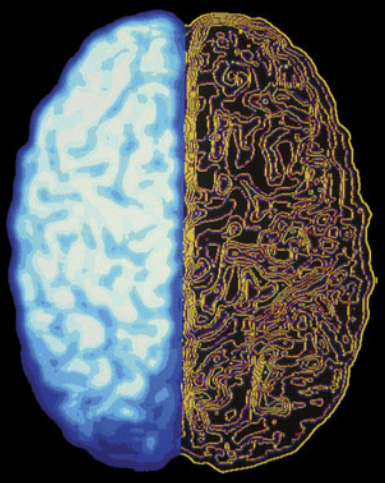
THE GREAT BRAIN DEBATE

IS IT NATURE OR NURTURE?



JOHN E. DOWLING

THE GREAT BRAIN DEBATE

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John E. Dowling

Joseph Henry Press
Washington, D.C.

Joseph Henry Press • 500 Fifth Street, NW • Washington, DC 20001

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Library of Congress Cataloging-in-Publication Data

Dowling, John E.
The great brain debate : nature or nurture? / John E. Dowling.
p. ; cm.
Includes index.
ISBN 0-309-09223-X (hardback) — ISBN 0-309-53245-0 (pdf)
1. Brain—Popular works. 2. Neurobiology—Popular works. I. Title.
[DNLM: 1. Brain—growth & development. 2. Brain—physiology —Adult. 3. Aging—physiology—Adult. WL 300 D747g 2004]
QP376.D697 2004
612.8′23—dc22

2004017413

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Printed in the United States of America.

For the next generation—
Madison, Quincy, Grace, and Olivia

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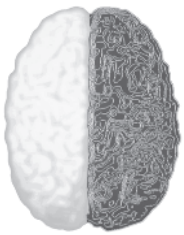


INTRODUCTION

The United States Congress designated the 1990s as the Decade of the Brain, but some suggest that the twenty-first century will be the century of the brain, when the last great frontier in biology —an understanding of the most complex biological system, the human brain—will be breached. Already the considerable advances made in neuroscience over the past 50-100 years are being called upon to explain many things about human behavior. Interdisciplinary programs are appearing in our colleges and universities asking what various disciplines and fields can learn from neuroscience and vice versa. At Harvard, I have been associated with the Mind, Brain and Behavior program since its inception in 1993, and I codirected it for a year. It attracts faculty from the Harvard Medical, Law, Divinity, and Business Schools as well as the School of Education and the Faculty of Arts and Sciences. Fields as diverse as philosophy, music, English, linguistics, anthropology, and history of science are represented, as well as the expected fields of biology, psychology, and computer science.

Many examples can be offered to illustrate the impact of neuroscience on other disciplines; I offer two here. First, studies of how we learn and remember things have demonstrated convincingly that memories are largely reconstructive and creative. False memories are not uncommon. These findings have fundamentally changed the way the law views eyewitness testimony. Contrary to the long-held belief that an eyewitness can faithfully record and remember an event, we now realize that what we remember or even perceive of an event depends on many factors—previous experiences, biases, attention, imagination, and so forth. Different eyewitnesses can give very different reports, though in each case describing what each observer firmly believes he or she saw.

A second example is the placebo effect—long thought to be without physiological basis. If a sugar pill is administered to someone experiencing pain, that person reports a lessening of the pain if told the placebo will help. We now know that the pain reduction is caused by the release of endogenous opiate-like substances in the brain. No drug trial today is carried out without a control cohort receiving a similar, but presumably inactive, agent. But placebo effects can greatly influence the outcome of such trials. How then do we decide what is efficacious and what is not? This question has enormous implications for medical therapies.

How far does the influence of neuroscience extend? Have studies on the developing brain, for example, told us much about how we should raise or educate our children? Some say yes, but others respond with a resounding no. The stakes are high—public programs such as Head Start, costing millions, if not billions, of dollars, are linked to notions supposedly neurobiologically based, but often the neurobiological evidence cited in support of one position or another is weak, controversial, or overinterpreted. The view that the young brain is more modifiable than the adult brain—which is certainly true—led to the notion that the first three years are the essential ones for raising a healthy, happy, and competent child. This extreme view, and the evidence on which it is based, has recently been critically examined in John Bruer's book *The Myth of the First Three Years.* As Bruer clearly docu-

ments, the first three years are important for brain development, but so are subsequent years. Nothing closes down completely after just three years—indeed, the brain continues to mature until the ages of 18-20, as we shall see.

What about the adult brain? How hard-wired is it? Once it is injured, is recovery possible or are we stuck with just what was there before the injury? Recent studies suggest that the adult brain is much more plastic than was long believed, but how much plasticity can there be? What about the influence of genes on behavior? How do genes and behavior relate? This contentious subject has generated volumes—with highly polarized views. The list of books written about it is long and includes provocative titles such as *The Mismeasure of Man*, *Not in Our Genes*, and most recently *The Blank Slate*.

And finally, the aging brain. Does the brain eventually fail in all of us, or is this a pessimistic view? Is it likely that maximal life span can be extended to 150-180 years? What about the age-related neurodegenerative diseases such as Alzheimer's and Parkinson's diseases? Are there reasonable approaches that might be taken to deal with these frightening and devastating conditions?

The purpose of this book is to lay out many of the neurobiological facts we have about the developing, adult, and aging brain. Clearly, the neurobiology is at a primitive stage compared to the richness of psychological observations that have been made on children, adults, and aging people. Nevertheless, not only have modern neurobiological studies given us some firm facts with which to ponder many of the issues laid out above, but neuroscience studies have also given us models—ways to think neurobiologically about the issues. The models in their details might not turn out to be right, but they suggest that we can get at many of the underlying phenomena and understand them.

Ultimately, we seek to understand the human brain, but our ability to study it neurobiologically is limited for the most part to noninvasive imaging or recording techniques. Occasionally we can get a piece of human brain to analyze, but this is the excep-

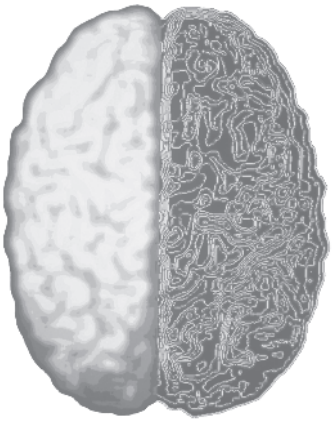
tion. On the other hand, we can study the brains of animals, and often the animal brain data are directly relevant to an aspect of human brain function or, at the very least, they give us a way to think about how the human brain might work. Throughout this book, I give examples of animal brain studies and what I believe they are telling us.

The book is not written for the expert, but for those nonexperts and nonscientists interested in the issues and how they are being approached. I have tried to portray the neurobiology fairly and accurately, but in a simplified way. The book is divided into three parts: I, The Developing Brain; II, The Adult Brain; and III, The Aging Brain. Three chapters comprise the section on the developing brain, two the section on the adult brain, and just one on the aging brain. This division reflects to a considerable degree the amount of research and focus on these three aspects of human brain biology. The emphasis might be shifting somewhat as our population ages and the devastation of the age-related neurodegenerative diseases looms greater. Nevertheless, the challenge of understanding how the brain develops and how that understanding might help in raising the next generations to the best of our and their abilities is key to the future of humankind.

Initial work on the book took place during a delightful stay at the Rockefeller Study and Conference Center in Bellagio, Italy. Much of the book was written during an equally delightful stay at the International Institute for Advanced Study in Kyoto, Japan. Lisa Haber-Thomson and Carla Blackmar expertly drew the figures, and Stephanie Levinson provided the crucial secretarial help needed to bring the project to fruition. Jerome Kagan, Mark Konishi, Brian Perkins, and Richard Sidman read parts or all of the manuscript and provided many useful corrections, comments, and suggestions. And last but not least, Jeffrey Robbins enthusiastically encouraged the book, edited it, and improved it immeasurably.

PART I

THE DEVELOPING BRAIN



BUILDING A BRAIN

Understanding how the brain forms is one of biology's greatest challenges. From a relatively few undifferentiated cells in the young embryo, all of the neurons and glial (supporting) cells arise. The adult human brain contains about 100 billion neurons (a conservative estimate) and perhaps 10 times as many glial cells. Because virtually all neurons and most glial cells form before we are born, an embryo would generate approximately 250,000 cells per minute in the womb if brain cell generation were constant over the nine-month gestation period. However, most neurons are generated in the first four months of gestation, so the number of cells generated per minute during this early period is much higher. Furthermore, many brain regions initially overproduce neurons and the surplus dies during the maturation process. Thus, at various times during the gestation period more than 500,000 cells might be generated per minute!

Our brain begins to form about three weeks after conception. A group of about 125,000 cells forms a distinctive flat sheet along

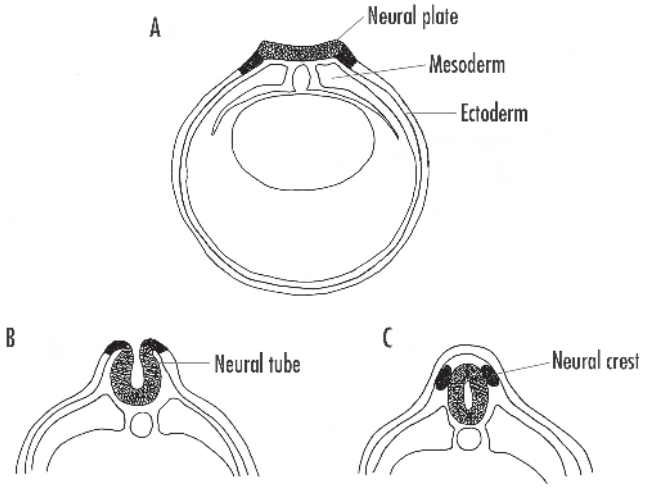


FIGURE 1-1 Formation of the neural plate, neural tube, and neural crest in young embryos.
A: The neural plate cells derive from ectodermal cells on the dorsal surface of the embryo. Signals coming from underlying mesodermal cells induce the dorsal ectodermal cells to become neural plate cells.
B: The neural plate invaginates to become the neural tube, and cells that initially lie laterally along the neural plate form the neural crest.
C: The neural tube becomes the central nervous system (brain and spinal cord), whereas the neural crest forms much of the rest of the nervous system (peripheral nervous system).

the dorsal or back side of the embryo. Known as the neural plate, all the neurons and glial cells derive from this early structure (Figure 1-1A).

Between the third and fourth weeks of development, the neural plate curves inward and creates a groove that slowly closes into a long tube, the neural tube, as shown in Figure 1-1B. The entire central nervous system—that is, the brain and spinal cord—develops from the neural tube. The anterior part of the neural tube becomes the brain proper, the posterior part the spinal cord. By the 40th day of development, three swellings become apparent along the anterior part of the neural tube as shown in Figure 1-2. These eventually form the three major subdivisions of the brain—the forebrain, midbrain, and hindbrain.

During formation of the neural tube, some cells on either side separate to form structures known as the neural crests as shown in Figure 1-1C. Much of the peripheral nervous system—those nerve and glial cells that lie outside the brain and spinal cord—derive from the neural crest cells.

Figure 1-2 shows the development of the human brain from the neural tube. The detailed drawings at the left are enlarged relative to the drawings on the right. By 60 days after conception, the forebrain, midbrain, and hindbrain regions can be readily distinguished. Infolding or wrinkling of the brain's surface—to increase the cortical area—begins at about seven months.

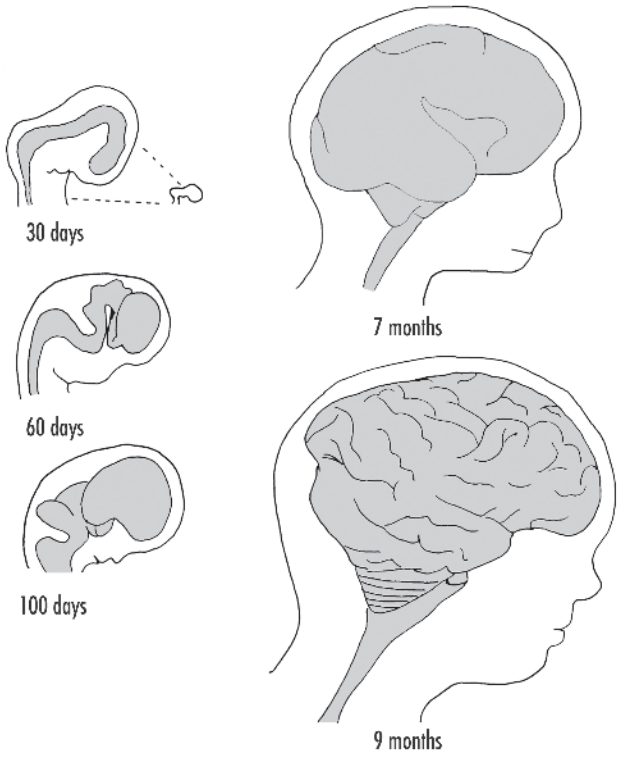


FIGURE 1-2 Development of the human brain from the neural tube. The drawings on the left are enlarged relative to those on the right. The tiny drawing at the top indicates the actual size of the brain at 30 days relative to size of the brain at 7 and 9 months.

At nine months of gestation, the brain overall looks quite adult, but it has far to go. The average newborn human brain weighs less than 400 grams, whereas the typical human adult brain weighs about 1,400 grams. Figure 1-3A shows the brain viewed from the dorsal (top) side in a newborn and at six years of age.

Much of the weight increase occurs during the first three years after birth, but the brain does not reach its maximum weight until about 20 years of age. Thereafter, brain weight declines slowly but steadily. Figure 1-3B shows graphically the average weight of the human male brain (based on measurements made on more than 2,000 normal brains) from birth to age 85. Female brains, on average, are slightly smaller at all ages, probably because women tend to be somewhat smaller than men.

I noted above that virtually all neurons are generated by about birth or certainly by six months of age. Thus, what underlies the remarkable growth of the brain in the first three to five years of life? A number of things are going on, including an increase in the number of glial and other supporting cells, growth of blood vessels, and, importantly, the ensheathing of the long axonal processes of the neurons by myelin. Myelin is formed by glial cells wrapping their cell membrane around axons, creating a highly enriched lipid layer that covers the axons. Myelin insulates the axons, making them more efficient in transmitting the electrical signals that travel their length.

However, the most important factor contributing to brain size increase in the early years is the growth and elaboration of the neurons themselves. Not only do their cell bodies grow in size, they also extend more dendritic branches during brain maturation. The dendrites grow larger and go longer distances as shown in Figure 1-4.

More than 80 percent of total dendritic growth probably occurs after birth. It is on the dendrites of a neuron that most synaptic contacts are made; thus, the elaboration of the dendritic processes of neurons that occurs during the brain growth of the

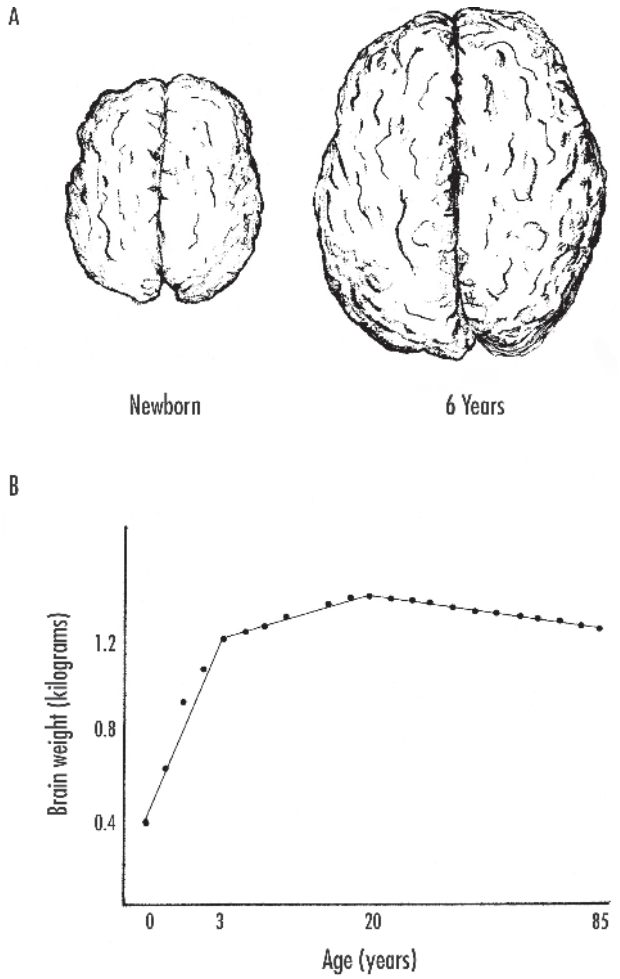


FIGURE 1-3 A: Growth of the human brain from birth (left) to age 6 (right). These are dorsal views showing the cortical surfaces of the brain. B: Brain weight as a function of age. A rapid increase in brain weight occurs in the first three years. The rate of increase then slows, but the brain does not reach its maximum weight until about 20 years. Thereafter, there is a slow and constant loss of brain weight.

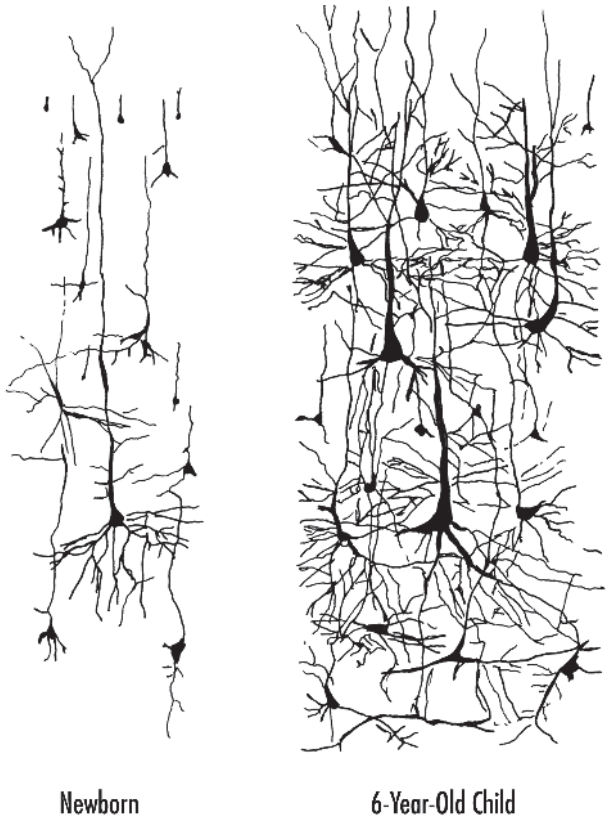


FIGURE 1-4 The elaboration of neurons during brain maturation. Not only do the cell bodies of the neurons increase in size, but there is an enormous increase in the number, extent, and complexity of their branches.

early years implies a substantial increase in the synaptic circuitry of the brain.

There is no question that there is an enormous increase in total numbers of brain synapses, not only prenatally but also postnatally up to at least age 2. But the situation is much more complex than just adding synapses. As we shall see, there is a substantial rearrangement and pruning of synapses during brain development and growth, so not only are many synapses added,

but many others are lost. Indeed, if one simply looks at the total number of synapses, the peak is between six and eight months postnatally, and then total numbers decline. Experience clearly influences the rewiring of brain synapses during brain maturation, but this rewiring is not just limited to the young brain. All of our lives our brains are being changed by our experiences, and these changes are reflected in the synaptic circuitry of the brain. (See Part II, The Adult Brain, for more information on these changes.) It is certain, however, that the young brain is considerably more plastic than is the adult brain, a topic we shall return to in the next chapter.

It is important also to emphasize that not all parts of the nervous system mature simultaneously. Maturation occurs in a roughly tail-to-head gradient. For example, the spinal cord and brain stem (which controls vital body functions such as respiration, heart rate, and gastrointestinal function) are essentially fully organized by birth, and myelination of the axons in these regions is quite complete. Shortly after birth, myelination of axons in the cerebellum (concerned with motor coordination) and midbrain begins, and thereafter—by the end of the first year or early in the second year—it begins in various parts of the forebrain, including the cerebral cortex.

The last brain structure to mature is the cerebral cortex, the seat of higher mental functions, including perception, memory, judgment, and reasoning, but here also maturation of all areas of the cortex does not occur simultaneously. Those cortical areas concerned with sensory processing mature earliest, followed by motor areas. But those areas concerned with the more sophisticated aspects of brain function—the so-called higher-order association areas of the brain, concerned with planning, intentionality, and other aspects of one's personality—are still myelinating axons and rearranging synapses up until the age of 18 or so! This includes much of the frontal lobes as well as parts of the temporal and parietal lobes of the cortex.

Recent imaging studies have extended our understanding of brain and cortical maturation. Studies have been carried out on

children between the ages of five days and 15 years, using positron emission tomography (PET) scanning to determine glucose utilization by various parts of the brain. Glucose is the primary energy source for neurons (and other cells); the more active a neuron is, the more glucose it uses. It was observed that glucose utilization in newborns is largely limited to the brain stem, parts of the cerebellum, and certain subcortical structures. Very little glucose utilization was observed in the cortex itself, indicating relatively low neuronal activity there. By two or three months of age, glucose utilization increases significantly in some cortical areas, especially in the occipital cortex, which is involved in visual processing and perception. Not until six to eight months is significant activity observed in the frontal lobes, and again some parts of the frontal lobes show more activity than others.

Glucose utilization by the brain increases through early childhood and, interestingly, it peaks between four and seven years of age (depending on brain region), at which point glucose utilization is about twice the level of that in the adult brain. Glucose utilization by the brain then slowly subsides to adult levels through childhood and adolescence. The peaking of glucose utilization by the brain at four to seven years of age perhaps relates to the enormous synaptic plasticity of the brain at these early ages. Many new synapses are being formed, others eliminated, and synaptic circuits refined; but now I am getting ahead of the story. We shall come back to these issues later.

Mechanisms Underlying Brain Development

Let us return to the earliest stages of nervous system development and consider what is known about the underlying biological mechanisms. All neural tissue derives from neural plate cells, as shown in Figure 1-1, but what causes these cells on the dorsal side of the very young embryo to become neural plate cells? Two layers of cells initially make up the very young embryo: ectodermal cells, which cover the surface of the embryo and will eventually form mainly skin, and endodermal cells, which line the embryo

and will form the digestive system and internal organs. A third layer of cells—the mesoderm, which will become muscle, bone, and connective tissue—develops next, and during its formation it migrates between the ectodermal and endodermal layers, initially on the dorsal side of the embryo. It turns out that the migrating mesoderm provides the signal for ectodermal cells along the dorsal surface of the embryo to become neural plate cells.

This aspect of brain development was first shown by two German biologists, Hans Spemann and his student, Hilde Mangold, who, in the 1920s, took mesodermal cells from the dorsal part of the salamander embryo and transplanted them to other parts of the embryo. They found that the transplanted mesodermal cells were capable of inducing any ectodermal cells to become neural plate cells, not just those on the dorsal part of the embryo. Thus, if they transplanted mesodermal cells from one embryo into another, they could induce the formation of two neural plates and, in some cases, the development of two nervous systems in the animal. Conversely, if they prevented mesodermal cells from migrating underneath the ectoderm in the early stages of embryonic development, no neural plate formed and the embryo lacked a nervous system.

How does the mesoderm cause ectodermal cells to become neural plate cells? It has long been suspected that a chemical signal from the mesoderm mediates this induction. For example, if pieces of embryonic ectoderm are cultured in the presence of mesoderm, they will become neural plate cells, but in the absence of mesodermal cells they will not. By placing porous filters between ectodermal and mesodermal layers, it is possible to define the size of the signal molecules, and these experiments suggest that the inducers are small proteins. If the porous filters are too small to allow small proteins to pass through, the ectodermal cells fail to become neural plate cells.

Three small proteins have now been shown to be neural plate inducers in amphibians: noggin, chordin, and follistatin. All of these proteins are thought to be secreted by mesodermal cells. Curiously, they act by binding to another secreted protein, called