Michael M. Merzenich

Born:

Lebanon, Oregon
May 15, 1942

Education:

Public Schools, Lebanon, Oregon (1924–1935)
University of Portland (Oregon), B.S. (1965)
Johns Hopkins University, Ph.D. (1968)
University of Wisconsin Postdoctoral Fellow (1968–1971)

Appointments:

Assistant and Associate Professor, University of California at San Francisco (1971–1980)
Francis A. Sooy Professor, University of California at San Francisco (1981–2008)
President and CEO, Scientific Learning Corporation (1995–1996)
Chief Scientific Officer, Scientific Learning Corporation (1996–2003)
Chief Scientific Officer, Posit Science Corporation (2004–present)
President and CEO, Brain Plasticity Institute (2008–present)

Honors and Awards (Selected):

Cortical Discoverer Prize, Cajal Club (1994)
IPSEN Prize (Paris, 1997)
Zotterman Prize (Stockholm, 1998)
Craik Prize (Cambridge, 1998)
National Academy of Sciences, U.S.A. (1999)
Lashley Award, American Philosophical Society (1999)
Thomas Edison Prize (Menlo Park, NJ, 2000)
American Psychological Society Distinguished Scientific Contribution Award (2001)
Zülch Prize, Max-Planck Society (2002)
Genius Award, Cure Autism Now (2002)
Purkinje Medal, Czech Academy (2003)
Neurotechnologist of the Year (2006)
Institute of Medicine (2008)

Michael M. Merzenich has conducted studies defining the functional organization of the auditory and somatosensory nervous systems. Initial models of a commercially successful cochlear implant (now distributed by Boston Scientific) were developed in his laboratory. Seminal research on cortical plasticity conducted in his laboratory contributed to our current understanding of the phenomenology of brain plasticity across the human lifetime. Merzenich extended this research into the commercial world by co-founding three brain plasticity-based therapeutic software companies (Scientific Learning, Posit Science, and Brain Plasticity Institute). Those companies have developed and validated neuroscience-based, computer-delivered rehabilitation training programs that have now been applied (by 2010) to more than 4 million impaired children and adults. Their research and treatment targets include developmental impairments that limit the cognitive, reading, and mathematical abilities of school-aged children; perceptual and cognitive impairments in normal aging; preventing and treating schizophrenia, bipolar disorder, depression, and other psychiatric diseases; rehabilitation strategies applied to treat traumatic brain injury and stroke; and the treatment of cognitive impairments arising from brain infections, toxin exposures, hypoxic episodes, and other environmental causes.

Michael M. Merzenich

I grew up in a German American family in a small farming and lumbering community in western Oregon. My father was a foreman in the primary industry in our town, a large plywood mill. My mother was dedicated to taking care of six rambunctious children and the gardens and livestock that supported a small-town/country life. My fundamental education as a young boy was enriched by a love of reading and by a wonderful family that, while largely self-educated, had mastered the practical arts of mechanics, engineering, and building, and took great pride in their practical good works. My mother and father were also masters of the art of Western hospitality, and our home was the gathering point for innumerable large and small celebrations with neighbors and kin. Everyone who came down our country lane was welcome to stay for supper!

My childhood at the edge of town provided the fields, forests, creeks, and mountains that became a play yard and a natural habitat for a natural game-playing and nature-loving child. Although we were expected to work to contribute to the family welfare at home, and worked from a young age as laborers on the fruit and vegetable farms in our community, my siblings and I were also granted a great deal of personal freedom throughout our childhood. That childhood combined strong lessons about personal responsibility and self-development, enriched by a goodly number of self-reliant and effective adult models.

Most important among these youthful influences were my maternal and paternal grandfathers Alois Hassler and William (Wilhelm) Merzenich. Both men operated with high professional standards; both were exemplary "self-made men." Both were at once stern and demanding, always gave a boy a chance to prove himself, and always showed just a small glimmer of approval (never backed up by more than three or four words) when it mattered most. Because my Grandfather Merzenich lived near our own home, I saw him often, and he had a strong influence in shaping my own youthful interests. Emigrating from Germany to the United States at the age of 9, his formal education ended upon his arrival because he worked from that time forward to contribute to his own struggling family's support. At the same time, he was one of the most broadly educated individuals that I have met in life—and certainly one of the most intelligent and interesting chaps a young lad could follow around. All that he knew he had learned through disciplined self-study and as an apprentice and on the job. Grandpa supported his family for most of his life as an architect and building contractor. During World

War II, he was first a government building inspector, then an "engineer of the ways" at a shipyard. William Merzenich was justifiably proud of the buildings that he designed and constructed in our part of the United States (including about 20 Oregon churches). He was also very proud of his several U.S. patents, the most important of which described the pneumatization of heavy shipyard equipment (drills, riveters), greatly increasing production speeds and cutting labor costs in wartime factories.[1] In the same way, my mother's father and his wonderful bachelor son (my uncle Edward) understood that science provided the basis for better agricultural practices. No citizens were a better audience for the latest agricultural college knowhow applied to the farm than Alois and Edward Hassler.

I was drawn to an interest in the great questions of philosophy and psychology, and to a practical engineering and scientific approach to understanding and discovering the truths in life from these childhood experiences. I also learned from my kin that every individual had an obligation of service, and that the most important works were those that benefited others. Training as an engineering-oriented scientist coupled with an interest in religion and philosophy (a young lad's way of framing an interest in the study of "the meaning of life") were natural outcomes of this upbringing. With a scholarship in hand provided by our local community that supported my college expenses, I matriculated at and graduated with highest honors with a degree in General Science from the University of Portland in Oregon. I chose this major because it gave me the greatest flexibility in choosing courses in mathematics, and in physical and biological science.

As a University student, I developed a close friendship with (soon-to-be Dr.) Robert Prusch, who had practical electronics knowledge acquired as a technician in the U.S. Navy. Bob Prusch and I shared a wonderful instructor in Physiology, Dr. Blondell Carlton, who liked our idea of initiating a recording experiment in worm and insect nervous systems. An alumnus of our University was a co-founding engineer of Tektronics, Inc., one of the world's leading medical instrumentation companies. He had donated a truckload of state-of-the-art electrophysiological recording equipment to our University laboratories. Bob Prusch and I opened the appropriate boxes, read the equipment user manuals, and set about recording action potentials from creatures that we caught in the lawn and nearby swamp! Puzzled about how to interpret our unit response recordings, I made an uninvited call to the Physiology Department at the Oregon Health Sciences Center asking for help. That call soon led me to the office of Dr. John Brookhart, a kindly, thoughtful, dignified man who almost immediately took me under his wing. I was stimulated by conversations with Professor Brookhart and

[1] He was rewarded for this invention with a $300 bonus and a "holiday" ride in the Captain's quarters 100 miles down the Columbia River in a newly launched light aircraft carrier.

his neurophysiology faculty colleagues Archie Tunturi and Alden Spencer. I explained to Brookhart that I had determined to dedicate my life's work to the neurological study of the origins of behavior and the conscious self, using a neurophysiological approach to address "the great issues of philosophy." In my juvenile mind, I thought of this career choice as the study of "experimental philosophy." Little did I know at the time that this distinguished gentlemanly professor whom I had adopted as an adviser was the President of the American Physiological Society and the Editor-in-Chief of the *Journal of Neurophysiology*, then the preeminent neuroscience journal! Brookhart told me that neurophysiology had not yet gotten off to much of a start in studying *my* issues. I asked him where I should go to study them. He said, "Mike, you should go to Harvard to study with David Hubel or Elwood Henneman, or to Johns Hopkins, to study with Vernon Mountcastle or Philip Bard. Or you can come here." I have no doubt that he spoke up for admission for this ill-formed country boy at these Eastern institutions, because I was accepted by both immediately upon application.

Neurophysiology ("Applied Philosophy" Level 0.1) Training

I was educated as a "real physiologist" at Johns Hopkins, which has advantaged my approach to neuroscience ever since. The same integrity and commitment to hard work, and the same respect for learning that marked my family's approach to life, were richly exemplified by my professor, Vernon Mountcastle. Professor Mountcastle read more and wrestled with the complex logic of his data and subdiscipline with greater discipline and intensity than anyone you know. He worked continually to shape strong conclusions from scientific fact—while never extending his verbal or written commentary beyond those facts in hand. I learned the importance of creating and continuously revisiting a grand logical construct related to neurophysiological science from this wonderful, intense, completely dedicated individual.

At the same time, from my own background arguing with a man of equal intelligence (my Grandfather Merzenich), I knew that you could extend your view and dare to use your brain, à la Descartes as your primary scientific instrument, to extend your logical constructs *beyond* your data—but *only* if you always kept the boundary between "what you really know" and "what logic tells you that you know" in clear sight. At issue is the degree of aggressiveness with which a scientist might attempt to succeed in achieving the greatest aim in science: advancing the boundary of the known. One might say that my approach to science has always been just a little contaminated by a logical extension of "the facts" through the more introspective approach of a philosopher or psychologist.

I completed two studies as a graduate student, one published, the other not. For my thesis, I demonstrated correlates between parametrically

documented tactile percepts and the firing characteristics of receptors innervating the glabrous skin of the hand dorsum and the hairy skin of the arm. These rather mundane studies showed that specific receptor classes must account for specific cutaneous perceptual phenomena (vibratory detection; stimulus magnitude). I also found, interestingly, that several classes of cutaneous receptors did *not* contribute to tactile perception, and I discovered to my great delight that the great 19th-century professor Friedrich Merkel had long before claimed that cutaneous touch domes were insensate spots on the skin, a fact that he had confirmed on the belly skin of fair-haired German boys! While these studies were methodologically routine, they did introduce me to an experimental strategy that I would repeatedly apply over the next decade: studies of human perception or cognition, directly paralleled by studies of primate or rodent behavior and neurology, achieved using the same psychophysical measures and/or training paradigms.

In a second, more inventive study, I demonstrated that responses in cortical field S1 evoked by vibratory stimuli in an adult monkey increased in amplitude to asymptote in the local neuronal population at a low stimulus level, while the growth of perceptual magnitude continued to grow across a far-broader intensive range. I concluded that the perceptual growth of perceived magnitude could only be accounted for by unit or local field potential activity in S1 by the spread of activity from the initially engaged "column" out across the horizontal cortical network. Mountcastle did not like this outcome, perhaps because (I think) he interpreted it as challenging the cortical column theory. He discouraged completion and publication, even while he was clearly very interested in this result. Several years later, Professor Kenneth Johnson (my favorite Johns Hopkins doctoral student compatriot) repeated this study with greater elegance and control, and came to the same general conclusion.

I was frustrated by my Johns Hopkins experience by the gulf between these kinds of elementary "information coding" experiments and any neurological understanding of "higher brain function." I did not agree with the operational Mountcastelian view (which Mountcastle himself cautiously abandoned a few years later) that any real understanding of complex (real) neurology was dependent upon a complete understanding of its more fundamental subforebrain coding precedents. Upon a review of the literature, I determined, perhaps foolishly, that the auditory system had important advantages for pursuing my more behaviorally expansive interests. The young reader might be interested to know that in making this decision in 1967, I read every published report from the beginning of time related to the anatomy and physiology of the auditory system—just as I had read (insofar as I could determine) every paper ever published about cutaneous receptors and tactile sensation in conducting my doctoral thesis work. In both cases, a large proportion of these studies were written in German or French. These few decades later, no students at the same stage of their career development

could begin to read all of the published literature related to their thesis project or to the subdiscipline of neuroscience that they might choose to pursue as a postdoctoral fellow.

In choosing to shift my attention to auditory neuroscience, most attractively, there were well-developed perceptual and cognitive subdisciplines (psychoacoustics, phonetics, linguistics) that provided a rich tableau for correlative studies. There were also great advantages for generating, calibrating, and controlling stimuli applied in the auditory versus the somatosensory or visual domains. The system seemed to be beautifully set up to study brain–behavioral relationships in behaving monkeys.

When I told Mountcastle that I was determined to shift my scientific focus to the hearing brain, he informed me immediately that, in that event, my postdoctoral studies would be conducted at the University of Wisconsin in the laboratory of Professor Jerzy Rose. The decision was made about 10 minutes before Professor Rose was told about it! The reader should understand that this kind of imperious treatment, professor to student, was accepted by me with respect: I knew that my mentor had my best interests at heart—and I knew that he had the greatest respect for Rose. Without hesitation, Mountcastle called Rose on the phone and said something like "Jerzy, I have a boy that I'm sending to you." The deal was closed within a few minutes. For my female readers, this is what they used to call "the old boy's network." It was not about being fair.

In the late 1960s and early 1970s, the Wisconsin auditory research group was equal to any in the world. Jerzy Rose was a distinguished German-trained Polish Jewish anatomist/electrophysiologist with a great scientific bloodline (Maximilian Rose was his uncle; Rose was trained by, and a great friend of, Cecile and Oskar Vogt), rescued from the Nazis shortly before the door closed. Rose was another man with extraordinary high standards of proof. Like Mountcastle (who had been strongly influenced by him through an earlier collaboration), he was exceptionally conservative in raising any arguments or extending any discussion in a manuscript or formal lecture past the cold hard facts of the study at hand.[2] But unlike Vernon, and just like my own kin, Rose was interested in *everything*, and he was willing to wrestle with the logic of any issue that you raised, usually initially taking a position that was contrary to yours! I suspect that this willingness to argue any issue was acquired at the Yeshiva. In any event, objectivity in perspective was the great lesson learned. Everything you "know," every rock in

[2] After he had delivered a formal lecture, a member of a scientific audience once asked Rose the kind of question he hated (and refused) to answer: "What, Dr. Rose, is your model [that you would apply to explain your data]?" Rose believed that an extended description of data in the form of an abstraction represented by a model was improper. "My model is Jesus Christ," he responded, with a delightful impish grin. He had nothing more to say.

your foundation of knowledge, should be turned over, because it might have a substantially different appearance when viewed from the other side!

At Wisconsin, I actually worked most closely with a wonderful scientist who has been a lifelong friend, John Brugge. Together, we derived the first detailed "maps" of auditory cortical fields in the macaque monkey, then conducted the first waking monkey recording experiments in these cortical areas. While these two studies were instructive and useful for experiments that were to follow, two off-the-beaten-track studies were actually more intellectually stimulating. First, Wisconsin had a wonderful mammalian brain collection, with well-preserved specimens gathered from about 130 mammals. I spent several months examining and documenting the auditory brainstems of all of these species, finding many marvels of comparative anatomy in the process. None was as astounding as the incredible specialization of the cochlear nucleus in a burrowing mammal, the "mountain beaver," *Aplodontia*. I talked a trapper that I knew in Oregon into catching a few of these primitive burrowing rodents, where this species is native. We quickly discovered that they had unbelievably sensitive subsonic hearing. I constructed a special apparatus by which we could induce minuscule changes of pressure, and with my colleagues Lindsay Aitkin and Leonard Kitzes discovered that this creature's inner ear could detect a 1 cc compression in a closed air volume of 30 cubic meters. This animal's ear was a highly sensitive, living barometer! This is a very useful ability when you live in a complex burrow that you can plug with your fat little body! How could this animal hear, if his body plugged his burrow (and his side-mounted ears)? His ear canal was an Eustachian tube 7 or 8 mm in diameter, exiting from the back of the palate; that is, this beautiful little animal heard through his mouth! These specializations plausibly explained how this animal could have the lowest birthrate of any rodent, occupy a large-diameter burrow that is easily entered by innumerable predators (my trapper friend caught weasels, a spotted skunk, two martens, and a fisher in their burrows), yet almost never end up as dinner! I later determined that fat cells blocked the scala tympani in the central turn of this mammal's pine-tree-like cochlea. This animal had evolved a kind of mechanical AC-to-DC converter in its inner ear! What a thrill it is, in science, to discover something about the nature of things that no one else before you had begun to imagine.

The second series of special studies arose through a wonderful, extended interaction with the great surface evoked potential cortical mapping authority in that epoch, Clinton Woolsey. Professor Woolsey and I had spent many wonderful hours together, talking about variations in the organization of cortical systems in different mammalian brains. Woolsey had encouraged a young neurosurgeon, Ronald Paul, to join his lab as a postdoctoral fellow. Because Clinton was no longer conducting experiments himself, he asked me whether I would agree to supervise Dr. Paul's research project. Paul had already determined that he wanted to reconstruct the cortical "maps" of the

hand surfaces in the macaque monkey after the surgical repair on the median nerve innervating the glabrous skin on the radial side of the volar hand. I agreed that this was a worthwhile study, and I enjoyed teaching the basic method of dense-array cortical recording (unit response "mapping") to Dr. Paul.

There were two important outcomes in these studies. First, we quickly discovered that there were at least three complete hand representations in the cortical area that up to that time had been viewed (by Penfield, Woolsey, Mountcastle, and others) as a single field, "SI."[3] Second, more provocatively, we were astounded by the nature of the changes in receptive fields and in topographic organization recorded after peripheral nerve repair. It had been well established, in elegant prior studies, that after repair peripheral nerve fibers randomly reconnected to follow Swann cell tubes in the distal nerve stump. Yet, despite this dramatically shuffling of distal-to-central addresses, every cortical site in cytoarchitectonic area 3b (one of the 3 S1 subfields) had recovered a small, single, sharply defined receptive field; while every site (column) in cortical area 1 (a second S1 body surface representation) had two to five small, almost always widely separated cutaneous subfields. I struggled mightily to try to understand how this had occurred, given the then-predominant view that the adult brain was aplastic. I wrote a long section in the Discussion section of the manuscript in which I argued that this *must* mean that all of the divergent and convergent projection anatomy on the path from the skin to the cortex was a kind of illusion; that the *only* way that these small cortical fields could be reestablished was if at each level in the central somatosensory system, all of the neurons excited by divergent projections from a single cutaneous source were precisely recollected to project forward to the next system stage, and that this must occur across three anatomically divergent stages (i.e., within the dorsal column nuclei, ventrobasal thalamus, and in area 3b itself).

Woolsey did not like this Discussion section; he was not so enamored with my using my Cartesian instrument (my imagination, which I regarded as my powers of "reasoning") as I was! He saved me the need for later embarrassing correction, because what we had observed was *not* a demonstration of precise divergent-convergent anatomy in a brain that was based on near-miraculous point-to-point connectional detail. To the contrary, *we had generated dramatic proof that the adult brain was massively plastic*, with that plasticity achieved on the basis of Hebbian-network rules of competitive connectional remodeling. Alas, at this point, I was too narrow in my perspective to tumble to this very obvious alternative.

[3] One of Woolsey's protégés, Dr. Wally Welker, had earlier shown that there was a complete representation of the body surface in cortical area 3b, one of the three cytoarchitectonic subfields of S1, in the prosimian galago.

My wife and I had talked about returning to the Western United States to be nearer our families as I sought a permanent faculty position. Our primary choices were to return to Johns Hopkins, to the University of Maryland (where Ron Paul had just been appointed Chairman of a new Neurosurgery Department), or to accept a position in Otolaryngology and Physiology (and in a new Neuroscience Program) at the University of California at San Francisco. For us, the continent naturally tilted westward.

Establishing a University of California at San Francisco Laboratory

My arrival in UCSF was blessed by my landing in a collaborative, interactive research environment that at that time had few equals in the scientific world. As the new "Director" of the John C. & Edward Coleman Laboratory (endowed by a California mining, banking, and insurance family in the 1920s), I quickly constructed one of the first computer-controlled electrophysiology laboratories at UCSF and initiated studies designed to define the functional organization of the principal midbrain auditory nucleus, the central nucleus of the inferior colliculus. My reasoning: It would be helpful to understand the basic ways in which information was integrated and "represented" at this level and at the level of the thalamus, before I charged into studying "big issues" in the cortex. With several outstanding young colleagues, we defined the three-dimensional functional organization of this key nucleus in relatively elementary response-related terms and, through a combination of physiological mapping and anatomical tracing studies, discovered that its isofrequency lamina topographically represented different sound parameter continua. This, astonishingly, was despite the fact that anatomical projections within the frequency dimension of representation were highly divergent; that is, every point on functional lamina from multiple input sources projected anatomically to every point across broad sectors of these central nucleus lamina.

It did not take us very long to determine that the auditory system again fed information forward to the medial geniculate body via a massively divergent projection—but again, as in the central nucleus of the inferior colliculus, functional maps in the medial geniculate body (MGB) were again highly refined and topographically ordered. And just to make a point, the system "destroyed" that emergent topographic "representation" a third time, via a highly divergent anatomical projection fed forward from the thalamus to the primary cortex.

From these laborious experiments came an important new insight into *(a)* how this great neurological system is organized *(b)* for what purposes. The auditory system extracts common information from the auditory nerve, processing it in five or six elemental forms. It combines this information from two ears, thereby generating three or four more forms of elementary

combinative extraction. It then converges (combines) *all* of this different monaurally and binaurally extracted information onto broad sectors of the isofrequency lamina of the central nucleus. It *always* keeps information sorted by frequency—but in other representational dimensions, every point source of information is dispersed very broadly across the next system level. From this massively convergent information, the next system level creates new, higher-ordered (topographic) representations of complex feature combinations across *its* frequency-band lamina, first in the inferior colliculus, then after a second recombination in the thalamus, then after a third recombination in the cortex. In the central nucleus, these selective and orderly representations across the nucleus's isofrequency planes are already pretty sophisticated and must be pretty important for the brain's sound feature representations. But alas, the auditory system repeatedly "destroys" them by feeding all information forward via those all-to-all isofrequency-plane projections.

One of the great joys of science is to have the data in hand, for the first time in human history, that can provide new insights into something that matters. I began to understand, by the mid-1970s, that the organization of the auditory system represented a fundamental challenge to the predominant model of brain organization that had been posited on the basis of more extensive visual system studies. With the exception of the physiological psychologists (who the scientists I had trained with did not pay much attention to) the overwhelmingly predominant view was that sensations, perceptions, and object recognition were a product of multiple-level anatomical construction. My colleagues and I were seeing something that challenged this simplistic model. Our system extracted information in a dozen ways; combined it all, then extracted again; then combined and extracted again; then again—just to get the cortical field A1! Even this country boy could understand the potential combinative selectivity and power of such an information processing strategy! And even this raw young scientist could see that there was a problem with understanding how the brain actually got the most out of this system. *How* does *the brain fully exploit this power, if the connections in the adult brain are aplastic?* Again, as with our findings following nerve transection and repair, for a second time in my scientific life I had powerful evidence about how the brain *must* be operating, without enough of a vision to fully understand its extended implications.

By 1973, I had worked my way up to the cortex in the adult awake animal (in these initial studies, the cat). I began by deriving the first detailed microelectrode maps of A1 and surrounding fields in this species—a duplication of earlier studies conducted in the macaque monkey—then turned to study cortical column organization in the waking animal. I quickly discovered something confounding. When you went beyond frequency organization, A1 in different individual cats could be very different in organization. Unlike V1, where the basic organization for any one cat and monkey pretty much

applied for all other cats or monkeys, A1 in every adult cat was "special." In some cats, we could define sharply bounded "cortical columns" with column-specific response characteristics, representing this or that complex sound feature combination. *In other cats, we saw no such thing*. In the second or third case I studied, we documented an elegant representation of stimulus durations and intervals, expressed across a series of cortical columns. It was never seen again, in any other cat in that series.

"Surely," I said to myself, "these differences must reflect the behavioral abilities that distinguish one cat from another. Surely they must arise from each individual animal's behavioral experiences." I was dangerously close, at this point in my research history, to understanding that the predominant scientific view that held that the adult brain was aplastic was bankrupt.

These studies also led me to ponder, once again, about the true nature of "cortical columns." "How," I asked myself, "can they be so prominent and well-defined in one animal, and so obscure and ill defined in another?" That reminded me, in turn, about the surprising outcome recorded in somatosensory cortex following peripheral nerve transection and regeneration. If you remember, in each vertical penetration into area 1, every neuron in a nerve-repaired monkey appeared to have the same odd set of two to five widely separated receptive fields. "Why wouldn't this provide us with a strategy for defining the true neuronal constituencies of, and the neurological processes that explained response sharing within, and the functional boundaries delimiting cortical columns?" I asked myself. "After all, every neuronal member of a column in this preparation would presumably share the same odd receptive field set, and its boundaries should be easy to define." The best place to achieve the very precise and highly spatially refined recording needed to address these questions of neuronal coupling and cortical column boundaries and neuronal "memberships" would be in an unsulcated primate brain. Fortunately, I had a great friend at Vanderbilt University, Dr. Jon Kaas, who had been conducting studies in the visual system of the lissencephalic New World owl monkey. Because the central sulcus terminated medial to the hand area in these beautiful animals, the dimensions and neuronal connections and memberships of hypothetical cortical columns defined following nerve repair could be very precisely determined.

The young reader might see this shift in the focus of my attention from auditory neuroscience back to somatosensory neuroscience as a kind of self-imposed distraction. My advice to you is to make sure that your questions supersede your methodological approaches or models. Go where the question leads you. Go where the answer lies. After all, it's all about making progress.

The owl monkey is an especially beautiful preparation for studying the orderly representations of the body surfaces in the brain, because most of their representations are exposed on the flat cortical surface. Our maps of the body surface in the S1 areas 3b and 1 were to become a landmark in

somatosensory cortical studies. They quickly revealed a third general finding that challenged how we think about cortical representation: Just as in the auditory case, all maps of the surfaces of the hands were *not* the same. Indeed, especially in cortical area 1, body surface representations could be very different in different adult monkeys. Monkey A could have a huge thumb representation, while monkey B had almost no thumb representation; monkey C could have a large and refined representation of the dorsal hand, while monkey D had a small and primitive representation of the dorsal hand. "Surely," the question again automatically rose to mind, "this must have something to do with what the monkey is and is not good at. Surely it relates to an individual monkey's adult hand use."

I had so much fun doing these experiments with Jon Kaas and a terrific group of young research fellows in his laboratory (John Wall, Randy Nelson, Daniel Felleman, Mriganka Sur, Roz Weller), driving them like slaves over a period of several months of almost continuous experimentation. While we were at it, we also mapped the somatosensory thalamus in three dimensions, as well as the somatosensory cortex in the squirrel monkey, in part to keep our little team busy while we waited for full recovery after repairing transected median nerves in a small group of owl monkeys. Those experiments were to lead to a radical change in my scientific career: the direct and unequivocal demonstration that large-scale plasticity was in play in the adult somatosensory cortex.

Before describing how that happened, I would like to complete one small detail of my narrative, because the finding is important but has never been published. Remember those two to five receptive fields that were recorded in a vertical penetration into S1? It turned out that each of these receptive fields engaged neurons across the dimensions of a distinctly delimitable column, but that every individual overlapping receptive field had its *own* column boundaries. Columns within and overlapping with other columns. And why were those two to five fields widely separated, one from another? Almost certainly because Hebbian-network processes established each receptive field, on the basis of differences in the temporal structure of its spatially separated inputs, as a competitor with the other emergent fields sharing the same cortical neurons. Columns are temporal neuronal alliances—a marvelous product of coincident input-based (Hebbian) plasticity! And their boundaries? A simple predictable product of competitive Hebbian-network plasticity.

The Cochlear Implant

Before I talk further about the origin of the work that I might be most identified with in the current era, brain plasticity science, it is appropriate to digress to discuss a second scientific program that was conducted in parallel in my laboratory across the decade of the 1970s and well into the 1980s.

The primary promoter of my recruitment in the Department of Otolaryngology at UCSF had been a highly distinguished otolaryngologist, Francis Sooy. This wonderful gentleman had the notion that the primitive scientific attempts that had been made to restore hearing by electrically stimulating the inner ear might have an important clinical future in his surgical field. He had already recruited an eccentric surgeon, Dr. Robin Michelson, to his Department faculty. Michelson had constructed and applied one of the first reliable "cochlear implant" models. As I heard Sooy talk about this subject during the process of my recruitment, I was intrigued by the possibility that something useful might be achieved. However, upon arrival at UCSF, I made the almost immediate decision that Robin Michelson was not scientifically prepared to achieve it, and although he pestered me incessantly asking for my help I shunned him, even while that is generally contrary to my nature. Robin (who later became a dear friend) had no real understanding of electrophysiology, and like most ear, nose, and throat doctors, had little understanding of the inner ear or auditory brain. I cringed when he told me "how his cochlear implant worked," and how and why it benefited his patients.

After about a year of his pleading with me, I finally gave in, in part because I wanted to resolve issues of argument to get this pleasantly persistent cuss out of my office and off of my back. I said "Robin, give me 2 weeks to make preparations, and have your best patient come to my laboratory. I'll set up psychophysical studies to determine what she can and cannot really hear. Then we'll talk about it." I prepared simple stimuli to play for her, so that we could systematically determine how she described and could discriminate between tones, tone stacks, noises, FM sweeps, et alia; and a young resident working in our labs, Dr. C. Robert Pettit, had a friend in the Music Department at San Francisco State University who helped generate aural speech and musical stimuli (different instrument voices, melodies, et alia). I thought that we were in for a long day of debunking.

I was wrong. By the end of a day of testing, this wonderful patient, Mrs. Ellen Bories, opened my eyes to what could be possible: the recovery of speech understanding through patterned electrical stimulation of the inner ear in a profoundly deaf individual. Implanted with a single pair of low-impedance wires introduced into the scala tympani (what I sarcastically called a "railroad track electrode") and excited with capacitively coupled (charged-balanced) pulsatile and analog stimuli, Ellen identified (for example) the sounds of a flute or bassoon, could easily identify the voices of different speakers, and could distinguish modulated frequency differences with reasonable fidelity up to 600 or 700 Hz. "What if she was being stimulated with 5 or 6 or 11 electrode pairs," I asked myself, almost immediately. After all, communication engineers had already shown that one could produce perfectly intelligible speech via "vocoders" (human voice coders) that reduced band-passed speech to the outputs of 11 fixed-frequency oscillators;

and they had shown that if the lowest sound processing channel representing first-formant frequencies (sounds up to 500–600 Hz) could rove to faithfully represent the strongest components in the first-formant (lowest) frequency range, fully intelligible speech could be achieved with a 5- or 6-channel device. Mrs. Bories' outcomes indicated that this second glorious possibility just might be within reach!

Young scientists beware. This is what can happen to a person. There is nothing more wonderful or sleep depriving than the infection of a personal awakening that supports grand forward scientific possibilities!

With support from Neurology Institute grants and contracts (the latter from a crucial Neuroprosthesis Contract Program led by a great NIH administrator, Dr. Terry Hambrecht), we assembled a world-class team of otologists (Robin Michelson, Robert Schindler), neuroscientists (Mark White, Patricia Leake), mechanical, electrical engineers, technicians (Chuck Byers, Steve Rebscher, Gerald Loeb, David Patterson, Peter Zimmerman), and behavioral (speech) scientists (Elmer Owens, Dorcas Kessler, Mike Vivion).[4] Over the first research decade (the 1970s), we focused on four fundamental problems that we thought must be addressed if we were to reduce the cochlear implant to a surgical/clinical reality.

1. *Device safety.* How can electrodes be mechanically designed to be inserted >25 mm into the spiral-form scala tympani without damaging this most fragile of biological structures? What materials could be applied to minimize tissue reactions and at the same time assure long-term device survival? How could we avoid untoward hazards that might apply for the heavy, continuous stimulation of surviving spiral ganglion cells?
2. *Controlling the patterned electrical stimulation of the auditory nerve array.* How could the requisite, discrete channel-by-channel excitation of the auditory nerve array be achieved? How could we most faithfully simulate normal auditory inputs via patterned electrical stimulation?
3. *Device electronics.* How should the implant electronics be designed to most effectively translate sound inputs into appropriately spectrally (spatially) and intensively patterned eighth nerve array stimulation? How, specifically, should speech be "encoded" by the cochlear implant?
4. *Constructing a reliable and repairable prosthetic.* How could implant materials, designs, and fabrication methods assure

[4] Several dozen other scientists and engineers also made important contributions to this project.

that an implant introduced into the inner ear in a young individual survivor for 90–100 years, that is, for a lifetime? If an implantable device did fail, how could it be replaced without removing an effectively hearing-restoring intracochlear electrode? And how could a device be designed to "grow" with the changing dimensions of the head and skull?

A Hard-Won Lesson about Patents

By 1979, we believed that we had reasonable answers to all of these questions.[5] We had produced an 8-channel (16-lead) electrode array with mechanical characteristics that enabled its introduction long distances into the scala tympani without inducing cochlear damage. We had shown that chronic implantation and electrical stimulation in at least the cat model did not induce any additional damage to the surviving auditory nerve fibers in normally or in chronically deafened animals. We had shown that discrete channel-by-channel stimulation of the spiral-form intracochlear nerve array was achieved with this model. We had constructed miniaturized current-controlled stimulators that could engage intracochlear electrodes for a hypothetical lifetime without significant loss of metal or performance characteristics. We had constructed speech-to-patterned-electrical-stimulation voice coders that implemented the sound-processing strategies used to represent intelligible speech via transmitting minimal information in the telecommunications industry. We had implemented gain control strategies required to equate sound intensities with stimulus-evoked loudnesses. We had demonstrated, by the use of behavioral indices recorded using model devices controlled via a percutaneous connector, that we had successfully realized our basic engineering design specifications in deaf humans. It was time, we thought, for prime time.

I contacted the technology transfer office of the University of California system and explained to them that we had our hands on a practical invention of potentially great human and commercial value. This led to a series of meetings with medical device companies in the UC patent office. The first question asked by the first company: "Dr. Merzenich, where [the hell] are your patents?" It turned out that no company wanted to invest the several

[5] We did not realize that one "answer" represented a basis for implant failure. We had developed implantable connectors (rubberized, and sealed under very high pressures) modeled after under-sea connectors used in transocean marine and other saltwater cables, to provide a strategy for replacing failed electronics. Unfortunately, these implanted connectors failed in human application because of salt deposits that formed around the very closely spaced leads; this "sophisticated" solution to "assuring" life-long, undisturbed electrode array implantation had to be abandoned.

to many tens of millions of dollars required to bring the cochlear implant to market without having any patent protection.

As a typical academic idealist, I had the notion that we worked for the public, and that patent applications were, by their nature, selfish. I realized, in a flash, that this perspective was ignorant. Back in the laboratory on the following day, I asked our research team what we might still be able to patent. The two patents filed shortly thereafter (we could have filed 20 or 30 earlier, but did not) were ultimately a key to finding companies that would invest in what became the UCSF-Symbion cochlear implant (now manufactured and marketed by Advanced Bionics, Inc., a division of Boston Scientific).

A second lesson about patents was to be learned 7 or 8 years later, when a competitive company filed a lawsuit claiming that Advanced Bionics infringed on *their* patents. It turned out that we were first to invent on most of the issues in question but, without having filed patents, were subject to capricious challenge. At about the same time, another scientist filed and was awarded a patent that was claimed to represent an advance in cochlear implant encoding. Alas, the principle described in that patent had been explained to the "inventor" and others during a grant review site visit to my laboratory.

The young scientist should understand that patents can provide protection against the aggrandizement of valuable ideas, and against an antagonist frustrating your own research efforts; and patents can provide necessary protection for an investor who is willing and able on scientific and commercial grounds to help bring a big idea out into the real world. These facts partially explain why I have subsequently filed more than 70 patents, more than 50 of which have been awarded by the U.S. Patent and Trademark Office.

In the mid-1980s, I decided to withdraw from further research related to cochlear implant development. Most aspects of this invention now had a good scientific footing. It was clear that the application of these devices was going to be a practical success, and that additional efforts on my part would be largely lily-gilding. At the same time, this research field had already provided me with five wonderful gifts as a scientist.

First, it helped change many tens of thousands of peoples' lives for the better. That achievement was a wonderful "bonus" for a laboratory scientist. Restoring useful hearing in an individual who has acquired profound deafness is, after all, the stuff of miracles.

Second, it elaborated my own self-development in the realm of technology transfer and practical engineering.

Third, it taught me about the problems of commercialization, and it gave me the great privilege and enjoyment of leading the first of a series of large multidisciplinary teams in which everyone worked together to achieve a great, common purpose.

Fourth, it taught my colleagues and me many new lessons about the value of applying alternate strategies, on the path to truly understanding the principles of one's scientific subdiscipline (in this case, issues of auditory coding and auditory system function).

Finally, it provided us with powerful new insights into how the auditory brain must *really* be operating, and it greatly reinforced the growing understanding, coming from other research in my laboratory (and from other scientists), that the adult brain is a powerfully self-adjusting (plastic) organ.[6] After all, the cochlear implant represents one of the great brain plasticity experiments conducted up to that time. Drive inputs into the brain that code complex signals (aural speech) in what must be a degraded and unequivocally different way (rather like playing a Chopin sonata with your fists), and not surprisingly, a patient initially understands almost nothing. Not too many weeks or months later, about 90% of patients understand almost everything, that is, can follow aural speech via hearing alone with few phonemic errors at relatively high word rates. When that recovery is achieved, most patients declared that their received speech now sounded "completely normal." And despite the unequivocally large differences in its encoding, the patient had a full, complete, seamless connection to all earlier acquired information gathered in earlier life from his or her aural speech listening. This is *not* a miracle of neuroscience-guided engineering. It is a manifestation of a remarkably powerful adult capacity for top-down- (experience-) guided brain plasticity. As we declared "victory" over acquired deafness and abandoned this field in the mid-1980s, even I now understood the greater implications of the recovery of hearing in these patients: The adult brain is *fundamentally* plastic.

Plasticity

I have earlier noted that beginning in the 1970s, I traveled to Nashville first to map in detail the S1 somatosensory cortical areas in the lissencephalic owl monkey, then, with this crucial foundation data in hand, to transect and surgically repair the median nerve, as the first step in an experiment designed to measure the true dimensions and nature of (somatosensory) cortical "columns." When we mapped the cortex after median nerve regeneration

[6] When I decided to join forces with Robin Michelson and work on practical issues related to developing a practical speech-encoding cochlear implant, I called Vernon Mountcastle and informed him of my decision. He told me, emphatically, not to do it. "You have the capability of being a world-class scientist. This would be a distraction, and will be destructive to your career."

Fortunately, he was wrong. When you *do* look at issues that are fundamental to your science in a completely fresh way (the cochlear implant provided a wonderful opportunity to test long-standing principles of auditory coding and brain organization, and rapidly turned many of them on their head), you have an *enormous* opportunity to move that edge of the known *forward*.

several months later, we had a great surprise: the majority of the territory that formerly represented the skin field of the median nerve was *now* occupied by *other* inputs, arising from either the ulnar side of the palm and fingers, from the back of the hand, or from the face—unequivocal evidence of large-scale representational plasticity. Moreover, we soon realized at this point that the recovery of the representation of the median nerve skin with its emergent, discrete, topographically represented patches of a restored skin field representation was a fabulous expression of coincident input-based (Hebbian-network) plasticity!

With this (for us very exciting) finding, we immediately initiated a second experiment, in which we cut the same large cutaneous nerve—but in this case did not allow its regeneration. Several weeks later, this very large cortical territory was completely occupied by expanded inputs from other hand and face surfaces. In a special variation of this experiment, we tracked the progressive reorganization of the cortex at different times in individual monkeys. That study not only documented the sequence of progressive remodeling of this large cortical zone, but showed that even areas remote from the nerve transection (for example, the cortical representation of the face bordering the hand area, or the far-ulnar side of the hand) were unequivocally different in detail, each time it was mapped in the same monkey.[7]

In addition to documenting a capacity for large-scale plasticity in adult brains, these studies supported a very important general conclusion about cortical representational processes. Because any given skin surface could be represented at different locations at different times in the life of an adult monkey, the common view that there was a fixed relationship between cortical location and perceived skin location (the "grandmother neuron" model) could not be correct. *Cortical representations* had to tolerate the fact of plasticity. They *must be relational*.

These simple and inescapable conclusions provided a basis for my happy abandonment of the fixed-location, aplastic-adult view of the brain that I had been carrying around as heavy, tired baggage, for more than a decade!

When I returned to San Francisco, we initiated several experiments that quickly confirmed that cortical representations of the skin surface were (as Donald Hebb had argued) coincident-input based: *considered in detail, cortical*

[7] We later realized that we had conducted another version of a historic study conducted in the 1920s by Karl Lashley. He had repeatedly mapped the motor cortex in an adult monkey using surface-stimulation procedures, discovering that the map was unequivocally different (the evoked movement was around another joint) if several weeks intervened between successive maps. This study provided the basis for his positing the principle of "cortical equipotentiality."

Randolph Nudo later directly repeated Lashley's experiments in my laboratory using modern intracortical microstimulation methods, and again documented large-scale variations in motor maps recorded in successive "maps" obtained over a several-month-long period.

"maps" were actually dynamic, temporally based (not stable, anatomical) *constructs.* Studies in behaviorally trained monkeys showed that the neuronal memberships of (the dimensions of) cortical columns were *highly* plastic, on these same "competitive Hebbian-network" bases. The "rules" governing this plasticity were revealed by studies in which we varied temporal inputs or varied the dimensions and separations of the skin-surface competitors that were engaged by training. Large-scale plasticity completely consistent with a competitive Hebbian-network model was recorded in all of these studies.

These findings strongly supported the view that brain remodeling provided the basis of skill acquisition at any age[8]—that skill acquisition was equatable with connectional "specialization" achieved via relatively simple plasticity principles. As our adult monkeys acquired or refined a skill or ability, their brain was "specialized" in ways that repeatedly accounted for that acquisition or refinement.

This perspective was contrary to the predominant view of neuroscientists in that era and, as I began to argue this position, my colleagues and I were subjected to very strong criticism by powerfully entrenched investigators—most operating from a visual neuroscience perspective. They held that the brain was plastic (connections could be remodeled) within a limited, early "critical period," evolving to a mature aplastic phase at the end of this epoch. How, then, could one account for the seamless elaboration of skills and knowledge that extended to the end of life? The most common analogy was to the computer, which had fixed functional elements and connections and a resident operating system and programs, now burned in from a strong inherited base.

Because this incorrect conclusion indicated that developmental potential ended with critical period closure, it had powerful, negative impacts on educational science and in medicine, because it led to the operational position that an individual was stuck with his or her postcritical-period brain through the remainder of his or her life—that deficits recorded when a child entered school, for example, would have to be accepted as a fixed (largely inherited) reality—and that the physical brain from a young age onward had only one trajectory: downhill. Nothing could be further from the truth.

While the mainstream of neuroscience held to this view as religion (Hubel and Weisel were awarded a Nobel Prize in 1979, in large part for positing it), there was a small group of neuroscientists, the "physiological psychologists," who had already documented many aspects of cortical plasticity. Almost no one in my mainstream camp—including myself—had paid enough attention to them. One limitation of their studies was the almost

[8] To double-check this conclusion, I located several aged monkeys early in this experimental series and found that their plasticity was little different from that recorded in vigorous young adults.

exclusive use of the Pavlovian (classical) conditioning model. Still, scientists like Charles Woody, Jerome Engel, Richard Thompson, E. Roy John, John Disterhoft, and Norman Weinberger (among others) had conducted compelling studies documenting large-scale changes in cortical responses that met all of the contingent requirements of Pavlov's model. For example, Woody and Engel recorded large changes in the neurological representations of both the unconditioned stimulus and the conditioned response in rabbits trained to avoid air-puff stimuli; Disterhoft first showed that changes selectively amplified the representations of conditioned stimuli; Weinberger's group repeated and greatly elaborated these studies, recording single-unit-level changes for conditioned stimuli that endured as long as conditioning was sustained, but that reverted to a pretraining status when conditioning was "extinguished"; while Richard Thompson and colleagues showed that all of the changes contributing to classical conditioning could be recorded in the same machinery (in deep cerebellar nuclei). In parallel with these studies, scientists like Mark Rosenzweig, Marian Diamond, and Roy Johns had shown that plastic remodeling is almost certainly a universal property of the mammalian forebrain. Train an animal any which way and watch it change before your eyes, by elaborating neuronal connections, or by instantiating the operational rules of classical (Pavlovian) conditioning! In the light of these important earlier studies, I have sometimes been very embarrassed to be called "the father of cortical plasticity"!

At the same time, my research group did rapidly extend these earlier studies in a number of important ways. We documented the fact of plasticity in the domain of operant conditioning, which is a primary route to human skills acquisition. We illustrated its nature and power in models of nerve and brain injury that bore strong implications for rehabilitation. We provided proofs that Hebbian-network plasticity principles accounted for primary plasticity phenomenology, which immediately brought plasticity research into a higher logical frame. We described "adult" plastic changes in terms of classical neurophysiological constructs: cortical receptive fields, cortical columns, cooperativity, competitive network plasticity, synaptic plasticity, inhibitory and excitatory processes, et alia. We added substantially to our understanding of how plasticity was controlled and regulated in adult brains. We provided compelling evidence that selective attention/working memory/prediction *controlled* adult cortical plasticity. We effectively demonstrated that plasticity could not be isolated to any one system level but, to the contrary, inevitably applied for brain systems and networks. By these studies, we helped define plasticity phenomenology in the operational terms of our then-current understanding of the fundamental machinery of the brain. Perhaps most important, we began to consider how these processes might be employed therapeutically to empower underfunctioning brains, or to drive neurologically or psychiatrically dysfunctional brains, through training, in strongly "corrective" (renormalizing) directions.

Lifelong Brain Plasticity

Before I discuss our efforts to translate this science into therapeutic strategies that could be applied in neurological and psychiatric medicine, it is useful to describe studies conducted primarily over the past two decades that I believe shall result in another fundamental correction about how we think about the brain and its plasticity. In understanding that brain plasticity operated by Hebbian-network "rules," we understood how to drive positive (refining) or negative (degrading) changes in cortical representation, that is, immediately appreciated that *plasticity processes are, by their nature, reversible.* In the late 1980s and early 1990s, we conducted several studies that demonstrated that these principles unequivocally applied for the adult primate brain. For example, studies conducted with a superb doctoral student, Gregg Recanzone, showed that training a monkey with locationally invariant point-like stimulation on the hand (the monkey was engaged in a vibratory frequency discrimination training task) resulted in a dramatic increase in cutaneous receptive field size and in a >100x expansion of the neuronal population (cortical column neuronal membership or volume) representing the engaged skin spot. By contrast, when we randomly moved the stimulation site to different loci over a small finger zone on each successive training session, *exactly the opposite occurred*. Receptive field sizes shrank to a fraction of their pretraining areas, and cortical columns and their neuronal memberships were reduced to about one-third of their pretraining dimensions! In the former case, that single constantly engaged skin location was a competitive "winner." In the latter case, each small stimulus location was a vigorous neuronal and territorial competitor![9] In the same general way, the Hebbian model—affirmed by direct animal model studies—quickly demonstrated that the same two-way (refining or degrading) plasticity applied for the representations of all other stimulus-parameter continua.

In later studies, we documented the changes in the cortex from the time of the onset of the critical period onward, marking the progression to "adult" cortex, then tracking changes forward into old age. Such studies led to a reinterpretation of the significance of the critical period. In the auditory cortex, it is a period of unregulated Hebbian-network plasticity through which cortical processing can be specialized in an extraordinary stimulus-exposure-specific manner. In the auditory system, its closure is defined locally, in the cortex itself, on the basis of the local schedule of activation by correlated inputs; there are *many* critical periods in play. Just as important,

[9] The large training-driven improvements in the monkey's vibratory frequency discrimination abilities were accounted for by a sharpening of temporal coordination of evoked spiking activity in the engaged cortical networks—in the first case, expressed across a single, very large cortical column, and in the second case, by an equivalent increase in coordination for neurons within several hundred cortical columns representing the same skin zone in highly resolved detail.

our studies led us to question the classical dogma that the brain is on a one-way trajectory of "development." We now know, in fact, *(a)* that we can rapidly "mature" a cortex by providing it with a hyperrich environment (accelerating representational refinement); *(b)* we can rapidly "age" the "mature" cortex by maintaining the animal in continuous, moderate-level noise (accelerating representational degradation); *(c)* we can almost completely rejuvenate the cortex of the old animal (establishing most of the physical and functional performance indices of a vigorous young adult) by appropriately and intensively training the animal (driving positively representational refinements); and *(d)* we can drive the cortex back to the state of infancy, as defined by its physical and functional status, in an animal of any adult age (driving negative representational degradation), again by adding to the noisiness of cortical process by delivering moderate-level extrinsic noise or by amplifying intrinsic process noise.

These studies documenting the fundamental bidirectionality of cortical plasticity provide a strong basis for understanding likely "failure modes" of this self-organizing machine—failure modes that we identify as plausibly underlying the "great illnesses" recognized in psychiatric and neurological medicine. They also support our growing conclusion that variations in the noisiness of cortical processes are a major contributor to variations in human performance ability. Cortical process "noise" could arise from intrinsic sources contributed to by hundreds of possible genetic faults. It would also be expected to result from variations in the richness and reliability of early childhood (or adult) experiences, and from variations in environmental exposures to a rich variety of factors (heavy metals; toxins; prescribed medicines; acoustic and visual noise exposures; hypoxic episodes; brain infections; bumps on the head; et alia). In our models, we affirmed these general conclusions by manipulating the qualities of early childhood and adult experiences, and by exposing animals to environmental toxins or physical embarrassments (PCBs, hypoxia, SSRIs, et al.). In every model, the cortex was driven to a more refined or a more degraded functional and physical state (development or adult functional status was accelerated and upgraded—or delayed and downgraded), just as predicted by these plasticity-is-inherently-reversible models!

These studies provide the basis of a second great correction in how we should think about the mammalian brain: The brain slowly organizes its selective processes plastically to a level of refinement that normally peaks in young adult life. Anything that contributes to greater process noise across this epoch will delay and frustrate the achievements of the brain's self-organizing processes. A rich early engagement with the world can accelerate and beautifully elaborate those achievements. Beyond its functional peak, as noise grows within the machinery of the average older adult (largely, we are convinced, due to limitations in a typical individual's brain use), the two-way plasticity processes slowly adjust "backward" (degrade functional

brain operations). Functions that were the last to be mastered in the old brain are the first to be degraded, as the selective processes of the brain progressively roll backward. Ultimately, the functional and physical status of the older brain progressively reverses to be more and more undifferentiated; that is, its physical, chemical, and functional characteristics are more and more like those recorded in the child and (ultimately) infant brain.

Fortunately, at any point in life, positive changes in the operational capabilities of the brain can be rapidly achieved through relatively simple forms of positive (refining) training!

Brain Plasticity-Based Therapeutics

By the late 1980s, we had begun asking ourselves: How does natural "negative" plasticity contribute to the functional decline recorded in almost every chronic psychiatric and neurological illness? Given its fundamentally reversible nature, could we more effectively employ plasticity to contribute to functional recovery in chronically impaired or "ill" individuals, or following brain injuries? How can positive brain change rates be optimized? What catastrophic failure modes apply for a self-organizing brain? Could we prevent them by strengthening brain function via plasticity, prior to disease onset? Would it be possible to drive what we know to be reversible plasticity processes "backward" to recover more normal function—or dare we imagine, to overcome or cure, long-enduring impairments or chronic "disease"?

All of these questions tumbled around in our arguments and minds across the early 1990s. They had already led us to the first crystallized understanding that the adult brain's inherent plasticity could provide the basis for a revolution in how we think about the neurological origins of ourselves and our operational abilities. And they inspired us to work hard to understand how we might be able to *control* the genie, to achieve potentially powerful therapeutic strategies.

As we were actively seeking a model for initiating an evaluation of these great prospects, one landed squarely in our laps. It came in the form of an invitation to a meeting organized by a Rutgers University professor, Dr. Paula Tallal. The meeting topic was "processing speed," a subject that had completely consumed Paula since her discovery, about two decades earlier, that kids who operated sluggishly in processing successive acoustic inputs were delayed in language development and struggled to initiate effective reading. I had told Dr. Tallal in conversation that this is a problem that I thought we could "fix" by intensive plasticity-based training. After we described how we believed this could be achieved at her symposium, Paula invited us to include a collaborative project supporting our construction of a suite of training tools in a consortium grant that was submitted to the Dana

Foundation. In this grant, we committed to construct brain plasticity-based training programs designed to progressively drive positive plasticity in ways that would enable more accurate and higher-speed processing in her speed-challenged language- and reading-impaired kids. Paula's part of the grant supported outcomes trials evaluating the effectiveness of our novel training approach.

With very important advice from Paula and from Steven Miller, a post-doctoral fellow leading the outcomes research in her laboratory, Bill Jenkins (a brilliant neuroscientist/psychologist/technologist) and I (with help from two engineers, Xiaoqin Wang and Srikantan Nagarajan) designed the first version of what would become the "Fast ForWord" language training program. Jenkins recruited UC engineering undergraduates and a brilliant high school student to construct these programs. The first models were completed in about 6 months.

Because Jenkins and I were anxious to understand what was happening in the outcomes trial, we designed the software to record performance data in detail, and with the help of another key technical collaborator (Bret Peterson) wrote custom software to assure the automatic transmission of that data back to us every day on the Internet. This was the first application of the automatic Internet/database tracking of trainee outcomes, a fact later acknowledged by awarded patents. As the days passed across this 1-month-long study, our excitement grew because we could see at a distance that all seven language- and reading-impaired kids were making great progress, ultimately achieving performance levels that applied for normal kids.

As Paula and Steve's team began their blind posttraining outcomes assessments, Bill and I were on the plane to Newark. We were greeted with very large smiles. The blind assessors had found that all seven children had made strong gains in their aural language abilities. Their improvement generalized richly to performance indices recorded *by every measure*, in a standard language assessment battery. Both their aural speech production and reception had markedly improved. Their speech reception accuracy in noise had been normalized. Different assessments of language and speech-in-noise improvements moved by about 1 to 2 standard deviations!

For several children, the training had been unequivocally transformative. I still remember one quiet, darling, almost-6-year-old boy who had a language age of about 2.5 at the beginning of the trial. One month later, this now-confident little chatter-box operated in language as a *normal* almost-6-year-old, and he now wore a smile on his face that could melt a rock!

This visit to Paula's laboratory at the end of this trial was one of the happiest days of my scientific life because I knew, in these kids' outcomes and in their faces, that our science could be extended to help hundreds of millions of children and adults in the world—to change the lives of many millions of individuals for the better.

At dinner that evening, I suggested to the group that we had to figure out how to deliver this training out to all of those kids who could be helped by it. "We'll have to write patents. We may have to help establish a company, or find a company that would do a good job delivering this kind of program to kids in need." Jenkins and Miller immediately signed on. Paula was more conservative by nature. She quite correctly insisted that nothing practical could really be accomplished until we had completed a controlled trial.

We all agreed that such a trial could be conducted with still-better software over the following summer. In the meantime, I would work "in my free time" to organize an effective technology translation strategy.

Birthing Scientific Learning Corporation

Upon returning to San Francisco, we began writing what would become a series of important patents summarizing our therapeutic tools. I then met with our wonderfully supportive Chancellor, Dr. Joseph Martin, and explained to him that I needed the University's help in determining how to help deliver these useful training strategies out into the world. Joe ultimately organized a team of advisors—a group of San Francisco's wealthiest citizens chaired by the investment guru Charles Schwab—to listen to my story. Mr. Schwab asked me to prepare a "business plan" to distribute to this group before our meeting.

In fact, I wrote a brief scientific treatise because I knew nothing about business or business plans. Mr. Schwab began the meeting by dropping my document down in front of me while he said, rather sharply, "This is no business plan…. Dr. Merzenich, what are you selling? Who are you selling it to? Who would control its purchase? How would you convince therapists or teachers or parents that this would be good for their children? How much would it cost?" On and on, went the obvious, business-101-level questions. My advisors were not impressed by my feeble preparations!

At the same time, this group did conclude in their report to Dr. Martin that "these scientists just might have something that could have a major impact on these child populations and could become a substantial business"; that "you'll have to let Merzenich be involved in creating a company, because it probably can't succeed without him [our team]"; and that "he'll probably have to play a leadership role in the business in its start-up phase." When Joe Martin got this report, he agreed to make an exception to the usual UCSF policy by allowing me to work to establish and lead this business on an 18-month-long leave of absence. I shall be forever appreciative of his help and generosity, because the meeting with these business advisors crystallized my appreciation of the seriousness of the business creation process and allowed me to focus on creating Scientific Learning Corporation without having to give up my cherished UCSF laboratory and professorship.

Of course, business creation depended crucially on the outcome of the controlled trial being conducted in Paula's laboratory. When it confirmed our initial findings, we quickly wrote two companion papers for *Science*. Their publication resulted in more than 40,000 phone calls to the Rutgers and UCSF switchboards by parents and other individuals asking for information about how a child they loved might be helped with this software. Business creation also required leadership from the business side, and wonderful assistance almost magically appeared in the forms of David Charron and Carl Holstrom as we struggled to create a new company and organize its initial financing. Bill Jenkins and Steven Miller agreed to leave their University positions to head key business divisions (product development; outcomes research). Paula was able to initiate a sabbatical, so that her wisdom and energy could be brought to bear in our early program designs and research planning. While it had absolutely nothing to sell to anyone in hand, Scientific Learning Corporation was off to a very strong beginning!

With support from "friends and family," then from an investment company (Warburg-Pincus), we rapidly created the initial forms of child-training software and enlisted the unpaid assistance of more than 30 high-quality speech therapists to help evaluate it. They relatively quickly returned data to us from many hundreds of impaired kids. Again, universally strong gains in longitudinal assessment indices were recorded in these children from every clinic. We now knew that we had a clinically validated product that should ultimately transform the lives of millions of developmentally limited kids.[10]

Crossing the Great Divide: A Neuroscientist in a (Brave) New World

As a scientist-CEO, I immediately began investing in science that could extend the application of brain plasticity-based training to impaired adult populations. Research initiatives targeting the treatment of motor disorders, schizophrenia, depression, traumatic brain injury, and other important human problems were begun. Patents were written. Prospects for great future business appeared to be wonderful.

In the meantime, I made preparations for returning to the University that began with the recruitment of a professional executive to lead Scientific Learning. That new executive almost immediately decided that the company had to "focus to win"; non-child research initiatives were abandoned. This decision was terribly frustrating, because I knew that our science could be applied to help many other human populations. The preliminary work

[10] At the time of this writing (2010), more than 4 million mostly struggling children in nearly 50 countries have benefited from the use of the brain-plasticity-based *Fast ForWord* training programs.

that had been accomplished and the patents that had been awarded that seemed to open up this far-wider window soon lay dormant.

After nearly a decade of trying to influence Scientific Learning to pursue wider interests, I finally negotiated an agreement with them by which we could apply "their" patents (some of the most important of which came from my laboratory's research) to help adult populations with normal aging-acquired or clinically acquired impairments. With that agreement completed in 2004, Posit Science Corporation was founded and immediately directed its sights on adult "brain health" (the losses accompanying normal aging) and toward developing effective treatments for a variety of psychiatric and neurological conditions that could be addressed via brain plasticity-based therapeutics. To further expand our scientific reach, The Brain Plasticity Institute was founded in 2008. Designed as an "incubator company," its goal is to conduct research and to create practical brain plasticity-based strategies that can potentially address many other human impairments and maladies that would otherwise receive little scientific attention.

This period of working to help deliver science-based therapeutic tools out into the world has been richly rewarding. Our first kid trainees are now of a college age; one wonderful young child in that first study is now pursuing her Ph.D. in psychology! Many thousands of patients and aged-infirm individuals and parents and therapists and teachers have written to us, or told us contributing scientists in person, how the programs that our teams have created have greatly helped them, and often literally transformed or recovered their (or their children's) lives. What a bonus such feedback is for an inveterate lab rat like me!

As these programs have come out into the world, their effectiveness has been repeatedly confirmed in controlled studies conducted in many hundreds of clinics and schools and university laboratories. Several hundred such studies employing the training programs that we have created are now in progress in clinics and laboratories across the world. Whenever a scientist has appropriately conducted a longitudinal brain recording or imaging study, he or she has found that the training that we developed—designed for whatever purpose—has driven the patterns of responses in the brain in the predictable "corrective" direction. Many such studies have now been published in the peer-reviewed literature. These behavioral and neurological outcomes provide powerful evidence that we *understand* (to an initial level of perfection) how to control neuroplasticity processes for therapeutic good.

Over the next decades, you shall witness the rapid maturation of this therapeutic field, as hundreds of tools developed to "reverse" plastic changes that limit the performance abilities of patients with many classes of neurological and psychiatric impairment and disease are brought into the world. I believe that in time, this "organic" medical approach—employing the powerful plasticity processes of the brain to "heal" itself—will largely supplant

less sophisticated, currently predominant neuropharmacological treatment strategies.

Back to Square 1: Understanding Myself

The great philosophers of the Age of Enlightenment understood that the brain is a trickster; that our realities are an almost unfathomable abstraction; that I am my own brain's creation. In their wake, scholars have repeatedly argued, from many directions, that the person that you or I are behaves according to the standards of our species, but with very powerful biasing in behavior stemming from our individual histories.

As a young scientist, my main goal was to understand the neurological origins of my own personhood, and of the consciousness that haunts it. As I've grown older, I am no longer as interested in the basis of consciousness itself. Continuous awareness is a glorious aspect of ourselves. We understand neurophysiological correlates of that awareness; it clearly arises through those processes as an important aspect of our personal evolution. Plasticity processes are designed, I believe, to sustain it no matter what. Our hypothesis has been that the brain specifically regulates its plasticity to sustain ongoing awareness, which is *sine qua non* with survival itself.

As my perspective grew as a scientist, it became increasingly obvious to me that there was a more important question than the origin of the flame of "consciousness": Why do I (why do we humans) *behave* the way that we do? Where does the *operational* person that we are come from? This question has been answered with increasing clarity, and to my satisfaction at a level of process and mechanism, across my scientific lifetime. We now understand that our specific functional skills and abilities arise as a product of our experiential (brain plasticity) histories. As William James argued more than a hundred years ago, our abilities and achievements reflect the simple sum of our experience-acquired and brain plasticity-achieved skills and abilities, which we have employed to record the massive body of information that shapes and ultimately controls our mental and physical actions.

In the same way, scientists have provided us with an understanding of the neurological origins of agency and the "self." Miyashita and Sakai first showed that associative learning is a fundamental achievement of brain plasticity. A variety of studies show that agency is a product of those associative memory processes. Put another way, for every feeling, thought, or action, there is an association with their source, literally billions of times a year. That source is creating powerful self-reference! The demonstration that the person you or I have become is a product of your/my brain plasticity within our lifetimes is, for me, a satisfactory answer to the great questions that originally motivated my entry into neuroscience.

But on the way to answering that question, what a rich panoply of other questions have arisen, only some of them answered. This scientist deeply

appreciates the privilege of being supported by his fellow citizens to work in this garden of earthly (scientific) delights.

An Afterword: Advice to a Young Scientist

The culture of science *and* modern culture and its technologies are advancing at breakneck speed, and any advice to a young scientist must be limited to general issues that related to the overall quality of your life and work. We could list them under the heading: "Top ten things that worked, for me."

First, identify a big issue (or two). Live it. Breathe it. Take a scholarly approach to wrapping your brain around it. Try to understand how prescientists and scientists have thought about your issue, from about 1000 BCE onward. Accept your responsibility to become a world authority on your subject. If not you, who?

Second, organize a personal self-development plan, to prepare yourself for scientifically approaching your "great issue." Think forward 10 years and ask yourself "what skills and abilities must I acquire, to make the most progress toward understanding my own, personal big question(s)?" Foremost among those abilities: Your skills at organizing, inspiring, and leading a *team* of fully empowered collaborators.

Third, create a logical construction that informs you in detail about what you know and don't know that is relevant to answering your great question. Feed and nurture this logical construct, almost every day. Before you know it, as in *The Little Shop of Horrors*, it will take on a life of its own—and if you're lucky, threaten to consume you!

Fourth, seek multidisciplinary enrichment. All of the best work that I have achieved has been with the collaboration with research fellows or clinicians or technologists who have special abilities that elaborate my own knowledge and technical proficiencies. The modern scientist who limits his or her knowledge and methodological repertoire to the boundary of his or her own experience, intelligence, and technical repertoire, or who selfishly controls what his or her collaborators do or think is a damn fool.

Fifth, look for the opportunity to carry your science out into the world. To help other scientists. To help the citizens who have been paying the bill for you having all that fun. To help yourself grow with the knowledge that what you do matters, not just for the growth of knowledge. It's not what *you* do. It's what your science does.

Sixth, leave the lily-gilding to the saints and angels. While it's often easier to get grant support to conduct studies with already-established answers, your time is far better spent conducting studies that really matter.

Seventh, don't limit your sources of information to the scientific literature—and especially to the incredibly arcane literature that relates to your sub-subdiscipline of neuroscience. Far too many scientists limit their knowledge and invention to those things that fall within the "religion" of their little scientific pocket. The more ways that you can nuance your flexible intelligence from domains outside your scientific sphere, the more likely you are to be *truly* intuitive and inventive.

Eighth, it's *not* about competition. It's about *progress*. "Cast your bread upon the waters," said an old mentor (Meyer Schindler). "Some of it will come back sponge cake!" Scientists who worry too much about telling other scientists what they think matters just aren't making progress fast enough.

Ninth, don't neglect the training of those who help you. Ultimately, their collective achievements will vastly exceed yours. The better prepared they are to achieve, the more impact your own efforts will have out in the world.

Finally, don't forget to carry your "heart" along for the ride. Think beyond yourself, as you think about who benefits from what you do. Care about it. And think beyond yourself, when you think of others you have invited to join you, in the lab and in your home, on this wonderful journey.

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