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TIME

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TOTAL RECALL

Scientists are beginning to grasp how memories are made and stored in the brain. Can "memory drugs" be far behind?

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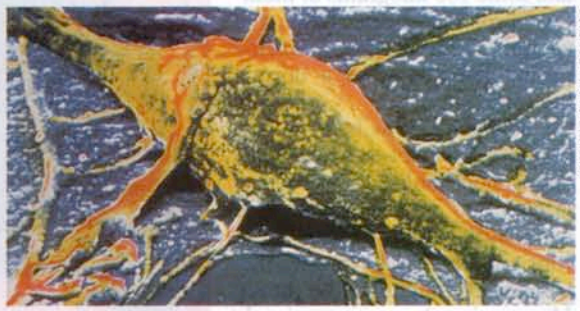
A TRIP DOWN MEMORY'S LANES



SCIENCE PHOTO LIBRARY

Scientists are mapping the many winding paths memory takes in the brain. Their findings could lead to Alzheimer's drugs—and a new wave of brain power boosters

By **JAMES GEARY** LONDON

PROFESSOR STEVEN ROSE, HEAD OF THE DEPARTMENT OF Biology at the Open University in Milton Keynes just outside London, is a farmer of sorts. The hallways of his laboratory are stacked high with bales of hay, there is a faint barnyard smell in the air, and the chirping of newborn chicks can be heard everywhere. But the furrows Rose has plowed over the past 30 years are not out in any country field; they're inside the convoluted folds of the chick cerebral cortex. And what he has unearthed there may well be the very stuff that memories are made of. Over the past several years Rose, together with other neurologists and neurobiologists, has broken new ground in the field of memory research. Scientists are now beginning to uncover the roots of memory that lie in complex patterns of biochemical and electrical activity in the brain.

These findings are of more than purely scientific interest, however. For the first time, there is the real possibility of effective treatment for the distressing memory loss suffered in neurodegenerative disorders such as Alzheimer's disease. The research also opens the way for the creation of so-called "smart drugs," chemical compounds that boost the ability of otherwise healthy individuals to learn and retain new information.

Soft as porridge and wrinkled like fingertips after a long, hot bath, the average human brain contains some 100 billion neurons, as the nerve cells that conduct the chemical and electrical traffic inside our bodies are known. Surrounding the billions of brain cells are at least 10 trillion synapses, the tiny gaps between neurons through which messages are transmitted from one cell to another. At any given moment millions of impulses are streaking through the neurons and synapses in our skulls, kindling this elaborate neural network into a flurry of signalling activity. The resulting barrage of neural firing forms the biochemical basis for all our perceptions, thoughts, emotions—and memories.

Until recently, recollections of the past were believed to be enclosed in compact bands of neurons called engrams. These tiny biochemical time capsules were thought to lie dormant in the brain until retrieved from storage by some present association. One engram, for example, might contain all the sensory and emotional data associated with your first kiss; another might contain all the information about what exactly you were doing when J.F.K. was assassinated on Nov. 22, 1963. In the early 1980s, some researchers even claimed to have identified individual proteins in worms that encoded memories for specific learned behaviors. Transfer this

Illustrations for TIME by Matt Mahurin

"memory molecule" from one worm to another, they proposed, and you transfer the memory too.

Neither the engram nor the memory molecule theory held up under closer scientific scrutiny, however. The engram concept proved itself too static a model for how the brain in general—and memory in particular—works. Research with positron emission tomography (PET) imaging, for example, has shown that many different brain regions—rather than specific clusters of cells—are at work in even the simplest acts of recollection. The existence of memory molecules, on the other hand, is unlikely for purely practical reasons. If each memory had its own protein, an individual's brain (or a worm's, for that matter) would accumulate some 100 kilograms of memory proteins—more than the weight of an average person—during the course of a normal lifetime.

Scientists now believe that memories are not to be found in any single molecule or neural group, but in an intricate and ever-shifting net of firing neurons and crackling synapses distributed throughout the brain. Memory is not, as was previously thought, some vast cerebral warehouse filled with rows and rows of neatly ordered filing cabinets. It is rather more like a labyrinth, the twistings and turnings of which rearrange themselves completely each time something is experienced and recalled. "It is impossible to ask where in the brain a particular memory is located," Rose says. "Memory is a dynamic property of the brain as a whole rather than of any one specific region. Memory resides simultaneously everywhere and nowhere in the brain."

THE SCIENTIFIC FOUNDATION FOR this hypothesis was laid by the American psychologist Karl Lashley some 50 years ago. To study learning and memory in mammals, Lashley taught rats to successfully negotiate complex mazes. He then began incrementally removing thin slices of the rats' cerebral cortex in an effort to pinpoint the memory locus for this task. But no matter which section of the brain Lashley removed, the rats were still able to run the maze. The rats' performance diminished as progressively more brain was excised, but Lashley found no one region whose ablation completely erased the memory. In a landmark research paper Lashley proposed the theory of "equipotentiality," which stated that memories are in fact scattered across the entire brain rather than being concentrated in specific regions.

Building on Lashley's work, and that of others in the intervening half century, Rose has worked his way through a few of memory's mazes himself. By studying learning and memory in newborn chicks, he believes he's found a model for how memories are actually made and later stored in the human brain.

GRAHAM TROTT FOR TIME

"Memory is a dynamic property, simultaneously residing everywhere and nowhere in the brain"
–Professor Steven Rose

Memory is composed of two complementary processes: learning something new and later remembering the experience. Using a passive avoidance learning experiment, Rose trained day-old chicks—which have a powerful pecking instinct—to avoid pecking beads that were coated with a bitter liquid. After only a single trial, more than 80% of the birds were able to learn and remember this simple task. Upon examination of sections of the chick cerebral cortex after training, Rose observed profound and permanent changes in the biochemistry and physiology of the chick brain, changes that could serve as a neural map of how memories are formed. In chicks—and by extension, humans—learning initiates a cascade of protein synthesis and neural bursting activity in the brain. Rose traced the biochemical ballistics of these firing mechanisms and identified two distinct stages through which an experience must pass before it enters long-term memory. While Rose has worked exclusively with chicks, researchers in other laboratories have discovered similar memory mechanisms in organisms ranging from mollusks to mammals.

The formation of short-term memories, which are unstable and easily disrupted, takes place 15 to 30 minutes after a chick is trained. During this phase—with the taste of the bitter bead still fresh on its tongue and in its mind—the chick's cerebral cortex is flooded with glutamate, the primary information carrier in both chick and human brains. Glutamate opens the communication channels between neurons so that data about the experience—encoded in electrical and biochemical signals—can be transmitted through synapses, the crucial first step in making memories. As a result of this torrent of glutamate—and the intercellular signals it transports—the chick remembers not to peck the bitter bead again.

The fact that this neurotransmitter shower is strongly increased in trained chicks and virtually absent in untrained chicks indicates that glutamate is intimately involved in the early phase of memory formation. But to check these results, Rose chemically blocked the glutamate receptors in the brains of a group of chicks. While these chicks were still able to learn to avoid the bitter bead, they were unable to recall the experience a few hours later.

While weak and rapidly decaying memories evoke only this first wave of glutamate synthesis, the formation of long-term memories requires a second wave that takes place some five to eight hours after training. Crucial to this phase is the production of a class of proteins known as cell adhesion molecules. As the name implies, cell adhesion molecules have "sticky ends," an array of velcro-like protrusions that enables them to cling to the sticky ends of their partner molecules. As the newly minted cell adhesion molecules latch on to one another, the arrangement of synapses in the chick brain changes. Like a river whose tributaries are constantly flowing into new configurations, the skein of synaptic connections shifts as the training

becomes embedded in the brain. The memory of the new experience—in this case, avoiding the bitter bead—is caught in this synaptic lattice like a fly in a spider's web. In neurobiological terms, this pattern of synaptic change is the memory itself.

In a paper published in February, Dr. Uwe Frey of the German Institute for Neurobiology in Magdeburg and Professor Richard Morris of the University of Edinburgh's Centre for Neuroscience present research that might eventually explain how memories are snared in this sticky neural web. By studying the effects of electrical stimulation on neurons in the rat hippocampus, a region located deep inside the brain and closely linked to memory, the scientists described "synaptic tags" that capture protein messengers at key junctions in the neural net. By anchoring proteins to the synapse, these molecular tags boost the synapse's ability to send and receive impulses. "This process," says Frey, "could result in the construction of markers for distinct neural patterns." Thus, when an experience alters the connections along a specific alignment of synapses, the new markers could note the configuration like a set of biochemical bookmarks. When the event is subsequently recalled, the brain could use these markers as handy reference points for recreating the neural firing pattern of the original experience.

If memories are indeed held and tagged in the brain as fluctuating patterns of synaptic connections, then how are they recalled? How does a childhood memory—

Should We Just Say No to Smart Drugs?

ALL ACROSS INDIA SCHOOL CHILDREN ARE POPPING LITTLE green and yellow pills—and claiming better grades as a result. Balding executives insist they are regaining lost hair as their memories improve. The country's Science Minister only half-jokingly prescribes the capsules for all members of Parliament. This new wonder drug, launched nationwide in January, is called Memory Plus, a compound derived from the brahmi plant found in India's marshlands. Memory Plus is just one of hundreds of so-called "smart drugs" available around the world, either in the form of over-the-counter herbal mixtures or synthetic prescription formulas. Though these potions vary widely in composition, effectiveness and toxicity, they are all intended to enhance memory by stimulating neural activity.

While the brahmi plant and other natural ingredients have been used for centuries in traditional brain tonics, recent neurobiological research promises whole new classes of compounds designed specifically to treat the memory loss that occurs in neurodegenerative disorders like Alzheimer's disease. These drugs could also have powerful—and controversial—spin-offs in the form of "cognitive enhancers" that enable otherwise healthy individuals to more readily absorb and retain new information. Just as vitamins are commonly taken as dietary supplements, memory pills could soon be available as do-it-yourself brain boosters.

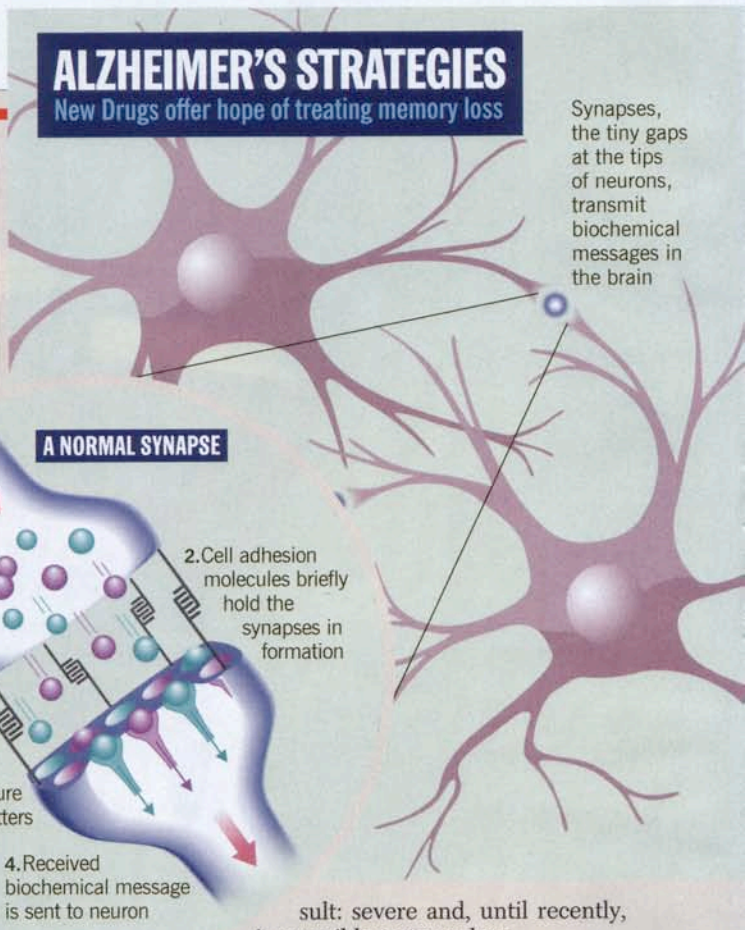
In neurodegenerative disorders like Alzheimer's and Parkinson's, the brain undergoes a rapid and devastating decline. In Alzheimer's patients, the function of the amyloid precursor protein (APP) is disrupted. As a result, another protein—beta amyloid, which is known to be toxic to neurons—accumulates into tangled plaques that prevent communication between synapses. As these plaques build up, neurons throughout the brain are gradually strangled to death. When these neurons are destroyed, levels of crucial neurotransmitters—especially acetylcholine and glutamate—drop. The result: severe and, until recently, irreversible memory loss.

But now that some of the mechanics of memory have been identified, scientists are better able to target potential sites for drug intervention. To date, some 200 different compounds are in various stages of clinical trials for Alzheimer's. One popular treatment strategy involves artificially increasing levels of failing neurotransmitters in the brain. Tacrine, for example, temporarily alleviates memory loss in the early stages of Alzheimer's by blocking an enzyme involved in the breakdown of acetylcholine. It is, however, highly toxic to the liver. A similar drug, called aricept, that is less toxic, has been approved for use in the U.S. and the U.K.

Although these drugs show great promise for treating Alzheimer's, their use is still shadowed by ethical dilemmas. One Alzheimer's sufferer involved in clinical trials for this type of drug in the U.K., for example, was eventually able to remember that she was married. What she failed to remem-

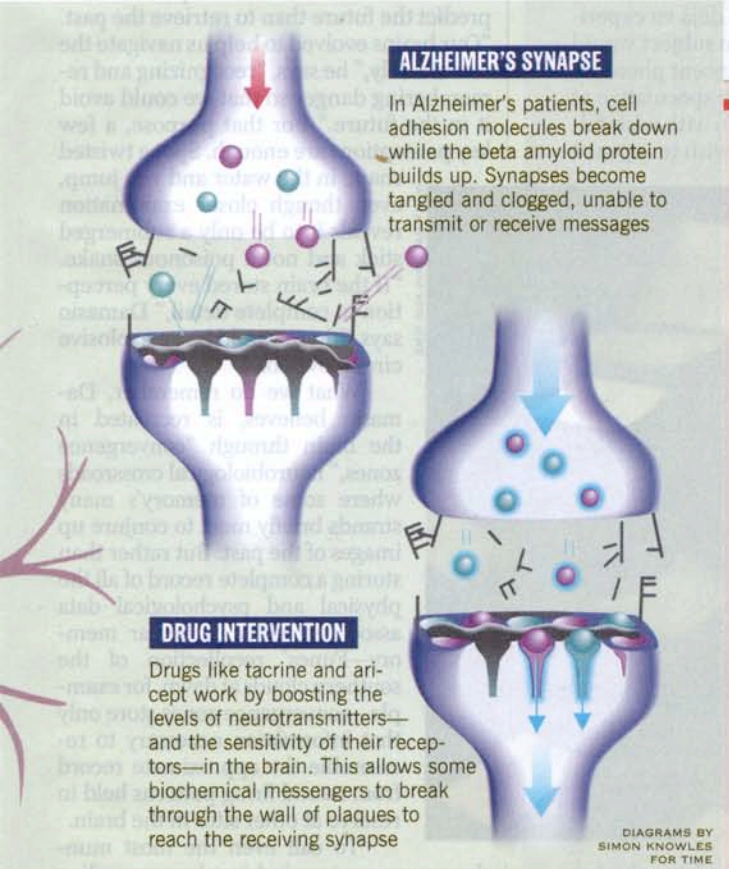
ALZHEIMER'S STRATEGIES

New Drugs offer hope of treating memory loss



of reading your first word, "f-o-x," when you were six—persist a lifetime while the name of someone you just met vanishes within minutes? Why did the taste of a morsel of cake dipped in tea remind Proust of his boyhood Sunday mornings with Aunt Léonie? And how does memory endow us with a sense of self and personal identity?

According to Portuguese-born neurologist Antonio Damasio, head of the Department of Neurology at the University of Iowa College of Medicine, remembering is neither a tranquil nor a passive process—assembly is required. The brain is not a computer, Damasio argues, so recall is not simply a matter of clicking the proper icon to call up the desired document from the brain's hard disk. Memories must literally be *re*-membered, put together again from pieces found in various parts of the brain. "The brain does not file Polaroid pictures," Damasio says. "Memory depends on several brain systems working in concert across many levels of neural organization." In the short story *Funes the Memorious*, the Argentine writer Jorge Luis Borges relates the fate of a young man who, after a fall from a horse, is unable to forget any experience—whether real or imagined, from the present or the past. "His perception and his memory were infallible," Borges writes. "He knew by heart the forms of the southern clouds at dawn on the 30th of April, 1882, and could compare them in his memory with the mottled streaks on a book in Spanish binding he had only seen once." For poor Funes, "the present was almost intolerable in its richness



ber, however, was that her husband had died several years earlier. This caused untold grief and consternation to both the woman and her family as she waited in vain every day for her deceased spouse to come home from work. Alzheimer's disease associations are now calling for more research into early diagnosis and drugs that delay the onset of the affliction rather than temporarily reverse its effects.

While cognitive enhancers were originally developed for the treatment of Alzheimer's patients, they can also be used as biochemical memory aids for the general population. In today's increasingly competitive marketplace, what struggling medical student or ambitious young lawyer wouldn't welcome the edge a memory pill could offer? And for that matter, what about overworked air traffic controllers, harried taxi drivers and aspiring actors—whose livelihoods depend on being able to flawlessly recall large quantities of information?

Ampakines, another set of experimental compounds still in an early phase of development, work by amplifying the sensitivity of glutamate receptors. Developed by neuropharmacologist Gary Lynch at the University of California at Irvine, ampakines could be effective in enhancing short-term recall not only in Alzheimer's patients, but in healthy individuals. In studies to be published later this spring, Lynch and colleagues report that young men scored up to 20% higher in certain standard tests of learning and memory. In a separate study, men over the age of 60 doubled their scores in similar tests. Should further clinical evaluation confirm these results, Cortex Pharmaceuticals—a company Lynch co-founded—could be expected to rush the new drugs to market.

But some researchers suggest the hype around smart drugs is vastly overblown. The brain, they argue, already functions at or near its maximum limits. "Memory evolved over about a hundred million years," says Swiss-born Cesare Mondadori, director of central nervous system research at the pharmaceutical firm Hoechst Marion Roussel in Bridgewater, New Jersey. "If it could be improved by adding a little more neurotransmitter here or there, nature would have done it long ago. You can fan the flames, but you can't add any more fuel to the fire."

Other scientists are convinced that smart drugs will work—and that demand will be enormous. Says James McGaugh, director of the Center for the Neurobiology of Learning and Memory at the University of California at Irvine: "On the evidence of animal experiments, I'm confident that drugs with strong memory-enhancing capabilities will be developed for human beings. When such drugs arrive, I believe they will be widely used."

If this scenario proves correct, could drug testing become mandatory at universities, as it is at the Olympics, to screen out users of cognitive enhancers? Could companies actually require employees to take memory drugs to maximize performance and efficiency? "The danger with smart drugs is: Where does it stop?" says Keith Wesnes, a psychologist and head of the British pharmaceutical consultancy firm Cognitive Drug Research. "Do you start sprinkling them on children's corn flakes?"

If these questions seem like science fiction, they're not. Researchers and clinicians agree that cognitive enhancers will be on the market within the next five to ten years. The Marquess of Halifax, a 17th-century English statesman, once remarked that "the best qualification of a prophet is to have a good memory." Before swallowing any promises of total recall, best remember to read the fine print. ***—By James Geary/London. With reporting by Meenakshi Ganguly/Lucknow and Helen Gibson/London***

Been There, Done That

IT HAPPENS TO US ALL AT ONE TIME OR ANOTHER: DÉJÀ VU, THAT UNCANNY FEELING of having experienced something before but being unable to recall exactly when or where. The term comes from the French for "already seen," and is defined by psychiatrists as "any subjectively inappropriate impression of familiarity of a present experience with an undefined past." But that clinical description hardly does justice to the eerie sense of mystery and unease we feel during such an episode of inexplicable recognition.

In *The Psychopathology of Everyday Life*, Freud placed the déjà vu experience in "the category of the miraculous" and predicted that "the subject would merit the most exhaustive treatment." But because it's an evanescent phenomenon, déjà vu is notoriously difficult to study. Most theories are speculative at best. Psychoanalysts, for example, maintain that déjà vu has to do with wish fulfillment. According to this theory, déjà vu is the expression of a wish to repeat a past experience—but this time with a more satisfactory outcome. Parapsychologists, on the other hand, suggest it's a fleeting glimpse of some past life. But as the brain's mechanisms for learning and memory become better understood, scientists are proffering more plausible—though still preliminary—explanations of this strange and miraculous act of recollection.

MATT MAHURIN FOR TIME

A model for one such explanation is the hologram. In a hologram, a kind of three-dimensional photograph, each point in the image contains all the data necessary to reconstruct the image as a whole. "Even the smallest fragment will give the complete picture," says Herman Sno, a psychiatrist at De Heel Hospital outside Amsterdam who has made an extensive study of the scientific literature on déjà vu. "But the smaller the fragment, the less sharp the picture will be."

If memories are indeed stored in the brain as holograms, each part of the memory contains all the sensory and emotional data needed to recall the entire original experience. A single detail—the sound of a child's voice, for example, or the smell of a lover's clothing—can evoke the complete remembered scene. According to this model, déjà vu occurs when a detail from a current experience so strongly resembles a detail from a previous experience that a full-blown memory of the past event is conjured up. "As a result of the mismatching," says Sno, "the brain mistakes the present for the past. You feel certain you've seen the picture before."

Another potential explanation involves a glitch in the exquisitely timed processes of perception and cognition. This theory proposes that sensory impressions of a current experience get detoured in the brain and are not immediately perceived. The information is, however, stored as a memory. This split-second delay in cognition creates the unsettling impression that the event "is being experienced and recalled simultaneously," says Sno. Whether it's a slippage of timing, a mental hologram or something else entirely, déjà vu will remain one of the mind's most tantalizing and elusive tricks. **—J. G.**

and sharpness, as were his most distant and trivial memories."

Fortunately for most of us, the neural organization for memory in our brains is not nearly as implacable as that of Funes. Memory is, in fact, a notoriously faulty and unreliable faculty. We tend to perceive and remember only what we consider novel or important. The rest is indiscriminately dumped and forgotten. We have such selective recollection, Damasio suggests, because memories were developed more to predict the future than to retrieve the past. "Our brains evolved to help us navigate the world safely," he says, "recognizing and remembering danger so that we could avoid it in the future." For that purpose, a few key perceptions are enough. Spot a twisted shape in the water and you jump, even though closer examination reveals it to be only a submerged stick and not a poisonous snake. "If the brain stored every perception in complete detail," Damasio says, "there would be an explosive circuit overload."

What we do remember, Damasio believes, is recreated in the brain through "convergence zones," neurobiological crossroads where some of memory's many strands briefly meet to conjure up images of the past. But rather than storing a complete record of all the physical and psychological data associated with a particular memory—Funes' recollection of the southern clouds at dawn, for example—convergence zones store only that information necessary to reassemble the approximate record from neural firing patterns held in reserve at other sites in the brain.

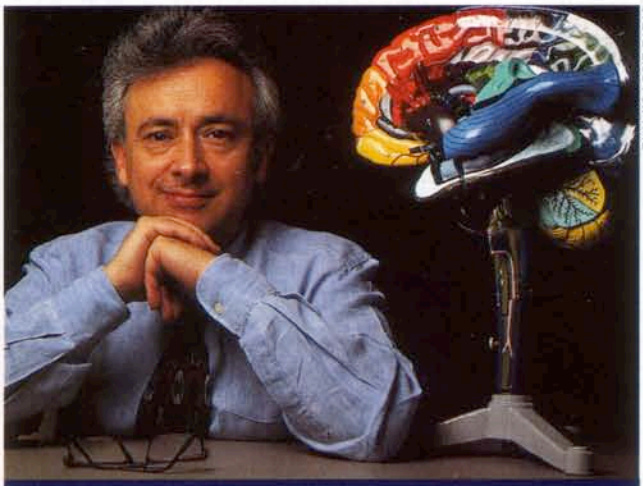
To call even the most mundane memory to mind involves compiling and collating enormous amounts of sensory and psychological information. When Funes watched the sun rise on that spring day in 1882, different regions of his brain were busy processing data regarding the color of the clouds, the sound of any birds that may have been singing, the smells in the air, the emotions he was feeling and thoughts he was thinking, as well as thousands of other impressions and sensations. All of this was held for an instant as a pattern of ignited neurons and chattering synapses. "But this massive load of data is never collected into one place for processing and interpretation," Damasio explains. "Instead, it remains distributed over a wide area of the brain."

This is where the convergence zone comes in. When we recall a person or an event, the convergence zone serves as a

kind of neurobiological instruction manual, directing the appropriate neurons in the appropriate brain regions to reassemble themselves in a firing pattern that approximates that of the original experience. Funes' view of the southern clouds at dawn set off a chain reaction of neural firing in his brain. The shape of the clouds reminded him of a particular book, and the convergence zone—perhaps with the aid of biochemical bookmarks—dutifully triggered the recreation of a synaptic pattern that exactly corresponded to Funes' glimpse of a volume in mottled Spanish binding he saw only once at a completely different time and in a completely different place.

Except in Funes' case of course, the memories thus recreated are not accurate in every detail. They are replications, not duplications, of the original event. Convergence zones do not therefore orchestrate the full symphony of past experience. They provide the score, but it's up to the synaptic ensembles involved in each individual memory to make the music. And just as with any musical performance, it's impossible to play the same note exactly the same way twice. "Whenever we recall a given object or experience," Damasio says, "we do not get an exact reproduction but an interpretation, a newly reconstructed version of the original."

Ironically, the volatile nature of memory is paralleled by the body's own internal dynamics. All the cells in the body—except for, significantly, nerve cells—are continually dying as new ones are being born. Blood cells, for example, have a life span of a mere 120 days. Though most of the cells in our bodies will be replaced many times over during the course of a lifetime, we still feel that "we" haven't changed. In this respect, our bodies are not our "selves."

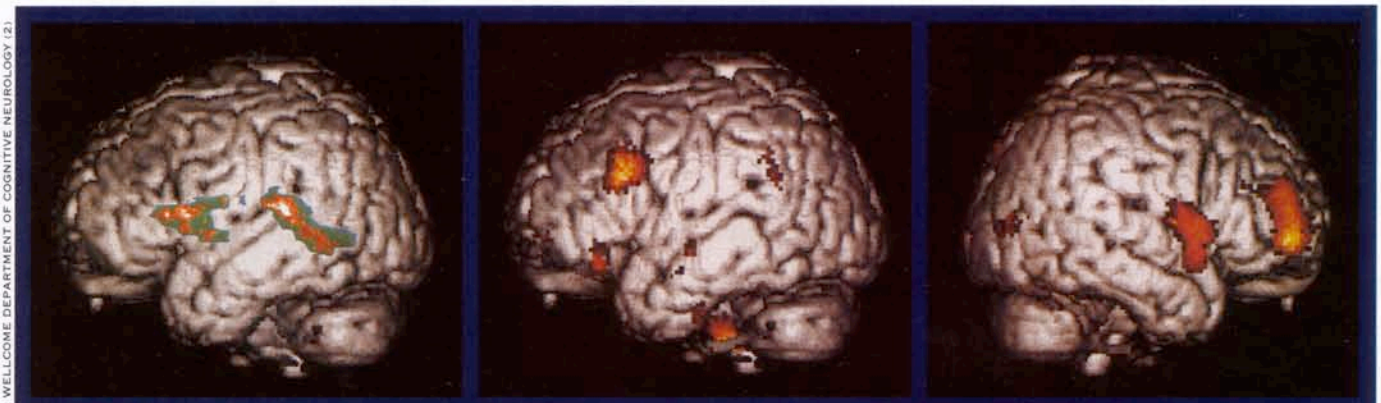


STEVE LISS FOR TIME

"The self is so continuously reconstructed that the owner never knows it is being remade"
–Professor Antonio Damasio

BUT WHAT IF ALL YOUR MEMORIES were suddenly replaced with new and different ones? Would you still be yourself? Strange as it may seem, the work of Rose and Damasio shows that—on a neurobiological level, at least—this is exactly what happens in the brain. Memory is a constant work-in-progress. When an object or experience is recalled, the neural pattern corresponding to that memory flashes through the brain as clearly and as quickly as a lighting bolt. But like lightning, it is as swiftly gone. And the next time that same event is remembered the pattern will be different, changed by a complex network of new associations and experiences. Despite these unstable foundations, we somehow still manage to construct a stable idea of personal identity from this welter of mercurial memories. "The self is not a little person inside the brain," says Damasio. "It is a perpetually recreated neurobiological state, so continuously and consistently reconstructed that the owner never knows it is being remade."

There is a parable from Buddhist lore that mirrors on a psychological level what Rose and Damasio have discovered on the neurobiological level. The Buddha once compared the self to the flame of a torch whirled so swiftly in the dark that it seemed to form one unbroken hoop of light. As anyone who has done the same with a flashlight can attest, this continuity is an optical illusion created in the same way we perceive the still frames of a film to be one seamless sweep of motion. Memories are very much like the flame of that torch—fickle, inconstant, flickering. To our imperfect senses, though, they seem to form a coherent whole. But memories are not fixed and immovable facts; they emerge from an ever-changing maze of neural firing formations and synaptic connections. They are in many ways fabrications, perpetually remade and replaced from raw materials that are in a constant state of flux. But oh from the tangled web they weave, what glorious things we do perceive! ■



SPL, WELLCOME DEPARTMENT OF COGNITIVE NEUROLOGY (2)

LISTENING This PET image shows areas in the left cerebral hemisphere involved in verbal short-term memory. Subjects were asked to briefly keep a string of letters in mind

LEARNING This PET image shows regions of the left cerebral hemisphere active during learning, or encoding. Here, subjects were asked to learn a series of simple word lists

REMEMBERING This PET image shows regions of the right cerebral hemisphere during word recall. Learning and remembering take place in different brain areas