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A MAGIC TOUCH FOR STROKE PREVENTION?

Neurons cut off by a stroke may have the inherent ability to reroute blood flow and save themselves

By Stephani Sutherland

You are visiting your elderly aunt, and you notice her speech begin to slur. She seems to be having trouble staying upright in her seat, and she looks confused. You recognize the signs of a stroke. You shout for your uncle to call 911 as you help your aunt lie down in a comfortable position. You run your fingers gently over her lips, face and fingertips as you sing into her ear and continue talking to her. The EMTs rush in and outfit her in what looks like a bathing cap encrusted with electronic bling—a kind of defibrillator designed to deliver electrical stimulation to her brain. As they carry her out on a stretcher, your worry is slightly eased, knowing that the sensory stimulation you gave her in those first minutes may have saved her from serious disability.

Today we can do little to help stroke victims. But if new research bears out, such stimulation might reroute the brain's blood supply to prevent cells from dying—a much needed breakthrough for the nearly one million Americans every year who suffer a stroke. As of now, the only intervention available is a drug that breaks up blood clots, and only a small number of patients benefit from it. In other words, although scientists have been studying stroke for decades, brain damage is inevitable in most cases. Stroke remains the fourth-leading cause of death in the U.S. and the most common cause of long-term disability. "We have so few therapies for this problem. We need to move more of them forward," says Steven C. Cramer, a clinician who specializes in stroke at the University of California, Irvine.

The new research, though currently still in animal studies, offers the tantalizing possibility of a low-tech, inexpensive treatment that could be dispensed immediately, anywhere, by anyone. In Ron D. Frostig's U.C. Irvine laboratory, rats were saved from brain damage after stroke when neuroscientists simply touched their whiskers or played sounds in their ear. Although translating these interventions into human treatments means overcoming significant hurdles, the revolutionary finding has invigorated a field fraught with dead ends and lackluster results. "Frostig is looking at something now that in 10 years will be obvious that we should all be looking at," says Cramer, who is not involved in Frostig's work. "He's reading the tea leaves of the field."

ILLUSTRATION BY STUART BRIERS

Stumped for Treatments

A stroke happens when a sudden loss of blood causes a part of the brain to stop working. The blood shortage may arise from either of two main causes: a blood clot or a hemorrhage. More than three quarters of strokes are clot-based or ischemic; the rest are hemorrhagic, in which a blood vessel bursts inside the brain. In both types, cells downstream of the clot or eruption are cut off from the vital supply of nutrients and oxygen.

By stimulating a single whisker immediately after stroke, the researchers had prevented any brain damage in the rats.

The paucity of treatments for stroke certainly is not for lack of research efforts. More than 1,000 compounds have been studied in animal models, but the dozens that have gone on to human clinical trials have all failed except one. Tissue plasminogen activator (tPA), the only treatment for stroke approved by the Food and Drug Administration, attempts to unblock a clogged blood vessel by breaking up the clot. It must be given in the first couple of hours after stroke, turning treatment into a game of beat the clock. Although tPA is potentially lifesaving for someone having an ischemic stroke, the clot-busting drug would spell disaster for someone with a hemorrhagic stroke, where clots must form to stop the bleeding. To make sure the wrong people do not get tPA, patients must undergo a brain scan before receiving the medication—a time-consuming step that delays treatment, disqualifying most patients.

Clot busters are one of the two main types of treatments that researchers have attempted to develop over the years. The other is neuroprotective agents, which employ a wide variety of brain-saving strategies, including dampening electrical activity and halting signaling molecules within brain cells. The wide range of approaches speaks to the complexity of the processes at work in the stroke-damaged and recovering brain. When brain cells go too long without access to oxygen-rich blood, catastrophe ensues: the balance of charged particles inside and outside cells is upset, a harmful amount of calcium flows into cells, and electrical activity runs rampant, leading to a dangerous state called excitotoxicity. Next, cell membranes break down, and free radicals—reactive particles that damage cells and DNA—build up. These events trigger programmed cell death, during which genetic material and cellular structures are destroyed. Even surviving cells surrounding the affected area are in danger; the sudden flood of oxygen and nutrients that follows a successful dissolution of a clot can further skew the delicate ecosystem of the brain and spread the damage wider.

Researchers have attempted to develop neuroprotective drugs aimed at certain elements of these destructive cascades, with little success thus far. Still, experts are hopeful; early failures could have been because of poor guesses about dosage or time frames. "We don't really know what went wrong. It could have been that the drugs themselves actually worked," explains Walter J. Koroshetz, deputy director of the National Institute of Neurological Disorders and Stroke. Efforts aimed at neuroprotection continue today; for example, a clinical trial called FastMag, headed by clinical stroke expert Jeffrey Saver of U.C.L.A., is in its final stages. In this trial, EMTs give patients an injection of magnesium ions in an attempt to quell the brain's hyperexcitability immediately after a stroke.

Stroke experts agree that the best form of neuroprotection is to restore blood flow to the area cut off by the stroke—and fast. To that end, an epiphany of sorts hit researchers when they realized that blood vessels in the brain look more like a connected matrix of loops than like a tree with branches. Vessel structure is "much like the streets of New York," according to David Kleinfeld of U.C. San Diego. "When there's a truck parked on 34th Street and you can't get through, you go up to 36th Street," Kleinfeld explains. Figuring out how to get blood rerouted through these existing networks in the brain could very well be the key to keeping cells

FAST FACTS

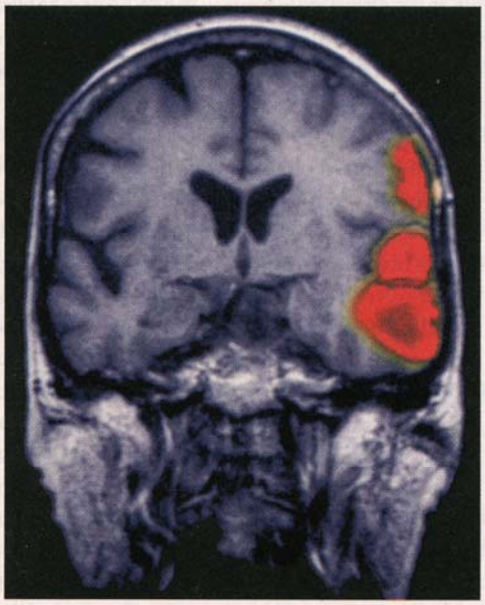
Saved by Caresses

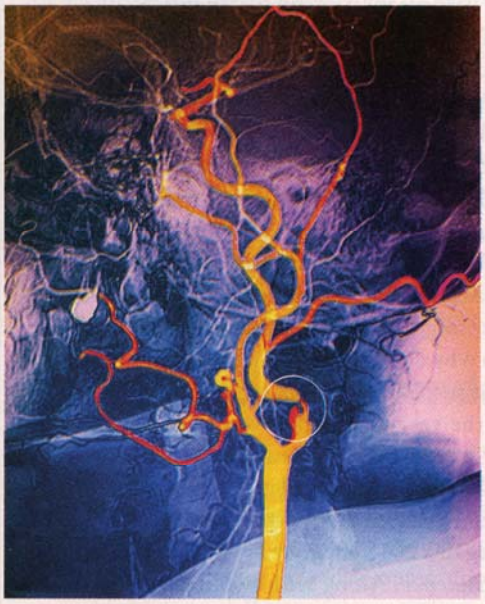
1» **Stroke research has been stymied for many years by the complexity of the brain's response and promising but failed therapies.**

2» **An accidental discovery in lab rats revealed that stimulating their senses, by wiggling a whisker or playing a loud noise, activated the neurons cut off by the stroke and rerouted the blood supply to nourish them.**

3» **Treatments based on this approach are a long way off for people, but experts are hopeful that touching a stroke victim's hands and face could have a similar beneficial effect.**

The Two Types of Stroke





Most strokes are caused by a blood clot (*right image, circled area*). This type of stroke, if caught early, can be treated with a drug that breaks up clots. Before administering the drug, doctors must order a scan to make sure the stroke is not hemorrhagic (*left*). This imaging often uses up the time window in which the drug will work. New research suggests sensory stimulation might help victims of both stroke types.

alive—but until now, researchers had no idea how to harness this network.

Recruiting Nearby Blood Vessels

Serendipitously, neuroscientists at U.C. Irvine discovered that the brain's vasculature might be at the beck and call of the very neurons it serves, providing a built-in defense against stroke. Five years ago Frostig, who studies neuroplasticity, had set out to test whether rats that were allowed to actively explore a natural environment might recover better after a stroke. Enriched environments or experiences have been found to improve brain health and function in many settings, particularly in rehabilitation. To mimic the occurrence of a stroke, Frostig and his team cut the middle cerebral artery (MCA), a major blood supply route, in an anesthetized rat. Immediately after cutting the MCA, they wanted to get a baseline measure of stroke-damaged brain activity, so they used a mechanical device to wiggle one of the rat's whiskers and simultaneously gauged the activity of the corresponding neurons in the cortex. They expected this baseline activity to be utterly destroyed by the stroke, and they hoped it might improve over time as the rat recovered.

Instead, during the stroke and a day later, the neurons looked and acted completely normal. Frostig was shocked; even the most promising therapeutic agents typically provide just marginal defense against stroke in lab animals. Only half-joking, he asked postdoctoral fellow Christopher C. Lay whether he was sure he had cut the artery. But after the result held up in 30 animals, they realized that something important was going on. "The neurons were completely protected," Frostig says. Eventually the researchers concluded that by stimulating that single whisker immediately after stroke, they had prevented any stroke-related brain damage.

Once Frostig and his team were convinced their results were real, they looked for signs of damage, and they looked hard. As they first reported in *PLOS ONE* in 2010, they could find no difference between the brains of rats with a wiggled whisker and control rats that had no interruption to their blood supply. A staining technique revealed no damage; brain imaging showed functional blood flow to the affected area; even direct recordings of the neurons activated by whisker movement showed the area was electrically active and healthy. And the animals behaved normally on waking. But the rats were protected only when they were stimulated within an hour or two of

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the stroke—any later, and they actually suffered worse damage than unstimulated rats.

"The time window is critical," Frostig says. In subsequent research published in *Stroke* in 2011, he confirmed that timing—not duration or pattern—of stimulation is key. Past the three-hour mark, stimulation does more harm than good. "We don't know yet what is the underlying cause of the switch," Frostig says. Although other animal studies have revealed that some molecules are destructive early in an attack but required for remodeling and recovery at later stages, many questions remain.

So why does wiggling a whisker save the brain? Frostig suspected that the sensory experience activates the very cortex that was deprived of blood flow. "The key issue is neuronal activity," he says. This flurry of activity and its attendant demand for oxygen recruited an alternative blood supply, according to a 2011 paper by Frostig in the *Journal of Neuroscience*. Along with two other major arteries, the MCA supplies blood to the cerebral cortex, its trunk splitting into progressively smaller branches. At their tips, the fine branches of these vascular trees interconnect with one another, forming a vast network. Blood does not normally flow through these loops, but Frostig's investigation using advanced brain imaging showed that after the stroke the rats' neuronal activity indeed recruited blood via these alternative routes. When Frostig sealed off the MCA network's collateral branches—in addition to cutting their supply trunk—no amount of stimulation could save the cortex.

Researchers do not yet know how, exactly, neuronal activity evokes the change in blood flow. Current research is investigating nonneuronal cells called astrocytes, which are closely coupled to blood vessels in the brain and seem to be involved in signaling for oxygen and nutrients. In the meantime, Frostig and his colleagues are investigating whether other types of sensory input can protect the brain as well. In work presented in November 2011 at the Society for Neuroscience meeting in Washington, D.C., Frostig showed that auditory stimuli—bursts of white noise—also protected from stroke, though not as completely as whisker stimulation. This result is not too surprising, says Melissa F. Davis, a graduate student in Frostig's lab who worked on the study. Whereas whisker stimulation "tickles" much of the blood-starved cortex, she explains, sound activates only the auditory cortex at the edge of the affected area.

A Much Needed Breakthrough

Moving from rodents to humans is a challenge for any therapy, and experts, including Frostig, are

How to Recognize a Stroke

Despite the best efforts of doctors and health agencies, the number of people getting to the hospital within two hours of a stroke has fallen in the past few years, according to a recent study by the U.S. Centers for Disease Control and Prevention. Study author Mary George, who presented the findings at the annual meeting of the American Stroke Association in February 2012, says that one of the biggest factors that delays stroke treatment is that people are using their own cars to get to the hospital rather than calling an ambulance. If you see these signs in yourself or someone else, call 911 immediately:

- Numbness or weakness of the face, arm or leg, especially on one side of the body
- Confusion or trouble speaking or understanding
- Disrupted vision in one or both eyes
- Dizziness, loss of balance or coordination, or trouble walking
- Severe headache
- The American Stroke Association recently revamped its efforts to get the word out with a mnemonic that spells out "FAST": Face drooping, Arm weakness, Speech difficulty? Time to call 911.

—S.S.

SPENCER ROWELL Getty Images

cautious about predicting a future of sensory-stimulated recovery for people. But hope-starved stroke researchers cannot help but be enthusiastic. "The beauty is that it's cheap and nontoxic," Cramer says. And the treatment remains effective even as Frostig's group has systematically expanded testing to address some of the differences between the response of humans and lab rats. The team has made sure that awake and anesthetized animals are protected because an estimated 70 percent of strokes occur in awake people. In a 2012 paper in the *Journal of the American Heart Association,* Frostig's team showed that elderly rats were protected as well as the juvenile animals commonly used in lab research; in humans, age is the number-one risk factor for stroke. Furthermore, the protection held up in rats that got sensory stimulation by exploring their environment and whose whiskers had been removed—a good thing for whiskerless humans. Most important, by studying ischemic attack in the territory of the brain supplied by the MCA, Frostig is investigating the conditions that account for the vast majority of human strokes.

One big challenge for this treatment to overcome is that humans do not have an exact analogue to the barrel cortex, the area in a rat's brain dedicated to sensing whisker movements. This area is huge in rats; in humans, the closest equivalent would be the cortical real estate dedicated to the fingers and lips. Because the relative size of our sensory cortex is much smaller than that of rats, Frostig predicts sensory stimulation of more than one type might be required. "Sing to them, stroke their hands, their face—while you're calling the ambulance," Frostig says. Engaging someone in whatever stimulation possible might increase the chance of activating—and thereby protecting—more cortex. As for that ambulance ride, which itself is noisy, it alone may not help, because EMTs do not necessarily make a point of actively engaging a patient. Taking sensory stimulation to that next level, such as by caressing the patient's face and hands, might make all the difference.

If even salient stimuli such as touch and sound are not enough to protect a human brain, direct brain stimulation might work, Frostig speculates. Transcranial direct-current stimulation excites neurons by delivering a small amount of electricity through the skull. The apparatus could conceivably fit in an ambulance alongside the defibrillator. Frostig's manipulation, however, "is really physiological," Koroshetz cautions—it is rooted in physical sensation—so attempting to mimic the stimulus with cortical stimulation would take "a little leap of faith," he says. "The key thing is to figure out the mechanism, then figure out ways of activating that mechanism," Koroshetz says. Those ways might range from sensory or electrical stimulation to new kinds of drugs.

Frostig's work shows promise for circumventing some of the other inherent problems in stroke treatment, too. Sensory stimulation is unlikely to be detrimental to someone with a hemorrhagic stroke, eliminating the need for time-consuming brain scans. If the treatment indeed reroutes blood flow, it could aid in the delivery of therapeutic drugs, including tPA—a major challenge in stroke treatment today. And the new finding underscores the importance of timing. People who miss the critical window for treatment, for instance, because they wake up from a night's sleep having had a stroke, might benefit from little or no stimulation at all—no sirens wailing, no medical team barking orders, no constant barrage of questions and tests.

The flurry of neuronal activity and its attendant demand for oxygen recruited an alternative blood supply.

Human trials based on Frostig's work are still far away—first the idea needs to be tested in larger animals such as monkeys or pigs. It could be years before we know if sensory stimulation can do for people even a fraction of the good it does for rats. But as the quest continues for clot busters and neuroprotectants, for new techniques and technology, stroke experts across the board agree that fresh ideas are welcome. So go ahead, sing to your aunt and caress her hands and face; if nothing else, she will feel comforted at a scary time. And you might just save her brain. M

(Further Reading)

- **Update of the Stroke Therapy Academic Industry Roundtable Preclinical Recommendations.** Marc Fisher et al. in *Stroke,* Vol. 40, No. 6, pages 2244–2250; June 2009.
- **Understanding and Augmenting Collateral Blood Flow during Ischemic Stroke.** Gomathi Ramakrishnan, Glenn A. Armitage and Ian R. Winship in *Acute Ischemic Stroke.* Edited by Julio César García Rodríguez. InTech, 2012.
- **A Rat's Whiskers Point the Way toward a Novel Stimulus-Dependent, Protective Stroke Therapy.** Ron D. Frostig, Christopher C. Lay and Melissa F. Davis in *Neuroscientist.* Published online October 9, 2012.
- For the warning signs and symptoms of stroke, see the American Stroke Association Web site: **www.strokeassociation.org/STROKEORG/WarningSigns/Stroke-Warning-Signs_UCM_308528_SubHomePage.jsp**