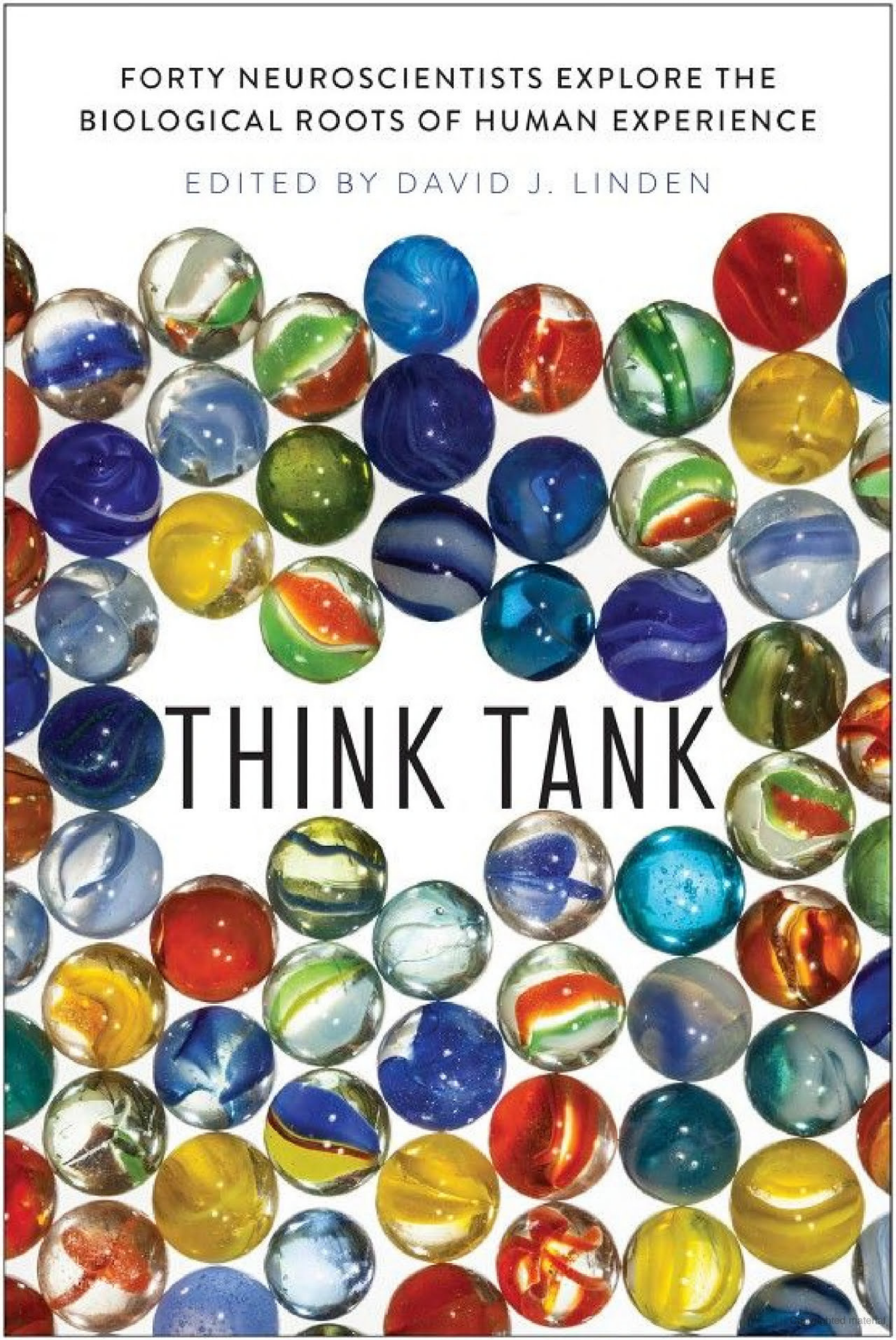
FORTY NEUROSCIENTISTS EXPLORE THE BIOLOGICAL ROOTS OF HUMAN EXPERIENCE

EDITED BY DAVID J. LINDEN



THINK TANK

Published with assistance from the foundation established in memory of Calvin Chapin of the Class of 1788, Yale College.

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Set in Scala & Scala Sans type by Integrated Publishing Solutions, Grand Rapids, Michigan.
Printed in the United States of America.

Library of Congress Control Number: 2017955418
ISBN 978-0-300-22554-9 (hardcover : alk. paper)

A catalogue record for this book is available from the British Library.

This paper meets the requirements of ANSI/NISO Z39.48-1992 (Permanence of Paper).

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PREFACE

Scientists are trained to be meticulous when they speak about their work. That's why I like getting my neuroscience colleagues tipsy. For years, after plying them with spirits or cannabis, I've been asking brain researchers the same simple question: "What idea about brain function would you most like to explain to the world?" I've been delighted with their responses. They don't delve into the minutiae of their latest experiments or lapse into nerd speak. They sit up a little straighter, open their eyes a little wider, and give clear, insightful, and often unpredictable or counterintuitive answers.

This book is the result of those conversations. I've invited a group of the world's leading neuroscientists, my dream team of unusually thoughtful, erudite, and clear-thinking researchers, to answer that key question in the form of a short essay. Although I have taken care to invite contributors with varied expertise, it has not been my intention to create an informal comprehensive textbook of neuroscience in miniature. Rather, I have chosen a diverse set of scientists but have encouraged each author to choose her or his own topic to tell the scientific story that she or he is burning to share.

But let's face it: most books about the brain are not written by brain researchers, and most of them are not very good.

Many are dull, and those that are readable are often uninformed or even fraudulent. This is the age of the brain, but thoughtful people have become understandably skeptical, having been inundated by a fire hose of neurobullshit ("looking at the color blue makes you more creative" or "the brains of Republicans and Democrats are structurally different"). I believe that readers hunger for reliable and compelling information about the biological basis of human experience. They want to learn what is known, what we suspect but cannot yet prove, and what remains a complete mystery about neural function. And they want to believe what they read.

The purpose of this book is not to launch a screed against neurobullshit but rather to offer an honest, positive recounting of what we know about the biology that underlies your everyday experience, along with some speculation about what the future will hold in terms of understanding the nervous system, treating its diseases, and interfacing with electronic devices. Along the way, we'll explore the genetic basis of personality; the brain substrates of aesthetic responses; and the origin of strong subconscious drives for love, sex, food, and psychoactive drugs. We'll examine the origins of human individuality, empathy, and memory. In short, we'll do our best to explain the biological basis of our human mental and social life and the means by which it interacts with and is molded by individual experience, culture, and the long reach of evolution. And we'll be honest about what is known and what is not. Welcome to the think tank!

David J. Linden

Baltimore, USA

THINK TANK

Primer

OUR HUMAN BRAIN WAS NOT DESIGNED ALL AT ONCE BY A GENIUS INVENTOR ON A BLANK SHEET OF PAPER

David J. Linden

THIS IS MY ATTEMPT to boil down the basic facts of cellular neuroscience into a small cup of tasty soup. If you've already studied neuroscience or you like to read about brain function, then you've likely heard much of this material before. I won't be offended if you skip this part of the meal. But if you haven't or if you're looking for a refresher, this section will serve to bring you up to speed and prepare you well for the essays that follow.

Around 550 million years ago it was simple to be an animal. You might be a marine sponge, attached to rock, beating your tiny whip-like flagella to pass seawater through your body in order to obtain oxygen and filter out bacteria and other small food particles. You'd have specialized cells that allow parts of your body to slowly contract to regulate this flow of water, but you couldn't move across the sea floor properly. Or you might be an odd, simple animal called a placozoan, a beast that looks like the world's smallest crepe—a flattened disc of

tissue about 2 millimeters in diameter with cilia sprouting from your underside like an upside-down shag carpet. These cilia propel you slowly across the sea floor, allowing you to seek out the clumps of bacteria growing on the sea floor that are your food. When you found a particularly delicious clump, you could fold your body around it and secrete digestive juices into this makeshift pouch to speed your absorption of nutrients. Once digestion was finished, you would then unfold yourself and resume your slow ciliated crawl. Remarkably, as either a sponge or a placozoan, you could accomplish all sorts of useful tasks—sensing and responding to your environment, finding food, moving slowly, and reproducing yourself—without a brain or even any of the specialized cells called neurons that are the main building blocks of brains and nerves.

Neurons are wonderful. They have unique properties that allow them to rapidly receive, process, and send electrical signals to other neurons, muscles, or glands. The best estimates are that neurons first appeared about 540 million years ago in animals that were similar to modern-day jellyfish. We aren't sure why neurons evolved, but we do know that they appeared at roughly the same time that animals first started to eat each other, with all of the chasing and escaping that entails. So it's a reasonable hypothesis that neurons evolved to allow for more rapid sensing and movement, behaviors that became useful once life turned into a critter-eat-critter situation.

Neurons come in a variety of sizes and shapes, but they have many structures in common. Like in all animal cells, a thin, outer membrane encloses a neuron. Neurons have a cell body, which contains the cell nucleus, a storehouse of genetic instructions encoded in DNA. The cell body can be triangular, round, or ovoid and ranges in size from 4 to 30 microns across. Perhaps a more useful way to think about this size is that 3 typical neuronal cell bodies laid side by side would just about span the width of a human hair. Growing from the cell body are large, tapering branches called dendrites. These are the location where a neuron receives most of the chemical signals from other neurons. Dendrites can be short or long, spindly or shaggy, or, in some cases, entirely missing. Some are smooth while others are covered with tiny nubbins called dendritic spines. Most neurons have at least several branching dendrites, and they also have a single long, thin protrusion growing from the cell body. Called the axon, this is the information-sending part of the neuron. While a single axon grows from the cell body, it often branches, and these branches can travel to various destinations. Axons can be very long. For example, some run all the way from a person's toes to the top of the spinal column.

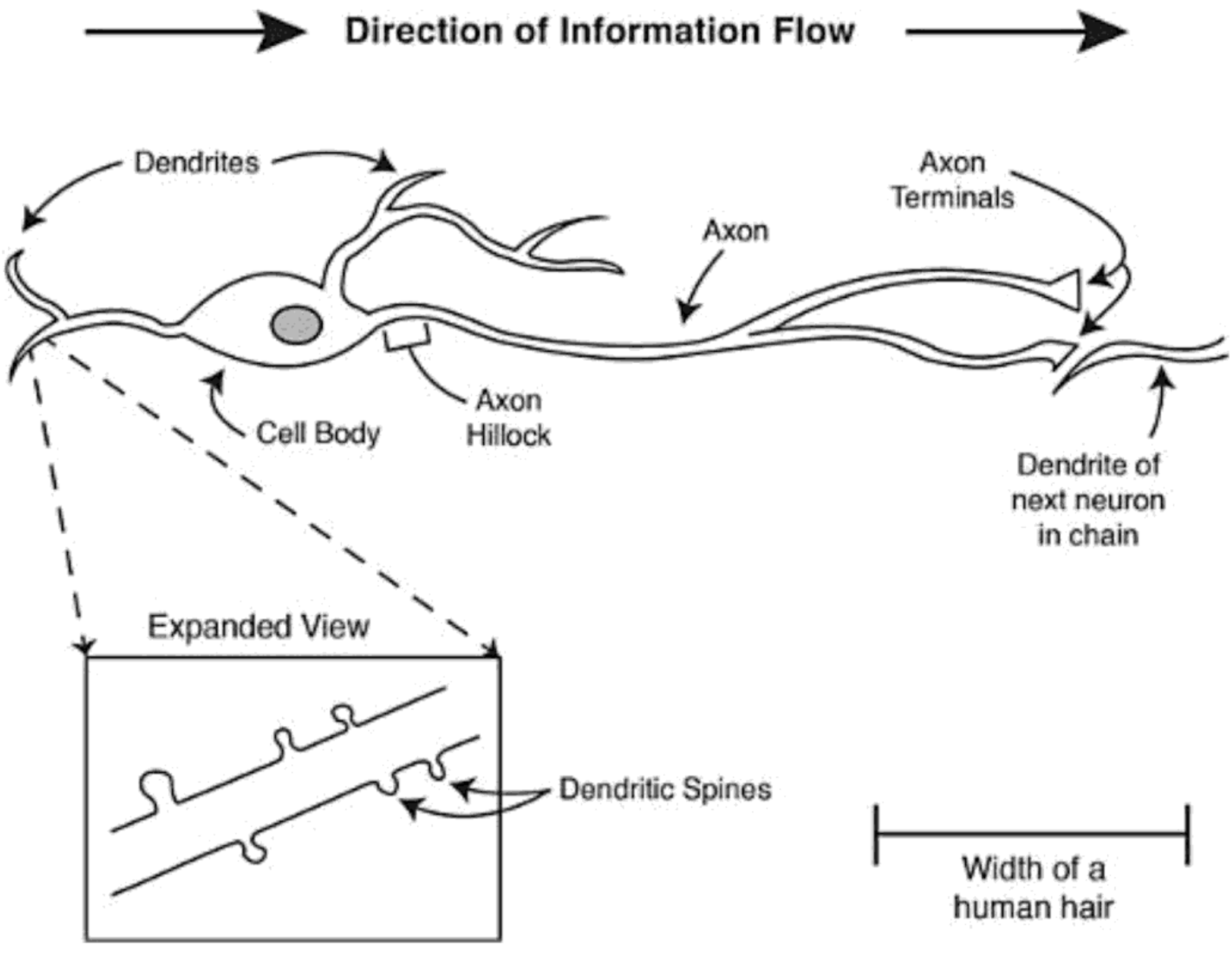

FIGURE 1. The major parts of a typical neuron and the flow of electrical information from one neuron to another.

Information is sent from the axon of one neuron to the dendrite of the next at specialized connections called synapses. At synapses, the tips of axons of one neuron come very close to, but do not actually touch, the next neuron (figure 1). The axon terminals contain many tiny balls made of membrane. Each of these balls, called synaptic vesicles, is loaded with about 1,000 molecules of a special type of chemical called a neurotransmitter. There is a very narrow saltwater-filled gap between the axon terminal of one neuron and the dendrite of the next called the synaptic cleft. On average, each neuron receives about five thousand synapses, mostly on the dendrites, with some on the cell body and a few

on the axon. When we multiply 5,000 synapses per neuron by 100 billion neurons per human brain, the result is an enormous number as an estimate of the number of synapses in the brain: 500 trillion. To put this number in perspective, if you wanted to give away your synapses, each person on the planet (in 2017) could receive about 64,000 of them.

Synapses are the switching points between two forms of rapid signaling in the brain: electrical impulses and the release and subsequent action of neurotransmitters. The basic unit of electrical signaling in the brain is a rapid blip called a spike. Spikes are brief, large electrical events, about a millisecond or two in duration. They originate where the cell body and the axon join, at a spot called the axon hillock. The brain is bathed in a special saltwater solution called cerebrospinal fluid, which contains a high concentration of sodium and a much lower concentration of potassium. These sodium and potassium atoms are in their charged state, called ions, in which they each have one unit of positive charge. There is a gradient of sodium ion concentration across the outer membranes of neurons: the concentration of sodium ions outside a neuron is about fifteenfold higher than it is inside. The gradient for potassium runs in the other direction: the concentration of potassium ions is about fiftyfold higher inside than outside. This situation is crucial for the electrical function of the brain. It creates potential energy, similar to winding the spring on a child's toy, and the energy can then be released in the appropriate circumstances to create electrical signals in neurons. Neurons rest with an electrical potential across their outer membranes: there is more negative charge inside than out. When a spike is

triggered, specialized doughnut-shaped proteins embedded in the outer membrane, called sodium channels, open their previously closed doughnut hole to let sodium ions rush in. A millisecond or so later, a different kind of ion channel, one that passes potassium ions, opens up, allowing potassium to rush out, thereby rapidly terminating the spike.

Spikes travel down the axon to the axon terminals, and when they arrive there, they trigger a series of chemical reactions. These chemical reactions cause synaptic vesicles to fuse with the outer membrane of the axon terminal, releasing their contents, including neurotransmitter molecules, into the synaptic cleft. The released neurotransmitter molecules then diffuse across the narrow synaptic cleft to bind neurotransmitter receptors, which are embedded in the outer membrane of the next neuron in the signaling chain. One form of neurotransmitter receptor, called an ionotropic receptor, is like a closed doughnut that only opens its hole when it is bound by neurotransmitters. If the ion channel in that receptor allows positive ions to flow in, then this excites the receiving neuron. Conversely, if the ion channel opened by the neurotransmitter allows positive ions to flow out of the neuron (or negative ions like chloride to flow in), this will inhibit spike firing in the receiving neuron.

Electrical signals from activated receptors at synapses all over the dendrite and cell body flow toward the axon hillock. If enough excitatory electrical signals from the synapses arrive together and they are not negated by simultaneous inhibitory signals, then a new spike will be triggered there, and the signal will be passed down the axon of the receiving neuron. Most of the psychoactive drugs that we consume,

both therapeutic and recreational, act at synapses. For example, sedatives like Xanax and related compounds work by enhancing inhibitory synapses and in this way reducing the overall rate of spike firing in certain regions of the brain.

Electrical signaling in the brain is fast by biological standards (in the range of milliseconds), but this signaling is still about a millionfold slower than the electrical signals coursing through the circuits of your laptop computer or smartphone. It is important that not all signaling at synapses is fast. In addition to the ionotropic neurotransmitter receptors that work on the timescales of milliseconds, there is a much slower group called metabotropic receptors. These receptors do not have an ion channel pore as part of their structure, but rather trigger or block chemical reactions in the receiving neuron and act on a timescale of seconds to minutes. The fast ionotropic receptors are useful for rapid signals like those that convey visual information from your retina to your brain or carry commands from your brain to your muscles to undertake a voluntary movement. By contrast, the slow metabotropic receptors, which respond to neurotransmitters including serotonin and dopamine, are more often involved in determining your overall state of mind like your alertness, mood, or level of sexual arousal.

A single neuron is almost useless, but groups of interconnected neurons can perform important tasks. Jellyfish have simple nets of interconnected neurons that allow them to adjust their swimming motions to respond to

touch, body tilt, food odors, and other sensations. In worms and snails, the cell bodies of neurons have become clustered into groups called ganglia, and these ganglia are interconnected by nerves that are cables consisting of many axons bound together. Ganglia in the head have fused together to form simple brains in lobsters, insects, and octopuses. The octopus brain contains about 500 million neurons, which seems like a large number but is only about 1/200th of the size of the human brain. Nonetheless, an octopus can perform some impressive cognitive feats. For example, it can watch another octopus slowly solve a puzzle box to get food hidden inside and then apply that learning to immediately open the puzzle box when given access to it for the first time. As vertebrate evolution has proceeded, from frogs to mice to monkeys to humans, brains have mostly gotten bigger (relative to body size), and the neurons within have become more interconnected with each other, with the largest expansion occurring in the neocortex, the outermost portion of the brain.

The evolution of brains or any other biological structures is a tinkering process. Evolution proceeds in fits and starts with lots of dead ends and errors. Most important, there's never a chance to wipe the slate clean and do a totally new design. Our human brains were not designed all at once, by a genius inventor on a blank sheet of paper. Rather, the brain is a pastiche, a grab bag of make-do solutions that have accumulated and morphed since the first neurons emerged. It is a cobbled-together mess that nonetheless can perform some very impressive feats.

That the design of the human brain is imperfect is not a

trivial observation; suboptimal brain design deeply influences the most basic human experiences. The overall design of the neuron hasn't changed very much since it first emerged, and it has some serious limitations. It's slow, unreliable, and leaky. So to build clever humans from such crummy parts, we need a huge interconnected brain with 500 trillion synapses. This takes a lot of space—about 1,200 cubic centimeters (cc). That's so big that it would not fit through the birth canal. Changes to the pelvis to make a larger birth canal would presumably interfere with upright walking. So the painful solution is to have human babies born with 400-cc brains (about the size of an adult chimpanzee's brain). Even this size is still a problem—the baby's head barely fits through the vagina. (In fact, death in childbirth, while common through most of human history, is almost unheard of in other mammals.) Once born, humans undergo an unusually long childhood while that 400-cc brain matures and grows, a process that is not complete until about age twenty. There's no other animal species in which an eight-year-old cannot live without its parents. Our extra-long human childhoods drive many aspects of human social life, including our dominant mating system of long-term pair bonding, an aspect that is very rare in the mammalian world. Or to put it another way, if neurons could have been optimally redesigned at some point in evolution, we likely wouldn't have marriage as a dominant cross-cultural institution.

Different brain regions can have different functions. There

are areas dedicated to the various senses like vision or taste or touch. When sensory information arrives in the brain, it is often represented as a map—that is, the visual areas of the brain have a map of one's field of view, and the regions of the brain that process touch signals have a map of the body surface. The brain also has many regions that are not dedicated to a single task like vision. Rather, they blend information from multiple senses together, make decisions, and plan actions. Ultimately, the brain exists to take action, and these actions are performed by sending signals that contract or relax muscles or stimulate glands to secrete hormones. It is important that most of the work of the brain is automatic, like the increase in your blood pressure so that you don't pass out as you get up from a chair or the cooling down of your core temperature while you are sleeping. Most of this subconscious regulation is done by evolutionarily ancient structures located deep in the brain.

The neurons of the brain receive information from sensors in the eyes, ears, skin, nose, and tongue (and other places too). Moreover, sensory information doesn't come just from detectors that point outward at the external world but also from those that point inward to monitor such aspects as the tilt of your head or your blood pressure or how full your stomach is. Within the brain, neurons are highly interconnected with each other. Crucially, all of this wiring, consisting of axons that run from place to place, must be specific: signals from the retina need to go to the vision-processing parts of the brain, commands from the motion-producing parts of the brain must ultimately make their way to muscles, etc. If mistakes are made and the brain is mis-

wired, even subtly, then all sorts of neurological and psychiatric problems can result.

How does this specific brain-wiring diagram become established? The answer is that it is determined by a mixture of genetic and environmental factors. There are genetic instructions that specify overall shape and the wiring diagram of the nervous system on the large scale. But in most locations the fine-scale neural wiring must be refined by local interactions and experience. For example, if a baby is born but its eyes remain closed in early life, then the visual parts of its brain will not develop properly and it will not be able to see, even if the eyes are opened in adulthood. When the brain is developing, in utero and through early life, about twice as many neurons are created than are ultimately used, and many synapses are formed and later destroyed. Furthermore, those synapses that are formed and retained can be made weaker or stronger as a result of experience. This process, by which experience helps to form the brain, is called neural plasticity. It is important in development, but it is also retained in an altered form in adulthood. Throughout life, experience, including social experience, fine-tunes the structure and function of the nervous system, thereby creating memories and helping to form us as individuals.

Science Is an Ongoing Process, Not a Belief System

William B. Kristan, Jr., and Kathleen A. French

ONE OF THE MOST DIFFICULT IDEAS to explain to the general public is what it means to "believe in" a scientific concept. In part, this difficulty arises because the word "believe" can have different meanings. In our daily lives, we use "believe" in many contexts:

I believe it will rain soon.
I believe my child when (s)he says that (s)he doesn't use recreational drugs.
I believe that the defendant is guilty.
I believe that the cerebral cortex is the site of consciousness.
I believe that A will make a better president than B.
I believe in gravity.
I believe in God.

In some of these examples, "I believe" means "I am certain of," whereas in other examples, it means something like "I hold an opinion" or "I suppose," as in the speculation about the possibility of rain. In all cases, the believer may well take action based upon the belief, and the action might be as trivial as grabbing an umbrella before heading outdoors or as far-reaching as basing one's life on religious teachings. Where does belief in a scientific concept fit into this spectrum? This question is difficult to answer because there are different stages in the development of scientific concepts, with widely different criteria for judging them. These stages arise because science uses a guess-test-

interpret strategy, and this sequence is typically repeated many times. In fact, in everyday life, we all act like scientists—at least sometimes.

Consider a real-life example. You sit down in your favorite chair to read the newspaper and flip on the switch for your reading lamp, but the lamp fails to light. Maybe someone unplugged the cord *(guess 1)*. You look at the wall, but the cord remains plugged into its socket *(test 1)*, so that's not the problem *(interpretation 1)*. Maybe the circuit breaker was opened: a reasonable *guess 2*, but the TV—which is on the same circuit—is working *(test 2)*, so it's not a circuit-breaker problem *(interpretation 2)*. Perhaps the problem is in the wall socket *(guess 3)*, so you plug another lamp into it, and that one works just fine *(test 3)*, so the wall socket is functioning properly *(interpretation 3)*. You work your way through successive guesses (bulb? broken cord?) and tests to arrive at an interpretation (bad lamp switch) that ultimately enables you to fix the lamp. Previous experiences with circuit breakers, wall sockets, and lamps, and a rough understanding of electrical currents, informed your guesses.

In its basic logic, doing science isn't so different from fixing your lamp, except that each step may be more complex. One approach—which started with Aristotle—is inductive: you gather all the facts you can about a specific topic, think hard, and then insightfully conclude ("induce") the general relationship that explains the facts.[1] This approach is common, and it has produced explanations both sacred (e.g., creation stories) and mundane (e.g., trying to decide why your car won't start). As experimental science blossomed in the past century or two, however, the value of this inductive technique has transformed from being the source of an ultimate explanation to formulating a guess. (Scientists like the term "hypothesis," philosophers seem

to prefer "conjecture," but both are essentially synonyms for "guess.")[2]

So has guessing become a trivial and unimportant part of doing science? Far from it! Good guesses require both a lot of background knowledge and great creativity. Typically, a good guess is at least somewhat surprising (no one else has either thought of it or has dismissed it), is broadly interesting, is testable, and holds up under many tests. Sometimes the term "falsifiable" is used instead of "testable"—that is, for a guess to qualify as scientific, it must be vulnerable to falsification by objective, repeatable tests.[3] The kinds of tests required to evaluate a hypothesis (i.e., to accept or reject the guess) are stringent. (Accepting a hypothesis means that it has not yet been rejected.) Reduced to its simplest level, science attempts to find causal relationships, so a scientific guess typically has the form "A *causes* B." Here is an example from our laboratory's study of the medicinal leech. We guessed that some neurons in the leech nervous system activated its swimming behavior. Based on her initial experiments, Janis Weeks, a graduate student, found a type of neuron that seemed to fit that role; she named it cell type 204.[4] How could we test her guess that cell type 204 caused swimming? In general, there are three common categories of tests for causality: correlation, necessity, and sufficiency. Janis's experiments with cell 204 employed all three categories.

Correlation. Electrical recordings from cells 204 showed that they were always active just before and continued throughout the time that the animal swam—that is, the cells' activity was *correlated* with swimming. Note that even this weakest test of causality could have falsified our guess if cell 204 was not active during swimming. In other words, tests of correlation can disprove a guess but cannot prove it.

Sufficiency. Stimulating a single cell 204 (one of the approximately 10,000 neurons in the leech's central nervous system) caused the animal to swim. We concluded that activating a single cell 204 is *sufficient* to cause a leech to swim. But this test could not show that activating cell 204 was the only way to induce swimming. Janis needed to do further tests.

Necessity. Inactivating a single cell 204 (by injecting inhibitory electric current into it) reduced the likelihood that stimulating a nerve would cause swimming, showing that activity in cell 204 was at least partially *necessary* for swimming. (There are twelve cells 204 in the leech nervous system and only two of them could be controlled at a time, a factor that explains the reduction in—but not total blocking of—swimming.)

Based on these results, and similar ones from other nervous systems, neurons like cell 204 have been called "command neurons" because their activity elicits ("commands") a specific behavior. The notion is that command neurons link sensory input with motor parts of the brain: they get input from sensory neurons, and if this input activates them, they initiate a specific motor act. Such neurons have also been called "decision makers," an implicit guess that their true function is to make a choice between one behavior (swimming) and other behaviors (e.g., crawling).

The basic experiments on cells 204 were performed nearly forty years ago, so we can ask the following: do we still believe the original guess-test-interpretation story?[5] The answer is yes and no. The basic data have stood the test of time (and many repetitions), but further experiments have uncovered additional neurons that produce results similar to those of cells 204, so our initial conclusion that cells 204 were uniquely responsible for swimming was too simple. In further experiments using dyes that

glow to report electrical activity, which allowed us to monitor the activity of many neurons at once, it became clear that subtle interactions among many other neurons acting together decide whether a leech swims or crawls. Cells 204, along with the additional "command neurons," carried out the motor behavior once these subtle interactions ended. So cell 204 is not a "commander-in-chief" but something more like a lieutenant who puts into action the commands issued by the joint chiefs, who actually make the decision.[6]

Remembering the experiments on cell 204, we return to the meaning of "belief" in science. Minimally, this question needs to be broken into at least three different levels:

1. Can the guess be falsified? If there is no way to falsify a guess by using objective, real-world tests, it can be interesting, but it falls outside the realm of science.
2. Do we trust the validity of the data? To answer this question, we must consider whether the techniques used were appropriate, whether the experiments were done with care, and whether the results are convincing. For instance, in a typical experiment intended to elucidate the function of a region of the brain, the function of that area will be experimentally modified, and experimenters will look for a change in behavior and/or brain activity. In looking for change, the experimenter applies a stimulus and scores the response. Often the data are messy: maybe when the same stimulus is repeated, it elicits a variety of responses, or two different stimuli may elicit the same response. A number of issues can cause such a result, and there are established ways to identify and solve these problems. For example, the person who evaluates the results is prevented from knowing the details of the treatment (it is called "blinding" the experimenter). Alternatively, the experiment may be repeated in a different laboratory, so the equipment, people, and culture of the laboratory are different.
3. Do we believe the interpretations? In general, an interpretation is the most interesting part of any scientific study (and it is the part most likely to be carried in the popular press), but it is also the most subject

to change. As shown by the findings about cell 204 in the leech nervous system, new data can change the interpretation considerably, and that process is continuous. Karl Popper, an influential twentieth-century philosopher of science, argued that science cannot ever hope to arrive at ultimate truth.[7] A well-founded current estimate of truth can explain all—or at least most—of the current observations, but additional observations will eventually call into question every interpretation, replacing it with a more comprehensive one. He argues that this process does not negate the old interpretation, but rather the new data provide a closer approximation to ultimate truth. In fact, the interpretations of one set of data generate the guesses for the next set of experiments, just as you found in repairing your faulty reading lamp.

So how does "scientific belief" differ from other sorts of belief? One major difference is that science—at least experimental science—is limited only to ideas that can be tested objectively, reproducibly, and definitively; if others do exactly the same experiments, they will get the same results. This qualification eliminates from scientific inquiry a large number of deeply interesting questions, such as "Why am I here?" and "Is there a Supreme Being?" These qualifications even eliminate whole disciplines, such as astrology, that act like science in that they gather huge amounts of data but whose conclusions cannot be objectively tested.[8] Scientific papers usually separate "results" from "the discussion." Belief in the results requires judging whether the experiments were done properly and whether other scientists can reproduce the findings; such judgments are relatively objective. Believing what is said in the discussion section is more nuanced: Do the data support the interpretation? Are the conclusions reasonable, based upon the results in this and previous papers? Does the interpretation point to further testable guesses? The discussion, although often the most interesting part of any scientific paper, is also the part that is least likely to stand

the test of time. To someone outside the field of study, the changes in interpretations can be confusing and frustrating (e.g., Is fat in my diet good or bad for me?), but these successive approximations are inherent in the process. The interpretations are where the poetry lies, where creativity is most obvious in science. The fact that interpretations change, however, means that all statements of belief carry an inherent asterisk: what a scientist believes today can change greatly with the next set of experiments that he or she does or—less happily—that another scientist does. Scientists must be able to let go of their fondest beliefs and adopt new points of view when data require it, and nonscientists need to understand the dynamic nature of these beliefs.

NOTES

1. Inductive reasoning as the best model for scientific thought had a remarkably long run, involving many great philosophers, including—in addition to Aristotle—David Hume (*Treatise of Human Nature;* London: Thomas and Joseph Allman, 1817), Immanuel Kant (*Critique of Pure Reason;* New York: Colonial Press, 1899), and John Stuart Mill (*A System of Logic;* London: John W. Parker, 1843). They argued that the job of a scientist was first to collect data about a topic of interest without thinking about the relationship among the pieces of information collected (because thinking about cause and effect might bias the data gathering), and then, in a blinding flash of insight, the answer would become clear. Twentieth-century philosophers like Karl Popper (*Conjectures and Refutations;* New York: Routledge, 1963) and Thomas Kuhn (*The Structure of Scientific Revolutions;* Chicago: University of Chicago Press, 1962) argued that true induction is barren (it is limited to the data at hand), and, anyway, scientists don't operate in that manner. Instead, they have at least a vague idea (a guess) about what is important, and that idea guides which data are crucial to be gathered, whereupon the iterative guess-test-interpret cycle kicks in. A wonderful discussion of this topic is in P. B. Medawar's essay, "The Philosophy of

Karl Popper" (1977), in his posthumously published book of essays entitled *The Threat and the Glory* (New York: Harper Collins, 1990). Every nascent scientist should be required to read this essay for inspiration before stepping into a laboratory, and every nonscientist should read it twice for clarity.

2. These formulations have also been called "happy guesses" or, more pompously, "felicitous strokes of inventive talent"; we'll stick with "guesses." The "felicitous strokes" quote is from William Whewell, *History of the Inductive Sciences* (London: John W. Parker, 1837), cited in an enlightening book by P. B. Medawar, *The Limits of Science* (New York: Harper and Row, 1984). Sir Peter Medawar was an extremely successful British immunologist (he was awarded the Nobel Prize in Physiology or Medicine in 1960) who wrote many essays and books for the general public on science and also on philosophy for scientists. They are models of clarity and a delight to read.
3. There are many books on this topic. A definitive treatment is Karl Popper's *The Logic of Scientific Discovery,* first published in German in 1935 and translated into English in 1959. It is readily available through Routledge Classics (New York, 2002), although it is a bit dense. (It is considered a bit old-fashioned by philosophers, but research scientists find it captures much of what they do every day.) A more accessible, more modern book on a similar topic is *Failure,* by Stuart Firestein (New York: Oxford University Press, 2016).
4. J. C. Weeks and W. B. Kristan, Jr., "Initiation, Maintenance, and Modulation of Swimming in the Medicinal Leech by the Activity of a Single Neuron," *Journal of Experimental Biology* 77 (1978): 71–88.
5. The latest review of the circuitry underlying leech swimming is in the following review article: W. B. Kristan, Jr., R. L. Calabrese, and W. O. Friesen, "Neuronal Basis of Leech Behaviors," *Progress in Neurobiology* 76 (2005): 279–327.
6. In recent years, it has become possible to do similar experiments in brains more like our own than leech brains are, allowing scientists to ask whether there are neurons in our own brains that act the way cells 204 act in the leech. The huge number of neurons in the brains of mammals has been a challenging obstacle for addressing questions about the functions of individual neurons. However, over the past decade, techniques for imaging and for selectively expressing activity-reporter

molecules in neurons have allowed the study of the behavioral functions of many neurons at once. As a result, the same sorts of experiments described for cell 204 are now possible in more complex brains, such as those of fish and mice. While scientists image neurons of known function, their activity can be correlated with behavior. By genetically manipulating the neurons to produce light-sensitive proteins, then stimulating them with appropriately colored lights, these neurons can be turned on or off during the performance of a behavior to test for their sufficiency and necessity in causing that behavior. Such experiments, among others, are revolutionizing the study of the neuronal basis of behaviors in animals with complex brains. For detailed information about this approach, the following references are a good place to begin. The first two emphasize the technique itself, and the last two address the kinds of experiments that are being done with the technique: K. Deisseroth, "Controlling the Brain with Light," *Scientific American* 303 (2010): 48–55; K. Deisseroth, "Optogenetics: 10 Years of Microbial Opsins in Neuroscience," *Nature Neuroscience* 18 (2015): 1213–1225; E. Pastrana, "Primer on Optogenetics. Optogenetics: Controlling Cell Function with Light," *Nature Methods* 8 (2010): 24–25; V. Emiliani, A. E. Cohen, K. Deisseroth, and M. Haeusser, "All-Optical Interrogation of Neural Circuits," *Journal of Neuroscience* 35 (2015): 13917–13926.

7. Karl Popper wrote about the notion of successive approximations to truth in several places, but the most accessible is in an essay entitled "Science: Conjectures and Refutations," which was originally given as a lecture in Cambridge, England, in 1953 and published in his book *Conjectures and Refutations: The Growth of Scientific Knowledge* (London and New York: Routledge, 1963). This essay is available online at http://worthylab.tamu.edu/courses_files/popper_conjecturesandrefutations.pdf.

Stuart Firestein, in *Failure,* agrees that a rejection of guesses is the usual way that scientific progress is made, but he makes the argument from a somewhat different perspective. Firestein argues that few scientists actually follow the guess-test-interpret strategy on a day-to-day basis, although they write their research papers as though they do. He calls the rejection of a guess one type of failure and makes the case that this type

of failure is the most beneficial for the progress of science.

8. Karl Popper revealed in *The Logic of Scientific Discovery* that he became interested in philosophy by wondering how science is different from such diverse areas of knowledge as astrology, metaphysics, and psychoanalysis. He concluded that the distinction between science and nonscience lies in the testability and refutability of scientific theories: "Every 'good' scientific theory is a prohibition; it forbids certain things to happen. The more a theory forbids, the better it is" ("Science: Conjectures and Refutations"). (Firestein, in *Failure,* adds to this list some more modern topics like Scientology, intelligent design, and many alternative medicine treatments as other examples of theories that do not lend themselves to refutability.) Popper pointed out that there are perfectly good areas of intellectual pursuit—like metaphysics and ethics—that are critically important for human culture and survival but that are inherently nonscientific because they are not testable. This issue was nicely addressed by Sir Peter Medawar in *The Limits of Science* in two pithy quotes:

> If the art of politics is indeed the art of the possible, then the art of scientific research is surely the art of the soluble. (P. 21)

> It is not to science, therefore, but to metaphysics, imaginative literature or religion that we must turn for answers to questions having to do with first and last things [e.g., "What is the point of living?"]. Because these answers neither arise out of nor require validation by empirical evidence, it is not useful or even meaningful to ask whether they are true or false. The question is whether or not they bring peace of mind in the anxiety of incomprehension and dispel the fear of the unknown. (P. 60)

DEVELOPING, CHANGING

Genetics Provides a Window on Human Individuality

Jeremy Nathans

ANYONE WHO HAS SPENT TIME in a room full of four-year olds has seen the evidence. Even at a young age, we humans show striking personality differences. Some children are outgoing; others are shy. Some children are focused; others jump from one activity to another. Some children are strong-willed; others, less so. Personality traits largely define who we are as adults—pessimistic or optimistic, sociable or solitary, authoritarian or free-spirited, empathetic or suspicious. Aggregated over thousands or millions of people, such traits define the characteristics of our societies.

What determines personality? To what extent is it innate? To what extent is it molded by experience? At their core, these are questions about brain development, function, and plasticity, and they are some of the deepest questions that we can ask of brain science.

More than one hundred years ago, the British polymath Francis Galton posed these questions in essentially their modern form.[1] Galton conceptualized the forces that mold personality, intelligence, and other mental characteristics as a reflection of the combined contributions of "nature and nurture." Over the past century, research in animal behavior,

psychology, and genetics has begun to converge and to focus this inquiry.

In a consideration of the lessons that we might glean from our nonhuman relatives, there is no better place to start than with the work of Galton's cousin, Charles Darwin, who was fascinated by the changes in physical appearance and behavior that could be elicited by the selective breeding of domesticated animals. Consider, for example, the personalities of dogs. As every dog owner knows, individual dogs have distinctive temperaments, skills (or lack thereof), and habits—in short, a set of traits that defines the dog's personality. Strikingly, these attributes have a strong genetic component. A golden retriever's warm personality, an Australian sheepdog's herding instinct, and a German shepherd's self-discipline are, in large part, the product of selective breeding. To dog owners and breeders, these behavioral traits are as valued and as distinctive as the dogs' physical features.

If we examine the broadest of canine behavioral traits—those that distinguish wild and domesticated dogs—we observe that the critical characteristic shared by all domesticated breeds is tameness, a fundamental change in the ground rules of interpersonal interactions with humans. This trait is exemplified by a dramatic change in the meaning of eye contact, from threat to affection. In a landmark study of Siberian silver foxes conducted by Dmitri Balyaev, Lyudmila Trut, and their colleagues, the behavioral transition from a wild to a tame temperament was achieved with only 30–40 generations of selective breeding of wild foxes.[2] This breeding program, carried out in Novosibirsk starting in the

late 1950s, ultimately produced foxes that exhibited many of the endearing traits that we associate with domesticated dogs, including tail wagging, hand licking, responding to human calls, and a desire for physical and eye contact with humans.

One of the lessons from the Novosibirsk study is that the underlying genetic variation required for the transition from a wild to a tame temperament preexisted in the wild fox population. Indeed, the researchers observed that "friendly" behavior began to emerge after only four generations of breeding ("friendliness" being defined by the interactions between foxes and humans). At present, the precise genetic changes responsible for tameness in Siberian foxes are not known, but Balyaev, Trut, and their colleagues have presented evidence that—whatever those changes are—they lead to hormonal changes that include a lowering of levels of stress hormones, such as glucocorticoids. Perhaps a "type A" personality is optimally suited to a world in which the next meal is unpredictable and every large animal is a likely adversary.

To what extent do these insights into the genetic control of behavioral traits in animals apply to us? In 1979, Thomas Bouchard, a psychologist at the University of Minnesota, launched one of the most ambitious attempts to answer this question. Over the next twenty years, Bouchard and his colleagues searched for those rare twins who had been adopted into different households and raised separately to determine the extent to which their psychological similarities and differences reflected shared genetics or different environments.[3] The Minnesota Study of Twins Reared Apart

(MISTRA) compared identical twins and fraternal twins, and, in collaboration with Bouchard's University of Minnesota colleague David Lykken, it also compared twins reared apart with twins reared together.[4]

Identical twins (also called monozygous twins) arise from a single fertilized egg that, early in development, divides to form two embryos. The two individuals inherit the same version of each gene from their parents and are, therefore, genetically identical. Since identical twin embryos also inherit the same arrangement of X- and Y-chromosomes, they are also the same sex. That is, identical twin pairs can consist of two boys or two girls but never a boy and a girl. Approximately 1 out of every 270 humans is a member of an identical twin pair.

In contrast, fraternal twins (also called dizygous twins) arise when two eggs are released during the same ovulatory cycle, are independently fertilized by two sperm, and then develop into two embryos. The two individuals are only as similar to each other as are any other pair of siblings. The distinguishing feature of fraternal twin siblings, as compared to other siblings, is that these siblings share the same uterus and are the same age. Geneticists loosely say (or write) that "fraternal twins share, on average, 50 percent of their genes."[5] Similarly, since fraternal twin embryos have independently inherited their X- and Y-chromosomes, they are as likely to be the same sex (boy + boy or girl + girl) as opposite sex (boy + girl or girl + boy). Approximately 1 out of every 115 humans is a member of a fraternal twin pair.

The simplest twin study design is one in which the values for some quantifiable trait—for example, height, weight, or

blood pressure—are determined for both members of a large number of fraternal and identical twin pairs. The differences in these values are calculated for each pair, and the results are compared between fraternal and identical groups. Since identical twins are always of the same sex, the study design limits the participating fraternal twins to those that are also of the same sex. One study of this type has shown, for example, that the average height difference between fraternal twins is approximately 4.5 centimeters, whereas the average difference between identical twins is approximately 1.7 centimeters. The smaller average difference between identical twins is attributed to their greater degree of genetic similarity.

The alert reader may have discerned a potential fly in the ointment for this type of study, especially as applied to traits with a psychological component. Identical twins often look so similar that they are confused with one another—an occasional source of amusement. As a result, they may find that their teachers, friends, or even relatives tend to treat them in similar ways, either because they cannot tell the twins apart or because they subconsciously assume that two people who look so much alike are also similar in other respects. A similarity in interpersonal interactions of this type creates what behavioral geneticists call a "shared environment," and it can confound the analysis of nature versus nurture. Additionally, as described below, identical twins do, in fact, tend to resemble one another on a wide range of personality traits and, perhaps in consequence, often develop an extraordinarily close bond with one another. This development leads to a second conundrum: maybe the close

interpersonal relationship between many identical twins tends to reinforce their psychological similarities and suppress their differences.

Studying twins reared apart from birth or infancy neatly solves such problems. As MISTRA showed, a comparison between identical twins reared apart and fraternal twins reared apart is particularly informative. In this comparison, the twin pairs are either 100 percent genetically identical or on average 50 percent genetically identical, respectively, but their rearing environments are largely uncorrelated. Two other useful comparisons are between identical twins reared together versus apart and between fraternal twins reared together versus apart. The latter comparisons provide another approach to assessing the influence of shared versus unshared environment during the formative years of childhood.

Over its twenty-year life, the MISTRA scientists studied eighty-one pairs of identical twins raised apart and fifty-six pairs of fraternal twins raised apart. At the time that they were studied, the twins averaged forty-one years of age. They had spent an average of only five months together before being separated and then had no contact with one another for an average of thirty years. During the study, each participant typically spent a week at the University of Minnesota and underwent a comprehensive set of physical, medical, and psychological tests.

The results from the psychological tests were striking. Across a range of personality features, such as extraversion/introversion and emotional lability/stability, genetic influences were substantial, averaging roughly 40

percent of the variance, a statistical measure of the variation across the population being studied. Moreover, vocational interests and specific social behaviors, such as religiosity and traditionalism, showed a similarly large genetic influence.

The single most intensively studied of all human psychological traits is the Intelligence Quotient (IQ), which is determined by performance on a written test of knowledge and intellectual skill. Although the name "IQ" is unduly grandiose, the test is of both theoretical and practical interest as its results are strongly predictive of educational and vocational success.[6] The data from MISTRA showed that for the population studied, about 70 percent of the variance in IQ test scores could be explained by genetics. In particular, the difference in IQ test scores between identical twins raised apart was only slightly greater than the average difference between two test scores obtained when the same person took the test on two separate occasions. A systematic analysis of the different adopted households in which the identical twins were raised showed little influence on IQ test scores of parental educational level or household cultural or scientific enrichment. These results are remarkable, but they need a few qualifiers because they do not address the influence of extremes of environmental enrichment or deprivation. Nearly all of the MISTRA participants were raised in households and in communities that provided opportunities for a solid education, and therefore the strength of the genetic influence applies to that broadly permissive environment.

I have emphasized MISTRA because of its large size and exemplary design, but many dozens of other twin and family

studies provide data on personality and IQ that closely agree with the results from MISTRA.[7] An especially intriguing comparison of 110 identical twin pairs and 130 fraternal twin pairs who were all over eighty years old found a higher degree of similarity for identical twins compared to fraternal twins on every measure tested, including general cognitive ability (IQ), memory, verbal ability, spatial ability, and processing speed.[8] This study also showed that the genetic influence on IQ does not decline appreciably with age, although this and other studies do not address the extent to which a person's IQ score reflects motivation, curiosity, and self-discipline, in addition to "intelligence" per se.

Twin studies can measure the average contribution of genetics to individual variation in personality and cognitive ability, but they cannot reveal the biological mechanisms responsible for this variation. We can think of twin studies as providing us with data that are analogous to the performance characteristics of different types of automobiles. We may learn that a Porsche accelerates more rapidly than a Toyota, but to understand the cause of that difference we will need to know in detail how these two automobiles differ. We will also need to know a lot about how automobiles work in general.

In biology, looking under the hood means understanding how cells grow, become specialized, interact, and carry out their particular functions. It also means understanding how the genetic blueprint that each of us inherits codes for the proteins that comprise the molecular machines that underpin all cellular structure and function. This is a tall order, and we are still far from having a fully satisfactory understanding of these processes. However, progress over the past fifty years

has been impressive. The fundamental mechanisms underlying communication between nerve cells are now known, as are many of the mechanisms responsible for assembling connections between nerves cells during development.

Progress in genetics has been especially rapid. We now have the complete DNA sequences of our species and many dozens of other species, and partial DNA sequences have been determined from hundreds of thousands of individual humans. These sequences show that our genetic blueprint is remarkably similar to the genetic blueprints of other mammals. Thus the large physical and mental differences among different mammalian species likely arise from the sum of many relatively subtle differences in gene structure and function. Additionally, a comparison of the DNA blueprints from different humans shows that we differ genetically from one another, on average, by only one part in one thousand.[9] Determining how these genetic differences contribute to making each of us who we are is one of mankind's greatest scientific challenges.

NOTES

1. F. Galton, *Inquiries into Human Faculty and Its Development* (London: J. M. Dart, 1907), available at www.galton.org.
2. D. K. Balyaev, "Destabilizing Selection as a Factor in Domestication," *Journal of Heredity* 70 (1979): 301–308; L. Trut, "Early Canid Domestication: The FarmFox Experiment," *American Scientist* 87 (1999): 160–169.
3. T. J. Bouchard, D. T. Lykken, M. McGue, N. L. Segal, and A. Tellegen, "Sources of Human Psychological Differences: The Minnesota Study of Twins Reared Apart," *Science* 250 (1990): 223–228.

4. N. L. Segal, *Born Together—Reared Apart: The Landmark Minnesota Twin Study* (Cambridge, MA: Harvard University Press, 2012).
5. The statement "fraternal twins share, on average, 50 percent of their genes" is really a compressed version of the more precise statement that "fraternal twins have a 50 percent chance of inheriting the same version of any particular gene from each parent." For example, if a mother has two different versions of a gene for eye color, then each of her children has a 50 percent chance of inheriting version one and a 50 percent chance of inheriting version two. From this statement, the reader can easily write down all of the possible combinations of inherited versions and see that, on average, fraternal twins inherit the same version half the time and different versions the other half of the time.
6. It is important to emphasize that, like all standardized testing, the results of IQ testing should be interpreted in a cultural context. Assuming that we could agree that "innate" intelligence exists and can be measured, it is unlikely that any standardized test could measure it in a manner that is free of cultural bias.
7. L. J. Eaves, H. J. Eysenck, and N. G. Martin, *Genes, Culture, and Identity: An Empirical Approach* (New York: Academic Press, 1989).
8. G. E. McLearn, B. Johnasson, S. Berg, N. L. Pederson, F. Ahern, S. A. Petrill, and R. Plomin, "Substantial Genetic Influence on Cognitive Abilities in Twins 80 or More Years Old," *Science* 276 (1997): 1560–1563.
9. E. S. Lander, "Initial Impact of the Sequencing of the Human Genome," *Nature* 470 (2011): 187–197.

Though the Brain Has Billions of Neurons, Wiring It All Up May Depend upon Very Simple Rules

Alex L. Kolodkin

THE IMMENSE COMPLEXITY of neural connections begs the following question: What labels, or cues, could possibly provide a code that instructs their precise organization? Imagine the task of connecting the thousands of phones in the new One World Trade Center building in New York City to their central switching stations—color-coded wires, numbered phone jacks, and lots of unique labels are the only hope to get it right. But to use this "unique label" strategy to wire up the human brain one would need trillions of specific molecular cues. Is such a wiring code even possible? Over one hundred years of neuroscience research has yielded only a few hundred molecules that are known to selectively direct the formation of connections among neurons. But even if all the genes in the human genome produced only wiring cues, that would result in approximately 20,000 unique cues, far fewer than necessary to uniquely code for all the connections in the human brain.[1] Recent work in the insect visual system shows that extremely complex neuronal connections among a very large number of neurons can be instructed by very simple rules; each individual neuron can follow these rules on

its own and, in the absence of myriad unique labels, wire up intricate and specific connections to many other neurons. So to what extent can a nervous system self-assemble? The answer is, surprisingly, quite a bit.

Some of the greatest contributions to our understanding of both the complexity and logic of neural connections were made early in the last century by the Spanish neuroanatomist Santiago Ramón y Cajal.[2] Using microscopes primitive by today's standards and a staining technique that allowed for only a very small fraction of neurons to be labeled in their entirety in a sea of unlabeled neurons, Ramón y Cajal sailed uncharted anatomical waters, characterizing distinct neuronal classes based on their morphology and the architecture of their connections with other neurons. He appreciated the complex and beautiful shapes neurons adopt, and his illustrations are exquisite.[3] Ramón y Cajal surmised that the axons extending from a neuron's cell body, often for very long distances, likely conveyed information to the next neuron down the line, contacting that neuron's dendrites (arborlike processes emanating from the neuronal cell body), which in turn receive this information and propagate it to the axon and then to the next neuron's dendrites and so on. This logic allowed Ramón y Cajal to speculate about neural circuit organization throughout the nervous systems of vertebrates and even invertebrates.

In addition to adult brains from creatures of many types, Ramón y Cajal also examined embryonic nervous systems and from this work provided insight into how the complex mature nervous system is assembled. He saw that axons extending to their targets had at their tips a handlike

structure we now call a growth cone, the fingers of which, called filopodia, appear to sample the external environment. When neuronal growth cones encounter a cue, either from a distance or very close by, they direct the axon toward an attractive cue and away from a repulsive cue. A wealth of data obtained over the last century has proved Ramón y Cajal extremely prescient.[4] We now know the identity of proteins secreted locally that can attract or repel extending neuronal growth cones at long distances and also of proteins associated with cell membranes that act locally to regulate neuronal growth cone guidance. We also know that axons laid down early in development can serve as scaffolds that later-developing axons follow. In this way we have begun to understand how the basic layout of complex neural connections from worms to insects to humans is elaborated. But just as a street map of New York City provides but a glimpse into its multilayered architectural and cultural heritage, we are still in the dark with respect to translating our rudimentary view of nervous system assembly into understanding how trillions of connections in the human brain are successfully wired up. Enter a useful model system: the fruit fly *Drosophila melanogaster.*

Throughout the history of biology, research organisms apparently less complex than humans have provided invaluable windows into fundamental biological processes; neuroscience is no exception. Pioneering work by several scientists, including the great geneticist Seymour Benzer, showed that *Drosophila* is an extremely useful model for studying neural development, the transmission of information across synapses from one neuron to the next,

overall neural circuit organization, and even complex behaviors.[5] With its defined neuroanatomy; unmatched genetic tools; and well-characterized neuronal guidance molecules, which are remarkably similar to human neuronal guidance molecules, the fruit fly is an excellent model system to study how complex neural connections are assembled, even when these connections number far more than the available guidance cues to set them up.

The wiring of the eye to the brain in the fly is one place where we can dig into this problem of neural connections with precision. The insect compound eye consists of about 800 units, called ommatidia, that are easily visible on the surface of the eye (figure 2A). Each ommatidium includes a small lens on its outer surface (the curved "cap" you see repeated in figure 2A), and beneath each lens in the fly eye resides a group of 8 light-sensitive neurons called photoreceptors (abbreviated PR—we consider only 6 here for simplicity). Photoreceptors in an ommatidium sense light of different wavelengths, ultimately resulting in the transmission of electrical signals along their axons (figure 2B). The photoreceptor axons extend to similarly repeated units, called cartridges, in the underlying brain region, which is called the lamina. What is important is that the number and arrangement of photoreceptors within each ommatidium are invariant across all 800 or so ommatidia in each fly eye. An interesting difference among insect eyes is that for diurnal (active during the day) insects, including the butterfly, each of the photoreceptors *within* an ommatidium points in precisely the same direction in space (parallel arrows in figure 2C), and these photoreceptors from a single

ommatidium extend their axons together to the same underlying cartridge (figure 2C), a relatively simple developmental event. However, insects with nocturnal activity periods, including flies such as *Drosophila,* have evolved an adaptation, called neural superposition, that increases light capture at twilight or at night without resulting in blurred vision.[6] This involves the 6 different photoreceptors, each one in an *adjacent* ommatidium, pointing precisely in the same direction (figure 2B, parallel arrows); the 6 photoreceptors in a *single* fruit fly ommatidium all point in different directions (figure 2D, divergent arrows). Yet the axons of these photoreceptors that point in the same direction and that reside in different adjacent ommatidia somehow manage to extend to the very same underlying cartridge in the lamina (figure 2B).[7] Unlike in the butterfly eye, this cannot be accomplished by simply having all photoreceptors in an ommatidium extend their axons directly down to an underlying cartridge (compare figures 2B and C), and herein lies the complexity of this wiring problem. Though figure 2B shows the wiring of only one set of 6 photoreceptors in adjacent ommatidia connecting to a single lamina cartridge in the fly brain, one must realize that this complex axon sorting is happening simultaneously for *all* the approximately 5,000 photoreceptor axons in *all* 800 ommatidia of the fly eye, a form of choreography easily outshining a Super Bowl halftime show. Producing individual labels for each photoreceptor-lamina connection is likely not the solution to preventing photoreceptor axons from forming a tangled mess as they extend across one another to their specific target cartridges.

However, if one compares the axon extension patterns of photoreceptors #1–6 in *different* ommatidia across the eye, they are identical. This suggests that each of the six individual photoreceptors has a unique intrinsic growth program that is executed in the same manner in every ommatiduim, defining a rule that underlies the assembly of complex neural wiring in the fly eye. If this rule is followed and all 6 photoreceptors extend in their designated directions and at their distinct speeds, the result is quite remarkable: the 6 photoreceptor axon growth cones extending from the 6 adjacent ommatidia that see the same point in space all meet at the same time at a single lamina cartridge, and then they stop (figure 2B). This defines a second rule, which is simply that axon extension ceases *only* when all 6 photoreceptor axon growth cones together contact each other and not before. So photoreceptor axons that point in the exact same direction can navigate through a teeming meshwork of axons and growth cones and still keep going since glancing contacts with one or a few growth cones that extend from photoreceptors pointing in different directions will not stop their extension. This mode of photoreceptor wiring to the brain in the fly is extremely accurate; mistakes rarely occur, and the result is that each lamina cartridge in the brain is innervated only by photoreceptors that point in the exact same direction. Therefore, processing of visual stimuli at higher brain centers is greatly simplified since directional information is already sorted out at the level of the lamina cartridge, the first relay station following photoreceptor sensation of light in the insect visual system. Computational modeling by Hiesinger and co-workers shows that the

simultaneous meeting of the 6 photoreceptor axon growth cones is enough to ensure correct targeting; no cue in the lamina cartridge is required. Therefore, the seemingly intractable problem of how to wire up the 5,000 photoreceptor axons, all at the same time, in the complex pattern required for neural superposition is actually accomplished by just 6 distinct photoreceptor axon growth programs. Neural superposition patterning emerges as these photoreceptor axon growth programs are executed during fly eye development. Apparently, no set of complex guidance cues is required to uniquely guide each of the approximately 5,000 photoreceptor axons to its target.

What are the implications of this work for understanding mammalian brain connectivity? While there is no arrangement of neurons in the human brain directly analogous to the almost crystalline organization of neurons in the fly eye, it is clear that a limited number of distinct neuronal cell types populate different mammalian brain regions. Neurons of the same type in the mammalian brain adopt remarkably similar patterns of axon and dendrite branching as they establish their unique connections with one another. Of course, several outside influences can act on neurons to sculpt these connections during embryonic and early postnatal neural development. These factors include guidance cues and even electrical signaling to a neuron by other neurons in a circuit. However, this work in flies reminds us that there are alternatives to instructing each individual connection in a complex neural network. It even leads to optimism regarding clinical approaches toward ameliorating damage to neurons from stroke or injury.[10] If

the history of neuroscience research is any indication, we can expect this work in flies to lead to a greater understanding of how simple rules establish complex connections among neurons in the human brain.[11]

NOTES

1. A combinatorial code for neural wiring is also a formal possibility. However, even if several hundred cues were able to generate a large number of unique combinations, this solution kicks the can down the road since it is an equally daunting task to precisely distribute these cues so as to selectively determine extremely complex patterns of connections among a very large number of neurons.
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3. J. DeFelipe, *Cajal's Butterflies of the Soul* (Oxford: Oxford University Press, 2010).
4. A. L. Kolodkin and M. Tessier-Lavigne, "Mechanisms and Molecules of Neuronal Wiring: A Primer," *Cold Spring Harbor Perspectives in Biology* 3 (2011): 1–14.
5. S. Benzer, "From Gene to Behavior," *Journal of the American Medical Association* 218 (1971): 1015–1022; D. Anderson and S. Brenner, "Obituary: Seymour Benzer (1921–2007)," *Nature* 451 (2008): 139.
6. E. Agi, M. Langen, S. J. Altschuler, L. F. Wu, T. Zimmermann, and P. R. Hiesinger, "The Evolution and Development of Neural Superposition," *Journal of Neurogenetics* 28 (2014): 216–232. This arrangement of neural wiring in the eyes of "advanced" flies such as *Drosophila* is called "neural superposition," and it has remained a mystery until now how this complex pattern of connections between photoreceptors in adjacent ommatidia and a single underlying lamina cartridge is established.
7. Ibid.

8. M. L. Langen, E. Agi, D. J. Altschuler, L. F. Wu, S. J. Altschuler, and P. R. Hiesinger, "The Developmental Rules of Neural Superposition in Drosophila," *Cell* 162 (2015): 120–133.
9. The photoreceptor neurons were labeled using genetic tricks so that only a very few photoreceptors in any one fly eye expressed the Green Fluorescent Protein (GFP), originally isolated from the jellyfish; GFP allows individual photoreceptor neurons to be easily observed in real time as they navigate to their targets.
10. The direct introduction into the injured human brain of specific neural cell types, derived from stem cells that have been coaxed to differentiate into these cell types, is one approach under study for replacing neurons damaged by stroke or injury. It seems likely that distinct neuronal cell types have intrinsic growth programs, and an exciting possibility is that these programs might help guide the appropriate wiring of these new neurons into existing circuits and thereby facilitate repair of the nervous system.
11. Credit to Thomas Lloyd for panel A and to Natalie Hamilton for panels B–D in figure 2.

From Birth Onward, Our Experience of the World Is Dominated by the Brain's Continual Conversation with Itself

Sam Wang

A NEWBORN DOES NOT KNOW what kind of world it will encounter. What language will people speak? Will assertiveness be rewarded? What kind of food will be available? Many of a developing baby's needs arise from conditions imposed by the environment in which he or she grows up. Brains adapt to this wide variety of possibilities because developing brain circuits are strongly shaped by experience. Somehow, the baby, who at first does not have the proper connections to process a fire hose of information, gradually makes sense of the gusher.

The brain achieves this feat largely by building itself.[1] Many people think of the brain as a computational object that is programmed to make sense of incoming information and act appropriately. But contrary to the brain-as-computer metaphor, the brain does not come out of a box ready to go.[2] It takes years of experience to build a brain—and much of this construction happens well after birth. This construction process comes with enormous changes. A newborn baby's brain weighs about a pound and contains fewer than one-third the number of synaptic connections found in an adult

neurons would do, even that arising from diffuse light. But to refine the path from the thalamus to the visual cortex, more was required: specific patterns of activity arising from visual scenes. In the end, the ability to detect color, form, and movement requires refinements of the visual cortex that depend on having a stream of input that is passed through the thalamus. Once the thalamic input has done its "teaching" work, the thalamus continues to have the job of conveying information—no longer to an unformed circuit but rather to a sophisticated brain system for vision.

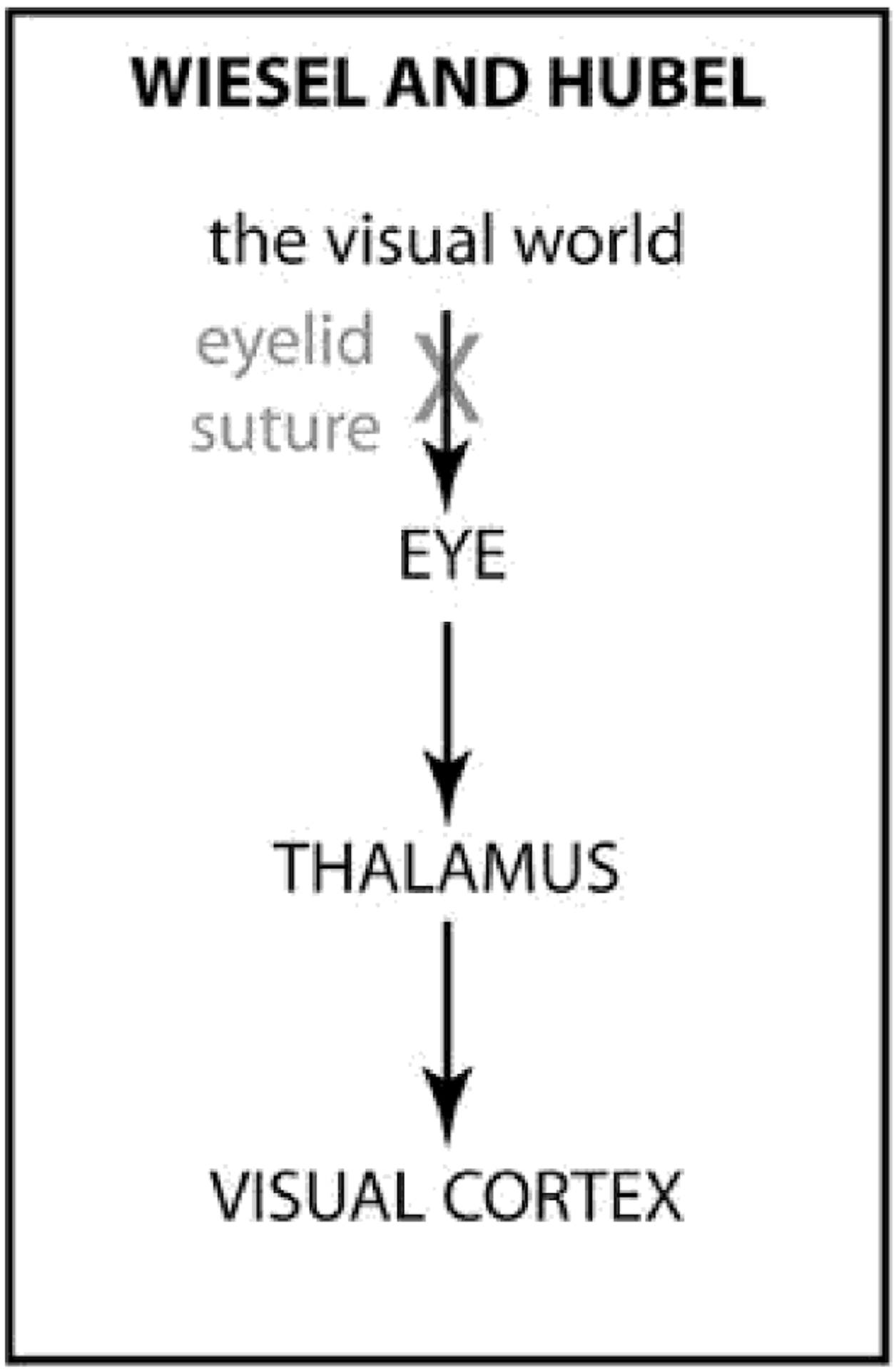

FIGURE 3. Flow of information from the visual world to the visual cortex and its interruption by eyelid suture in the classic experiments of

Wiesel and Hubel.

Sensitive periods arise not only in the development of vision, but also for the growth of cognitive and social abilities.[5] A devastating example occurred in Communist-era Romania when many infants and toddlers were placed in orphanages that gave them almost no tactile or social interaction. Many of these children failed to develop normal abilities in language or social communication—a syndrome that is reminiscent of autism. If the children were rescued from the orphanage by age four, they could return to a normal path of development. But if they waited too long, the changes were difficult to reverse. The brain's sensitive period for developing social abilities had passed.

The thalamus is probably not the only teacher of other brain regions. When a necessary source of information is disrupted during development, brain regions that receive the information may fail to develop properly. This idea is called "developmental diaschisis." Diaschisis (dye-AS-ki-sis; Greek *dia-*, across;*-schisis,* cut or break) is used by neurologists to describe the fact that when a brain region is damaged, activity and blood flow can change abruptly at some distant site. The probable reason is that the two brain regions are strongly connected by information-sending axons, and losing a stream of incoming information leads to sudden changes. Developmental diaschisis refers to the idea that such actionat-a-distance can have lasting and profound consequences if it happens during a developmentally sensitive period. Since many brain regions are heavily connected to one another, within-brain influences may be

quite important—a form of the entire brain lifting itself up by its own bootstraps. Through an experience-guided process of brain regions getting each other organized, brains build themselves up over time (see figure 4).

My own laboratory is interested in the idea that developmental diaschisis may arise from problems in the cerebellum, which sits at the back of the brain.[6] When the cerebellum is injured in adulthood, clumsiness and uncontrolled movements result. But if the injury occurs at birth or in infancy, a very different outcome can ensue: the neurodevelopmental condition called autism spectrum disorder. Cerebellar injury at birth increases the risk of autism by a factor of forty.[7] This massive increase is on a par with the additional cancer risk that comes from cigarette smoking. Yet adults who sustain damage to the cerebellum never become autistic.

This kind of oddity is quite familiar to pediatric neurologists, who have long known that the consequences of damage to a brain region in a child can resemble the results of injuring a different brain region in adults. Such topsy-turvy clinical outcomes suggest that in babies and children, brain regions must have some kind of distant effects on one another. Autism is caused mostly by a mix of genetic and prenatal environmental factors, and one way these factors may act is by affecting the function of the cerebellum.

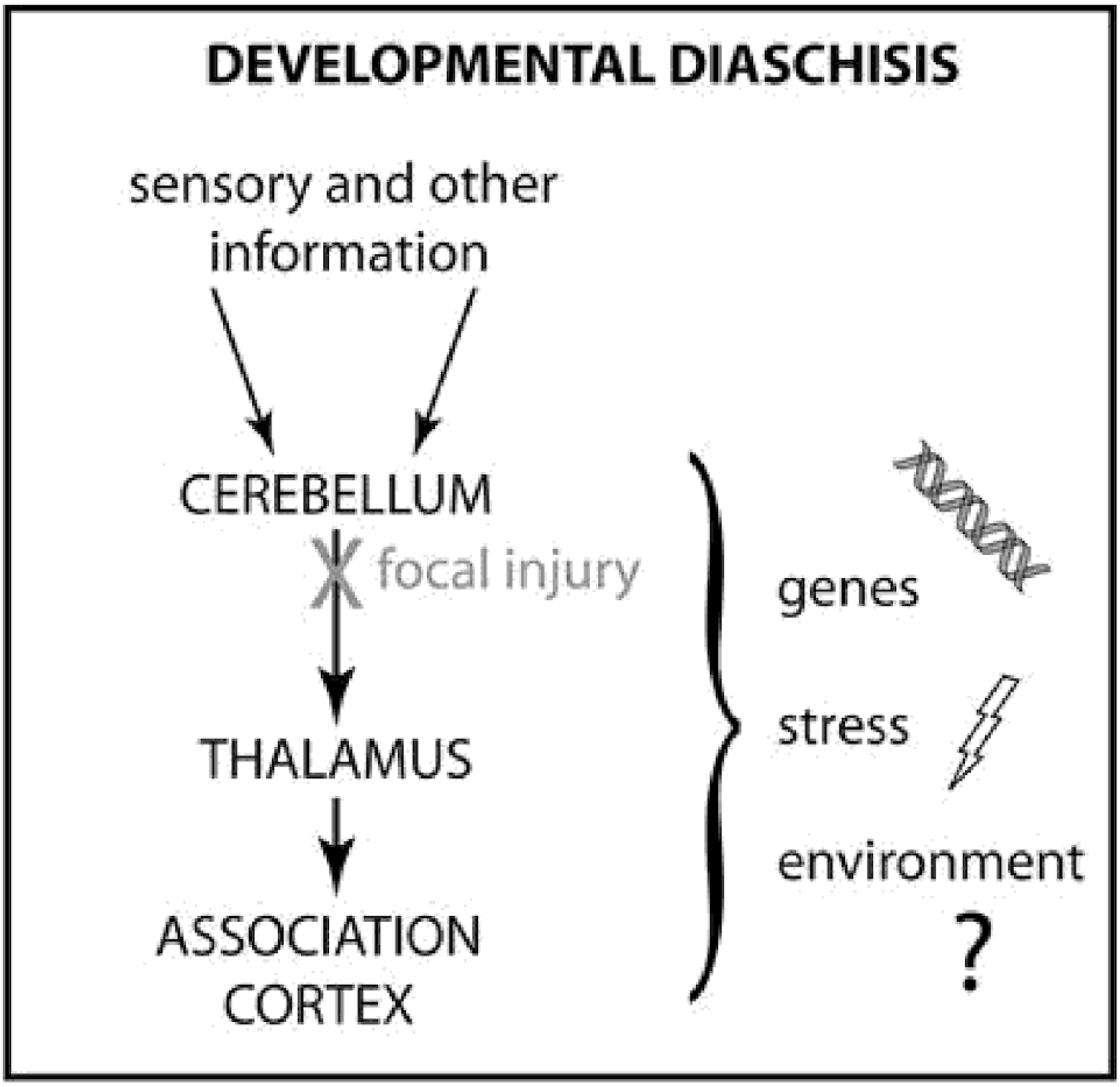

FIGURE 4. Developmental diaschisis. Like the retina of the eye, the cerebellum sends output to the thalamus, which is the principal gateway for information to pass to the cortex. Some parts of the cerebellum project to the association cortex, defined as regions that are neither sensory nor motor. During development, the interplay between the cerebellum and the cortex may be acted on by genetic programs, by stress, or by environmental events.

How does the cerebellum affect cognitive maturation? It processes many kinds of information, including sensory inputs and commands to elicit movements, within the brain to guide and refine action. It sends its output to the neocortex by way of the thalamus—the same structure whose activity is

needed to guide visual development. The cerebellum is thought to predict what the world will be like one moment into the future and thus help with planning. In this way, the cerebellum may adjust and guide both movement and thought.

The developmental diaschisis hypothesis has important consequences for the treatment of autism. Developmental diaschisis opens the possibility that in early life, autism treatments may end up focusing on brain regions that were previously unsuspected to contribute to cognitive or social function, such as the cerebellum. For instance, failure of the cerebellum to predict the near future could make it hard for babies at risk for autism to learn properly from the world. Consistent with this, the most effective known treatment for autism is applied behavioral analysis, in which rewards and everyday events are paired with one another slowly and deliberately—as if compensating for a defect in some prediction process within the brain. Applied behavioral analysis works on only about half of kids with autism. It might be possible to manipulate brain activity in the cerebellum to help applied behavioral analysis work better or for more kids.

In this way, a basic principle of neuroscience may eventually help millions of children avoid the path to autism. The road to helping kids start their lifelong conversation with the rest of the world may begin with helping different parts of their brains to talk to one another.

NOTES

1. S. Aamodt and S. Wang, *Welcome to Your Child's Brain: How the Mind*

don't *really* understand the how's and why's of learning abilities in human development. But we do know a few interesting things.

What is special about a child's brain? Ask almost any neuroscientist, and he or she will probably say, "A child's brain is more plastic." This answer is not terribly helpful because it does not address what "plastic" means, what makes a brain plastic, or why it becomes less plastic in adulthood. Here I will use a simple definition of "plasticity": the ability of the brain to change its own connections and functions as a result of new experiences. There are many cellular and network level mechanisms in the brain that contribute to this plasticity (see the essay by Linda Wilbrecht in this volume).[1]

One of the most dramatic aspects of brain development that could underlie plasticity occurs in infancy and early childhood and involves a massive proliferation of neural connections.[2] The brain of a two-year-old child has twice as many neural connections as the adult brain. The number of contacts between neurons (i.e., synapses) explodes during infancy, with some estimates suggesting that hundreds of new synapses are formed every second! This is a highly dynamic process—connections are changing constantly throughout early life. There are chemical signals in the developing brain that help guide the correct connections and repel incorrect ones. This abundance of neural connections is eventually pruned back throughout childhood and adolescence to reach adult levels.

One important influence on whether connections stay or go is whether those connections are used. Thus the variety,

intensity, and type of experiences of infants and young children are incredibly important for their developing brains.[3] Connections that are used as a child moves, listens, sees, thinks, and feels are the ones that are more likely to stick. Without doing these things, the connections may be weakened or removed. Thus the child's brain structure may be optimized early on for learning very different kinds of things, ranging from speaking Mandarin Chinese to playing professional tennis. The important step is that the child engage in these activities so that the right connections are laid down. This is, of course, a crude simplification of the amazing and complex processes that are going on within young brains. But experience-dependent brain plasticity in childhood is undoubtedly an important factor that may produce a heightened learning ability in children for specific behaviors.

It is also important to define what constitutes heightened learning ability in children compared to adults. We think of children as super-learners across the board, but is this really the case? It depends on what we mean by "super-learner." Learning can be measured many different ways—for example, how fast you learn, how much you learn, the quality of what you learn, and how much you retain. And there are many types of learning that depend on different brain systems and are driven by unique behaviors, so learning in one domain may not transfer to another. Consider learning a second language. Children are super-learners in the sense that they can learn to be more proficient compared to adults—that is, they can gain fluency in a second language that is comparable to that of a native speaker. But this does not mean that every

aspect of language learning is better. In fact, children learn a second language more slowly than adults; it takes them longer to learn to read, speak words, and use the appropriate grammatical rules.[4] So young children are ultimately better in proficiency but not in their speed of language acquisition.

Similarly, it appears that younger children learn new movements at a slower rate compared to adults. Some work in this area has shown that this motor learning rate gradually improves (i.e., speeds up) through childhood and becomes adultlike by about age twelve.[5] Children also start at a lower level of motor proficiency compared to adults; they are more variable and less accurate in their movement.[6] The lower proficiency is likely because parts of the brain that are involved in movement control are still maturing throughout childhood.

If children learn more slowly and are more variable in their movements, why do they appear to learn certain tasks like skiing better than adults? First, children are smaller than adults; thus their center of mass is lower, a factor that may make activities like skiing easier to learn to control. However, this factor would not explain their learned proficiency across fine motor skills, such as playing a video game, an activity that involves only hand movements. Second, the variability in children's movements might also work to their advantage, as they get to try out many different ways of moving for a given situation in order to find the best one. We know that this movement exploration is an essential part of motor learning. Adults may be less willing to explore different movements and therefore tend to settle on a suboptimal motor pattern. Third and perhaps the most important factor is that children

may be more willing than adults to undergo massive amounts of practice to learn motor skills. For example, when infants are learning to walk, they take about 2,400 steps and fall seventeen times for *each hour* of practice. This is an intense amount of activity; it means that infants cover the length of about 7 American football fields per hour! And in the six hours of the day that they might be active, they will fall a hundred times and travel the length of forty-six football fields.[7] Thus the intensity of practice that infants and children are willing to undergo, coupled with the heightened level of experience-dependent plasticity in the child's brain, may be why they can learn motor skills to levels beyond those of adults.

Unfortunately, there is also a downside to experience-dependent plasticity in childhood because *any kinds* of experiences affect brain development, not just the positive ones. So although plasticity can make children learn better, it can also cause problems. Stress and negative experiences can lead to maladaptive changes in a child's brain.[8] For example, young children who experience events such as neglect, abuse, or poverty have an increased risk of developing problems such as anxiety, emotional dysfunction, and cognitive deficits. It is thought that these problems are not merely a direct reaction to the negative experiences but also reflect a fundamental change in the brain circuitry that mediates these processes. Further, the lack of experience can have extremely deleterious effects during development.[9] If a young child has to have one eye patched for an extended period of time, thereby occluding vision, it can lead to irreversible changes in the development of visual areas in the brain and

difficulties with depth perception. Similarly, young children who are not read to when they are young can show slowed learning of language and poorer literacy.[10]

Ultimately, all experiences, as well as the lack of them, count a lot during early development. Children can take advantage of early plasticity to learn many things better than adults, including zipping down a ski slope and speaking French. But this plasticity can also put children at risk when they have negative experiences or are deprived early in life. Scientists don't fully understand the processes that contribute to childhood brain plasticity, but it seems clear that early life experiences are incredibly important. Future work will help to uncover how we can make the most of this remarkable time of life.

NOTES

1. J. Stiles and T. L. Jernigan, "The Basics of Brain Development," *Neuropsychology Review* 20 (2010): 327–348.
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frontal lobes, a region involved in self-control, planning, and foreseeing consequences of one's actions, as the last area to mature.[3] That the frontal cortex does not yet appear adultlike is marched out in practically any issue concerning teens: screen time, drug use, voting, sexual behavior.[4] The "immature" frontal cortex is blamed for the acts teenagers do that we do not like, and it is used to justify why teenagers should be prevented from gaining access to things that are dangerous or powerful.

It is easy to focus on the negative and view teenagers as transiently deranged by their biology or in a state comparable to frontal lobotomy.[5] Yet if you take a closer look at what is going on inside the brain, you might warm with the pride of a grandmother. There is no lobotomy to be found, no black hole where the frontal lobes should be. There are neurons there, and they are up to something that looks pretty creative, smart, and useful.

In the last two decades, new imaging technology has granted us a view into what is happening to individual neurons in living tissue in mice and other laboratory animals.[6] Previously, we could look at what the neurons were doing in snapshots taken from post-mortem tissue fixed at a particular moment in time. Since around the year 2000, we have been able to use special laser scanning microscopes to follow the neurons in the mouse brain as they grow up and before and after the brain has a new experience. In terms of getting to know what the neurons are doing and what they are like, this is like going from having a single black-and-white photo to having hours of childhood video.

We can now see that juvenile and adolescent frontal lobe neurons are busy *exploring.* They are hungrily exploring all they can know in the world, and such exploration mainly concerns their potential connection to other neurons in the brain.[7]

Neurons are shaped like craggy trees and bushes. Even before we hit puberty, the neurons have already achieved their full height, and their branches and roots are tightly interwoven in a dense thicket. In lab animals like mice, we can illuminate a single neuron at a time inside this thicket and take pictures or videos of it as it matures. What we see in the late childhood and adolescent brain are a multitude of changes in tiny, thornlike structures called dendritic spines (see figure 5). From looking at still images of dead tissue, we know that these dendritic spines become less numerous by the time humans and common lab animals reach the early adulthood phase.[8] When, however, a neuron is alive, we can see these spines are sprouting too, extending and retracting as they explore the beckoning outputs of other neurons.[9] Information can pass between neurons when one spine firmly connects to the arbor of another neuron by making a synaptic connection at the end of the spine. This connection can later be broken when the spine retracts back into the dendritic branch from which it originated.

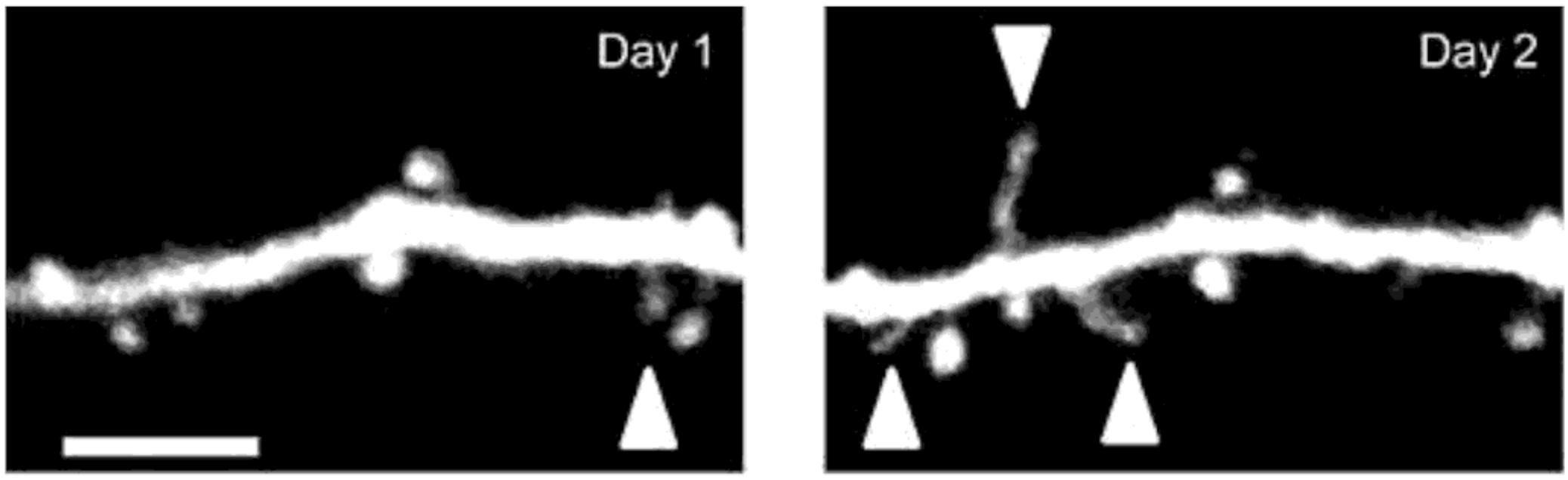

FIGURE 5. Time-lapse image of new spines sprouting overnight in an adolescent mouse. Arrows indicate a spine that will be lost after day 1 and new spines that are gained between day 1 and day 2. Scale bar = 5 microns. Photo credit: Josiah Boivin (Wilbrecht lab).

Repeatedly observing neurons, day after day, we can see them sprouting these new connections and then losing most of them again on subsequent days. In these new growths and retractions, we presume they are exploring their potential connectivity to other neurons. As the brain nears puberty, neurons may grow and lose 25 percent or more of their connections every week.[10] As the brain enters young adulthood, this turnover of connections can sink to 10 percent or less, depending on the brain region examined. Because the connectivity of a neuron is important for its function in the network, the functional identity of each neuron can undergo radical change from week to week in the developing brain. (Just imagine you were 25 percent different next week! What might your family say?) As we become adults, the total number of connections diminishes, and the potential for a new connection wanes.

What useful conclusions might be drawn from knowledge of neuronal exploration in the teenage frontal lobes? The large-scale turnover of neural connections might explain why

the frontal lobe may not be as efficient in teenagers as compared to adults. However, it may also enable greater capacity for some forms of learning or flexibility in the face of change. These neural connections in the frontal lobes may be the main substrate upon which an individual's adult personality and tendencies are built. We can imagine that a unique, individual mind may readily be sculpted from this rapidly budding neural topiary. This raises the following questions: How is this topiary shaped? And by whom? Or by what?

This is where experience comes into the picture. As you read this, in each developing brain across the world, unfathomable numbers of new synapses are in a tenuous state. Which will survive and why? As best we can tell, trial-and-error learning gained through active experience drives this process. By observing and quantifying changes in the gains and losses in connections between neurons, researchers can see that a whole cohort of new connections may be kept when a new skill or rule is learned. For example, the motor areas stabilize a crop of newly sprouted spines as a new motor skill is learned.[11] New frontal lobe connections are also sustained when the brain is learning that two things tend to go together—for example, when a sound, sight, or smell is associated with something painful[12] or pleasurable.[13]

Most recently, experiments have suggested that neurons also track aspects of the self. That is, growth and pruning of synaptic connections in the frontal lobe seems to be doing more than just reflecting what happened in the external world and whether it was good or bad. This process also appears to be tracking self-generated strategy along with

outcome: "What did I just try in the world?" and "Was that good or bad for me?"[14] These findings suggest that self-generated trial-and-error exploration is playing a role in the formative shaping of the frontal neural topiary. So you might differentially sculpt your frontal circuits when actively doing something versus just passively observing.[15]

If you are not fond of gardening, topiary, teenagers, or neurons, you might question whether these observations are important. You might think, "So what! This has been happening quietly in all the frontal lobes in the long history of mammals; it changes nothing now that we can see it. The bottom line is still that the frontal lobes in teenagers are immature." However, I think seeing and imagining the sprouting, connecting neurons undergoing their own formative years turns things 180 degrees.

If we go back to the beginning and imagine that teenagers are comparable to patients lacking a frontal lobe, then we might decide that they need protection from themselves and from the world. We might place them away in a safe space and just wait for them to grow up.[16] On the other hand, if we imagine that the frontal lobes are populated by neurons wildly grasping for information upon which to form themselves and we realize their capacity to change is waning by the day, then we will want to thrust teenagers out into the world of harsh life lessons. Sign them up for Arctic wilderness camp!

Of course, these strategies are extreme ends of the spectrum, but the plight of countless new neural connections reframes teenage experience from something frivolous to something serious. It suggests warehousing teens in

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15. This is probably no surprise to a teacher but hopefully good ammunition to support the extra effort to create active learning environments.
16. Chris Erskine of the *Los Angeles Times* pretends to cope with pubertal changes in his thirteen-year-old by locking him in a puppy crate but then sends him to camp instead; http://www.latimes.com/home/la-hm-erskine-20160718-snap-story.html.
17. This idea is also represented in popular parenting books like Wendy Mogel's *The Blessing of a Skinned Knee* (New York: Scribner, 2001) and Jessica Lahey's *The Gift of Failure* (New York: Harper Collins, 2015).

How You Use Your Brain Can Change Its Basic Structural Organization

Melissa Lau and Hollis Cline

CERTAIN MEMORIES STICK WITH YOU—for example, sitting in the sunshine at your graduation. Or that embarrassing piano recital when you were eight. Or the first time you held your child. Or that time a bat flew into your house. Each single experience can leave a biological trace because memories are formed, at least in part, by changing the connections between neurons. But how is your brain affected by years of repetitive training on a single subject? How do those incremental changes add up? Is it possible to see dramatic alterations to the fundamental organization of the brain from repeated experience?

For London taxi drivers, an intimate knowledge of the city's twenty-five thousand streets and twenty thousand landmarks is hard won. To earn their license, the drivers are required to recite the shortest route between any two points in that chaotic city. Even after several years of studying, not everyone passes the exams to become a taxi driver. Is this remarkable navigational skill reflected by measurable differences in their brains? In fact, when compared to the general public, London taxi drivers have larger posterior hippocampi—a region involved in spatial memory.[1] But does

their rigorous training actually change their brains, or are people with naturally large hippocampi just more likely to pass the taxi driver exams? How much effect, if any, can our individual experiences have in shaping our brains?

Like humans, birds use their hippocampi for spatial maps and memory. Unlike taxi drivers, some bird species have seasonal fluctuations in the size of this brain region. For example, black-capped chickadees have larger hippocampi in October, which also happens to be the peak season for food-hoarding.[2] These birds stash their food in multiple locations for later meals. Given the dramatic seasonal differences in hippocampal volume (it's 30 percent larger in October than in August!), it's tempting to speculate that this brain region enlarges because the chickadees need to remember where their food is hidden.

Other seasonal behaviors in birds have also been linked to changes in the brain. The size of the brain region called HVC, which is involved in song production, fluctuates for the male birds of some species.[3] Male great tits, who sing complex courtship and territorial songs during the breeding season, have larger HVCs in the spring. In contrast, willow tits, who sing all year round, have no seasonal changes in HVC volume.[4] However, it's not clear what causes the seasonal changes in either of these brain regions. Such changes in volume could be driven by an environmental trigger (like temperature or length of day) to prepare for seasonal behaviors like food hoarding or singing. Alternatively, is it possible that certain brain regions can expand from increased use?

To address that question, several research groups began

training monkeys in a variety of tasks. For example, adult owl monkeys were trained to touch a rotating disk.[5] The whole contraption was placed just within reach so that if the monkey held its fingertips on it, he'd be rewarded with a banana-flavored pellet. Much like a spinning record (but with raised bumps on it), this machine delivered a steady stream of tactile stimulation to the monkey's fingertips. By mapping the monkey's brain activity before and after training, the researchers tested whether repeated stimulation of the fingertips induced changes in the somatosensory cortex, the part of the brain that processes touch. In just a few months, there were already measurable differences.

The somatosensory cortex can be divided into separate regions, each dedicated to different body parts. After the training, more of the somatosensory cortex was devoted to processing touch in the fingers—and specifically only in those fingertips that were stimulated. Because adult brains no longer generate new neurons (except for certain regions, like the hippocampus) the size of the cortex is fixed and becomes valuable real estate. Like squabbling landowners competing to expand the borders of their prescribed properties, increased cortical representation of the fingertips comes at the expense of neighboring brain regions. In this case, more of the cortex is assigned to the stimulated fingertips; that increase comes from a loss in representation of neighboring (unstimulated) fingers and even a shift in the border between hand and face. Here, experience, or the use of specific neural circuits, does expand the cortical area allotted to that brain function—but it is not without costs.

This strategy of compromise, where increased cortical

representation of a single function comes at the loss of another, is a general principle that's been observed in a variety of scenarios. Like the somatosensory cortex, the motor cortex is organized into a map where portions of the cortex are responsible for directing movement in specific body parts. By training squirrel monkeys to complete tasks that isolate certain muscle groups, researchers can look for corresponding changes in those specific parts of the motor cortex. In a task that requires skilled finger movements, monkeys are trained to remove banana-flavored pellets from a tiny hole. Alternatively, other monkeys are trained in a key-turning task that requires forearm motion. Repeated use of the fingers increased the area of motor cortex devoted to finger movement, and the increase came at the expense of the neighboring area for the forearm. Likewise, repeated training for key-turning increased representation of the forearm area while decreasing the cortical space for fingers.[6] As for the permanency of these changes, the phrase "use it or lose it" comes to mind. After the monkeys stopped training, the motor cortex shifted back toward the original representation of these different body parts.

In humans, specific types of training can also lead to discrete changes in the organization of the somatosensory and motor cortices. Much like the monkeys touching the rotating disk, blind people who learn Braille have measurable differences in their sensorimotor cortex.[7] Their reading finger has a larger cortical representation than their nonreading fingers and is larger than the corresponding representation for fingers of non-Braille readers.

Musicians also have significant differences in their motor

bodies.[14] This observation suggests that additional mechanisms are at work. Other studies indicate that residual connections from the missing hand activate phantom pain,[15] and changes in the excitability of the spinal cord may contribute as well.[16] Regardless, there are many examples in which increased cortical representation of one area comes at the expense of a neighboring area.

Might there be functional consequences for this reorganization of limited cortical resources? Let's return to the London taxi drivers. What we have yet to mention is that the taxi drivers' expansion of the posterior hippocampus comes at the cost of the anterior hippocampus.[17] The overall volume of the hippocampus is the same between drivers and controls; it's just the regional volumes that differ. The posterior hippocampus is thought to store spatial representation of the environment, such that an expansion here could allow for a more detailed mental map. In contrast, the corresponding reduction in anterior hippocampus might explain some of the functional deficits seen in taxi drivers. Most broadly, they're worse than nondrivers at forming new visual and spatial memories. For example, when given a complex line drawing to copy, they're worse at redrawing the figure in a later memory test; this task tests the ability to remember how visual elements are spatially arranged.[18]

A more recent study, following a group of prospective taxi drivers over the course of four years, was able to definitively show that training causes changes in the hippocampus. After several years of studying, the trainees that passed the taxi drivers' exams had an expanded posterior hippocampus and

performed worse on visual and spatial tasks. In contrast, the brains of trainees who failed or dropped out were no different from controls. It's the experience of training itself that drives structural changes in the hippocampus, and it can have unintended functional consequences, like the deficit in forming visual and spatial memories.

Still, it's important to remember that this isn't necessarily bad—it's just your brain's response to meet the functional demands of your environment. Just look at retired London taxi drivers. They have smaller posterior hippocampi and better visual and spatial memory than full-time drivers.[19] With decreased demands on the neural circuitry for spatial navigation, the brain seems to shift back to conditions seen in nondriver controls. This all illustrates that our brains are constantly changing.

Amazingly, it's our daily experiences that can alter the basic organization of our brains in dramatic, tangible ways. The utility of this biological phenomenon is elegant in its simplicity: it is the brain that defines our perception of the world around us, and yet, with beautiful symmetry, it is our perceptual experiences that can shape the underlying structure and functional capabilities of the brain itself.

NOTES

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Neuropsychologia 47 (2009): 1088–1095; K. Woollett, H. J. Spiers, and E. A. Maguire, "Talent in the Taxi: A Model System for Exploring Expertise," *Philosophical Transactions of the Royal Society of London B: Biological Sciences* 364 (2009): 1407–1416; K. Woollett and E. A. Maguire, "Acquiring 'the Knowledge' of London's Layout Drives Structural Brain Changes," *Current Biology* 21 (2011): 2109–2114.

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10. Not to be confused with another common neuroimaging technique, functional MRI (fMRI), which is used to infer regions of brain activity based on dynamic changes in blood oxygen level.
11. Note that the previous studies (Jenkins et al. [note 5]; Nudo et al. [note 6]) didn't use techniques that specifically measure structural changes. Instead, they focused on testing the functional consequences of sensory and motor experiences. There may well have been (unrecorded) changes in volume that accompanied the observed functional reorganization. In fact, training-induced structural changes *have* been recorded in the somatosensory cortex—namely, increased cortical thickness in the lip region of wind instrument players. U. S. Choi et al., "Structural and Functional Plasticity Specific to Musical Training with Wind Instruments," *Frontiers in Human Neuroscience* 9 (2015): 597. It's possible that structural and functional changes are concurrent. But to know for sure, each training scenario has to be tested with both structural and functional analyses. For example, some training regimens induce functional reorganization without overall changes in brain volume (Maguire et al. [note 1 above]).
12. T. Elbert et al., "Input-Increase and Input-Decrease Types of Cortical Reorganization after Upper Extremity Amputation in Humans," *Experimental Brain Research* 117 (1997): 161–164; H. Flor et al., "Phantom-Limb Pain As a Perceptual Correlate of Cortical Reorganization Following Arm Amputation," *Nature* 375 (1995): 482–484; E. Raffin et al., "Primary Motor Cortex Changes after Amputation Correlate with Phantom Limb Pain and the Ability to Move the Phantom Limb," *Neuroimage* 130 (2016): 134–144.
13. Flor et al., "Phantom-Limb Pain As a Perceptual Correlate of Cortical Reorganization Following Arm Amputation"; H. Flor, L. Nikolajsen, and T. Staehelin Jensen, "Phantom Limb Pain: A Case of Maladaptive CNS Plasticity?" *Nature Reviews Neuroscience* 7 (2006):

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14. Flor, Nikolajsen, and Staehelin Jensen, "Phantom Limb Pain: A Case of Maladaptive CNS Plasticity?"; S. M. Grusser et al., "The Relationship of Perceptual Phenomena and Cortical Reorganization in Upper Extremity Amputees," *Neuroscience* 102 (2001): 263–272.
15. T. R. Makin et al., "Phantom Pain Is Associated with Preserved Structure and Function in the Former Hand Area," *Nature Communications* 4 (2013): 1570; T. R. Makin et al., "Reassessing Cortical Reorganization in the Primary Sensorimotor Cortex Following Arm Amputation," *Brain* 138 (2015): 2140–2146.
16. Flor, Nikolajsen, and Staehelin Jensen, "Phantom Limb Pain: A Case of Maladaptive CNS Plasticity?"
17. Maguire et al., "Navigation-Related Structural Change in the Hippocampi of Taxi Drivers"; Maguire, Woollett, and Spiers, "London Taxi Drivers and Bus Drivers"; Woollett and Maguire, "Navigational Expertise May Compromise Anterograde Associative Memory"; Woollett, Spiers, and Maguire, "Talent in the Taxi."
18. Maguire, Woollett, and Spiers, "London Taxi Drivers and Bus Drivers"; Woollett and Maguire, "Navigational Expertise May Compromise Anterograde Associative Memory"; Woollett and Maguire, "Acquiring 'the Knowledge' of London's Layout Drives Structural Brain Changes."
19. Woollett, Spiers, and Maguire, "Talent in the Taxi."

world—but fortunately, there are mechanisms that are specialized for this adjustment to occur.

An important property of somatosensory maps is that they can be altered by experience. Overstimulation of some parts, like the fingers of a violinist who practices for six hours a day, can cause the relative area that represents those fingers in the neocortex to increase.[1] As body size changes—for example, with weight gain or loss—somatosensory maps must also shift. Every pregnant woman has had the experience of trying to squeeze through a crowd of people only to realize that she is now much larger than she predicted! After that, she must readjust her expectations for where she can comfortably fit. This day-to-day, experience-dependent plasticity in somatosensory representations happens routinely, not just under rarified laboratory conditions.

Somatosensory loss from catastrophic events, such as the amputation of a limb—or the removal of a tooth, a more common experience—can also lead to the redistricting of brain territories, where intact sensory areas can eventually "take over" the cortical space vacated by the absent input. When the tooth is removed, our instinct is to continuously touch and feel that absent area, obsessively moving across the space. But within a few days or weeks, that empty space becomes again part of us, unnoticeable. The plasticity of neural connections in the brain is responsible for this ability to readjust our expectations about the size and shape of our bodies. Scientists are developing an increasingly sophisticated appreciation for the way that neurons in the brain can anatomically rewire based upon experience. In many cases, experience-driven rewiring can be stable and

long-lasting. In other cases, neural circuits are rewired functionally, without a corresponding anatomical change, by changing the strength of synaptic connections between neurons. This is an efficient strategy—since it takes advantage of connections that are already present—and it enables rapid switching of somatosensory representations depending on the task at hand. It is also incredibly advantageous to us as a species.

Just as impressive as long-lasting adjustments in how we feel ourselves in the world—how we appreciate our size and shape—are cases where our somatosensory representations can be instantly adjusted depending on the task at hand. Think, for example, about when we start the car to pull out of a garage and immediately know when the side mirror is going to hit the wall. Or when we pick up a knife and fork. The edges of our body are immediately transformed to incorporate this tool so that it becomes part of us, extending the sensory reach of our fingers. Holding the fork, we can feel the plate and the morsel of food we pick up. Our "edges" extend to the tines of the fork, inches past the tips of our fingers. In fact, this form of experience-dependent plasticity in the somatosensory system may enable our expert use of tools, so the brain readjusts our sense of bodily boundaries, allowing us to use these tools as an extension of ourselves.

Why does expert tool use require practice? Because we need time and repetition—with feedback so that we learn by trial and error—to enable this remapping. That can be costly, as new drivers (or their parents) are dismayed to find, since it might take a scrape or two to figure out how far exactly one must be from another car to avoid an accident. But in fact,

our brains are exquisitely prepared to accommodate new somatosensory inputs, extending the size and shape of our bodily edges to enable us to acquire new skills. The feedback we receive from trying to use chopsticks is in getting them to do what we intend. When our intentions become reflected in successful actions, the remapping of our body space becomes strengthened and consolidated. Other studies indicate that such trial and error periods, punctuated by success and repeated trials separated by sleep, are particularly important in enabling neural plasticity.[2] Over time, we move from a clumsy attempt to use two sticks to the sensation that the chopsticks are an extension of our hands. This change in mental representation with expertise was first described by psychologists over one hundred years ago and has been well characterized by many others since.[3] This constant process of experience-dependent brain remapping has happened to us since we were toddlers learning how to wear our first pair of shoes, to school children learning how to use a pencil, in skiing or painting or flipping a burger or playing the piano. There are changes in the way that cells in the brain respond to inputs that underlie this expertise—some of which are restricted to parts of the brain that control movement but others that unquestionably occur in sensory areas.

The brain is composed of almost 100 billion neurons, and the properties of these neurons can be changed by experience, disease, injury, or drugs. There are so many neurons in the brain that it can be hard to decide which ones we need to examine. When we think about tool use, we can narrow our focus to neurons that are in a discrete area and are activated by tactile manipulation and correspond to

specific body areas. We know a few things for certain: training with one hand does not easily transfer to another hand (or foot, for that matter);[4] expertise requires practice (suggesting long-term changes in neural wiring properties); and the sense of tool incorporation into our body schema can be nearly instantly reversed. This reversal is apparent when we step out of the car or put down the fork—the body's edges snap back to their original state, suggesting that the changes in wiring properties can be activated or masked in a situation-dependent manner. Our everyday experience tells us that we can master many different types of tools, and this implies that these "tool maps" must coexist and probably overlap.

Experimental work in animals shows that visual feedback can aid the expansion of neural response properties, where the tool becomes part of the body representation. One brain area implicated in this process in nonhuman primates is called the intraparietal sulcus, which can combine visual and somatosensory information.[5] We need to understand how different types of neurons—both excitatory and inhibitory varieties—and the connections between them are dynamically changed by expert tool use. Without this understanding, it will be hard to develop an explanation of how biological components of the brain can give rise to somatosensory plasticity, let alone harness it for recovery and repair of brain function.

It is very likely that the normal mechanisms of plasticity and sensory memories are coopted to enable expert tool use, in the same way that repeated tactile input can drive changes in neural firing in the neocortex.[6] This process almost

certainly includes an increase in the strength of connections between excitatory neurons in somatosensory areas[7] as well as changes in motor brain areas.[8] However, long-lasting change in excitatory neural connections would not be enough to explain the rapidity by which we can pick up and use a tool, switch between tools, or return to our original, naked, tool-less state. After all, the critical aspect of this situation-dependent expansion of what we consider "self" is that it can be instantly reversed. Thus the brain must have an ability to mask these strengthened connections through inhibition—when we put down the spatula, get out of the car, or take off our boots.

It remains mysterious how maps altered by tool use can remain separated from each other so that we can use different and varied objects without confusing, for example, a hammer with a pair of tweezers. Are there methods that we could highjack to enhance the acquisition of expert use? How is the natural variation among individuals manifested in the skills—are some people better at acquiring certain skills and why? All these questions remain active areas of research. One thing is clear: our brains were built by ancient evolutionary processes that did not anticipate that we would pick up objects in our environment to extend our physical abilities. Whatever normal cellular and synaptic mechanisms for experience-dependent plasticity existed in the central nervous system can be adapted for new purposes to enable us as a species to achieve ever more complicated skills. As we enter into an era where virtual reality becomes commonplace, we may discover new ways to reorganize our perceptual capacities, not just limited to how we use an object

Life Experiences and Addictive Drugs Change Your Brain in Similar Ways

Julie Kauer

WHY CAN'T WE REMEMBER our most wonderful experiences as vividly as we would like? Why can't we quickly forget something painful no matter how hard we try? A memory has its own time course, fading slowly over time, whether we like it or not. Surprisingly, drug addiction has features similar to memory. If a substance abuser tries to quit, he or she faces a problem analogous to trying hard to forget a bad experience: a lack of voluntary control over the drug-associated memories that drive relapse. Why does addiction have this mnemonic character?

Every day you learn and experience new things. Some memories are quickly forgotten (where you parked your car yesterday morning), while others are remembered. Even if the new experience is so commonplace that you barely notice —let's say you see your neighbor driving a new car—that information is still stored for later retrieval. The only way this retrieval can happen is if your brain subtly changes as you store the memory of the new car. The newly rewired brain has incorporated the information so that later you can retrieve this new fact.

Memories are formed in the brain by a process of strengthening and weakening synapses, the connections

between individual neurons. As a result of synaptic strengthening, synapses between two neurons will subsequently more strongly drive electrical activity in the receiving cell in the circuit. From personal experience alone, we can identify some features of learning and memory that appear to be encoded in the brain by synaptic plasticity. First, we can learn very rapidly. If we meet someone new, it takes only seconds to encode a memory of that moment and the person's face and name. Second, some memories are more fleeting than others. For example, after meeting someone we may remember the face, but the name may escape us the next time we meet. Third, life events that are particularly important or emotionally charged can be remembered for a long time in exquisite detail. The first day of school, the day we bought our first guitar, the day a child was born—these and other critical moments are laid down in memory immediately and persist for years. Salient memories like these can also be difficult or impossible to erase. The memory of what we were doing on 9/11 or the day a hurricane hit can stay with us for years, even if we want nothing better than to forget them.

The rewiring of synapses through changes in synaptic strength (synaptic plasticity) shares and can account for the properties we recognize in learning and memory formation. Synaptic rewiring takes place within seconds. Some synaptic changes last longer than others, and synaptic plasticity can be highly persistent, lasting long enough to account for long-lasting memories. These synaptic changes are localized in specific brain regions, such as the hippocampus, that are known to be required for learning and for encoding memory.

Remarkably, a nearly identical brain-rewiring process occurs if you take an addictive drug. Like memory, the development of drug addiction is also caused by brain changes.[1] Perhaps this is obvious, but it is worth thinking about. Even taking a drug a single time persistently changes the way your brain works, thereby altering the way you experience the world thereafter. And while every addictive drug changes synaptic strength, antidepressants like Prozac or drugs used to treat epilepsy target the brain but are not addictive. Unlike addictive drugs, antidepressants and antiepileptic drugs do not release dopamine or promote synaptic changes in the brain's motivational circuitry, and this may explain their nonaddictive nature.[2]

Drugs of abuse act on specific target molecules in the brain and alter brain function rapidly and for long time periods after exposure.[3] These brain changes are the reason addiction is such a difficult problem to treat and reverse. The ventral tegmental area and nucleus accumbens regions of the brain comprise a dopamine-using neural circuit that can be thought of as a motivation center; these areas are active during motivated behavior, and motivated responses are lost if they are damaged. Strong evidence for this is that damage to the nucleus accumbens, for example, but not to other brain regions, disrupts addiction to nicotine in human smokers.[4] A determination to stop being addicted is as much an uphill battle as being determined to forget a bad memory—not impossible but very difficult. Substance abusers experience drug craving, an inability to do or think about anything else. Craving is exacerbated by anything associated with the previous drug use; if you always smoked a cigarette after