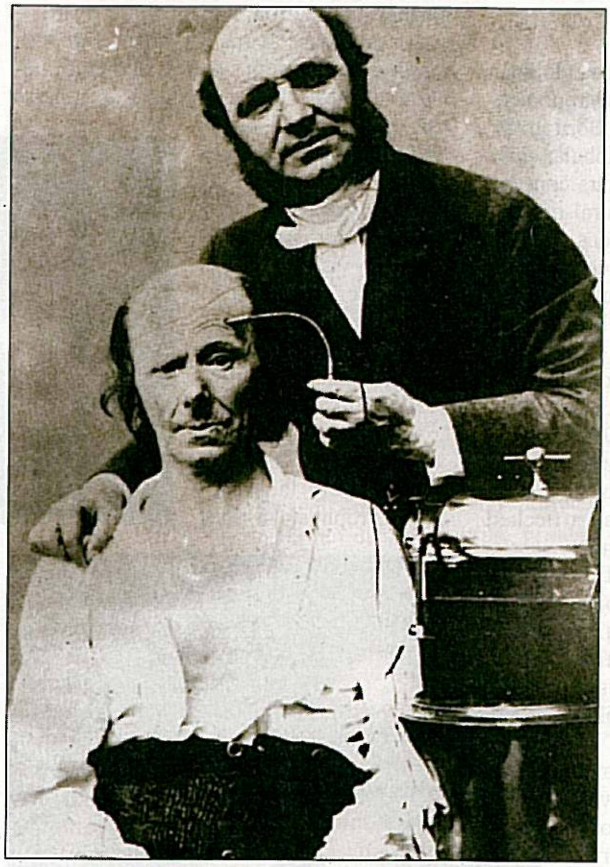
Stimulating the brain with magnetic fields is not only a useful research tool but can apparently a cognition and ease depression. But exactly how it works is a bit of a mystery

Boosting Brain Activity Fron The Outside In

Recent claims about the powers of a brain stimulation technique might sound like testimonials for healing crystals. Fights depression! Speeds reaction times! Enhances reasoning abilities! But despite the link to magnets, which have long inspired goofball theories, so-called repetitive transcranial magnetic stimulation (rTMS) is being described not in the back of astrology magazines but in articles in journals such as *The Lancet*, *Neurology*, and *Science*.

A slew of recent clinical trials in the United States and abroad has indicated that rTMS can lift depression in some patients who are resistant to other types of therapy. Canada's Health Ministry is convinced; in March it approved the technique for treating people with major depression. The U.S. Food and Drug Administration is considering a similar move; for now, the treatment is only available in the United States in clinical trials. So far, no one is claiming that rTMS will help you lose weight fast, but a few studies have suggested that it can also ease symptoms of schizophrenia, obsessive-compulsive disorder, and Parkinson's disease, although these findings aren't as well established as those on depression. And one recent study even shows that well-aimed rTMS can speed one's ability to solve puzzles.

Since it was introduced in 1985, rTMS has been used mostly as a research tool to figure out what different parts of the brain are doing and how they interact. Researchers still don't completely understand how rTMS modifies brain activity, but its ability to do so is well established. "This is a great neuroscience tool for testing the relationship between brain and behavior," says neurologist and psychiatrist Mark George of the University of South Carolina, Charleston. George helped conduct the first study showing rTMS can relieve depression, and that has opened the door to using this therapy as a potential treatment for other psychiatric disorders. "We're just beginning to understand how to use it," says George.



Beta version. Direct electrical stimulation alters brain activity (and raises eyebrows, as in this 1861 demonstration by Guillaume Armand Duchenne), but rTMS is more comfortable.

Charging neural batteries

The rTMS technique is a fairly noninvasive way to stimulate brain tissue, George says. It works because neurons are in some sense electric creatures: They fire in response to changes in the concentration of charged particles inside and outside the cell. People have known for years that direct electrical stimulation can cause neurons to fire (see photo on this page). The trouble is that it hurts; direct electrical stimulation zaps pain-sensitive neurons in the scalp and thus tends to scare away research subjects.

In contrast, rTMS gooses neurons indirectly and painlessly. Repeated pulses of electric current are sent through a metal wire, which is usually round or figure-eight–shaped. This electric current generates a perpendicular magnetic field. (Remember the right-hand rule from physics class.) The magnetic field, in turn, generates another electric curren material—in t rTMS, the cu through brain ti low where the c on the scalp (see

If the induc current is stron can overwhelm munication in where it is fo cause a "tempo Many single-b posed to repet studies marshal to test whether brain region con given task; for in ping the visual been shown to in visual imaging April 1999, p. 1

Under the rig stances, howeve applications ha lasting effect th burst of stimula this effect, resea calibrate the inte magnetic stim placing the coil son's motor co move the coil aro just the intensity find what Georg sweet spot"—a region of motor when stimulated, causes the twitch. The researchers then use inducing intensity to deliver repe to other parts of the scalp. In g frequency stimulation of about 1 per second tends to depress brain terward; higher frequency stin about 25 pulses per second in citability. Both effects last abo long as the initial stimulation, t few minutes to about an hour.

Why different stimulation f trigger different responses in n rons is "absolutely unclear," Wassermann, chief of the brain unit at the National Institute of N

ient, including a seismometer and a elemetered Global Positioning System (GPS) receiver, into the sparsely instrumented region as the winter's snow recedes. GPS should tell them within a few months whether a rapid uplift is continuing. If it is, they'll want to be ready should any of the Three Sisters or their relations awaken.

–RICHARD A. KERR

ASTROPHYSICS

Star-Cluster Census Shows Surprises

The ancient balls of stars known as globular clusters are a favorite place for astronomers to test ideas of stellar evolution. Born in the dark ages before our own sun, globular clusters contain many old, heavy stars concentrated at their cores. Those central regions are so star-rich that near-collisions abound, and heavy stars frequently grab companions to form binary star systems that can reveal crucial information about the history and destiny of the cluster.

Astrophysicists trying to understand the intricacies of the globular heart have a new weapon: the Chandra X-ray Observatory, uniquely equipped to spot the x-rays emitted by many of the core's inhabitants. Past x-ray studies revealed little more than a flecked smudge compared with new results reported online by *Science* this week (www.sciencexpress.org) from a team at the Harvard-Smithsonian Center for Astrophysics (CfA), which has used Chandra to produce a sharp, color-coded x-ray map of a core.

"It is a big step in x-ray astronomy to have actually resolved what is happening in the middle of a globular cluster," says Andrew Fabian of the Institute of Astronomy in Cambridge, United Kingdom. Although radio astronomers and the Hubble Space Telescope have uncovered many secrets of cluster cores, resolving individual x-ray sources and their energies is something new, Fabian says.

The cluster, known as 47 Tucanae, is one of about 150 globular clusters sprinkled through our galaxy. The million or so stars in each are made of the material from which our galaxy grew. Because stars in a cluster all formed at about the same time and are all at about the same distance from Earth, globular clusters are a perfect space lab for astrophysicists to study how stars mature as they age. Heavier stars, more than eight times the mass of our own sun, have collapsed via a cosmic firework display—a supernova—into neutron stars. Many lighter cluster residents, their fuel likewise exhausted, have crumpled under their own weight to form white dwarfs.

But stars in clusters don't merely grow old; they also learn to tango. "Clusters are so incredibly dense in their cores that stars are, in the everyday vernacular, nearly smacking into each other," says Jonathan Grindlay of CfA, who led the new study. As a result, he says, "globular clusters are binary factories," creating new double stars or swapping partners in existing binaries even today.

In a typical binary pair, a small, dense partner—a neutron star or white dwarf—sucks material from its larger but less massive companion. As this accreted material crashes into the smaller star, it heats up, emitting x-rays. Different types of x-ray emitters have distinct x-ray signatures, but only Chandra has both the crisp vision and energy discrimination to pick out and label individual sources. As a result, it can provide information about neutron stars and accreting white dwarfs that has been "sorely lacking," says astrophysicist Sterl Phinney of the California Institute of Technology in Pasadena.

Round numbers. An inventory of x-ray sources in globular cluster 47 Tucanae (*top*) casts doubt on a suspected link between x-ray binaries (*bottom*) and millisecond pulsars.

Grindlay and his collaborators, Craig Heinke, Peter Edmonds, and Stephen Murray, set out to use Chandra to survey the relative numbers of x-ray sources in the well-studied globular cluster 47 Tucanae—"everyone's favorite globular cluster," according to Phinney. In the central core of the cluster alone, they picked out 108 distinct x-ray sources. By setting out the whole sample on an intensity-color diagram—an x-ray analog of the brightness-color diagr optical-light astronomers use to stars—they claim to be able to estir relative numbers of four different typ ray sources in the cluster's core. Ab are millisecond pulsars (MSPs), ir the x-ray pulse, with a period of jus milliseconds, comes from a neutron spins madly after gobbling mass fron dinary-star companion. About 30% creting white dwarfs, also dubbe clysmic variables, which are binarie prising a white dwarf and an ordina Some 15% are pairs of ordinary stars just two or three are what's termed qu low-mass x-ray binary (LMXB) star tron star–ordinary star combos that slowly and bright at intervals.

The sheer num neutron stars "is re bit of a surprise," lay says. Those ple neutron stars derive heavy stars, but physicists expect clusters should cc many more lightw stars than heavy one only that, but ne stars, freshly forge supernova inferno, at speeds of several dred kilometers per second—so fas they should just "zip out" of a cl Grindlay says. But Fabian thinks the lem may be an illusion. Relat lightweight white dwarfs may well number neutron stars in the cluste says. But because they emit few x and don't form pulsars, the x-ray c may simply have undercounted them.

Another mystery is why MSPs so outnumber the handful of LMXBs. pendent evidence suggests that MSP the children of quiescent LMXBs, many astrophysicists believe such trar mations can run backward as well. the population of MSPs and LM should show a delicate balance, Grir explains—a balance that Chandra doe see. The new results instead support native routes for the creation of M Grindlay says. Perhaps the pulsars r from the direct collapse of accreting dwarfs. Or perhaps—as Fred Rasio Saul Rappaport of the Massachusetts I tute of Technology have suggeste LMXBs made a one-way transforma into MSPs long, long ago. In any case trophysicists agree that puzzles, at least one thing 47 Tucanae is likely to keep ducing in abundance.

–ANDREW WAT

Andrew Watson writes from Norwich, U.K.

Disorders and Stroke (NINDS) in Bethesda, Maryland. But researchers and clinicians can take advantage of the lingering buzz.

Detour for depression circuits

Although rTMS can spark an electric current in the brain, it's nowhere near as powerful as a better known treatment for depression: electroconvulsive therapy (ECT). Shock therapy fell out of favor because of its often severe side effects, but it can cure stubborn cases of depression. It works by causing a seizure. "After a seizure, all brain function is radically changed," Wassermann explains, and somehow that kicks the brain out of its depressive rut. In testing rTMS, says Wassermann, "our idea was to [change brain function] in a focal way, incrementally."

Wassermann and others have found that, compared to sham stimulation, tickling the left prefrontal cortex with rTMS relieves depression in some people who haven't responded to drugs or other treatments. The target, near the top of the forehead, isn't arbitrary; in functional imaging studies "the lateral prefrontal cortex comes up again and again as part of the mood circuit underlying depression," says psychiatrist Holly Lisanby of Columbia University in New York City, who has conducted rTMS studies on Parkinson's disease and other disorders. The left prefrontal cortex is less active in people with depression, and neuroimaging studies show that rTMS gives it a boost.

In a standard clinical trial, a depressed patient receives rTMS over the left prefrontal cortex for 20 to 30 minutes once a day for 2 to 4 weeks. Most studies to date have used this model, even though it's "based on something Mark George and I pulled out of a hat," says Wassermann. "It's implausible that we stumbled on the most effective combination" of stimulation frequency, intensity, timing, and location, cautions George. But as Wassermann points out, there's not a lot of funding directed at perfecting clinical rTMS techniques. Unlike drug companies, Wassermann says, "the equipment manufacturers' [pockets] are not deep." Most studies have been funded by private institutions or the National Institutes of Health.

In this and other applications, the stimulation is probably not easing depression simply by juicing up the neurons directly below the coil. As neurologist Alvaro Pascual-Leone of Harvard Medical School in Boston points out, rTMS is "not a light form of ECT but a way of modulating a circuit." In depression, the left prefrontal cortex is connected to a network of maladjusted brain areas. "I think a lot of the therapeutic effect we're seeing is not related to stimulation of the area we're targeting," speculates Pascual-Leone. "But through there, we're getting access to the limbic system," which decades of research have implicated in the regulation of emotions.

If rTMS can indeed jump-start—or calm—entire neural circuits, many disorders might yield to targeted stimulation, Lisanby says. Researchers can determine through functional neuroimaging where a circuit rises to the surface of the brain and focus treatment there. In schizophrenia, for example, a study reported last year in *The Lancet* showed that low-frequency rTMS to the temporoparietal cortex (above the ear) reduced auditory hallucinations. Such studies are in their early stages, but "the field is aggressively pursuing" the strategy, Lisanby says.

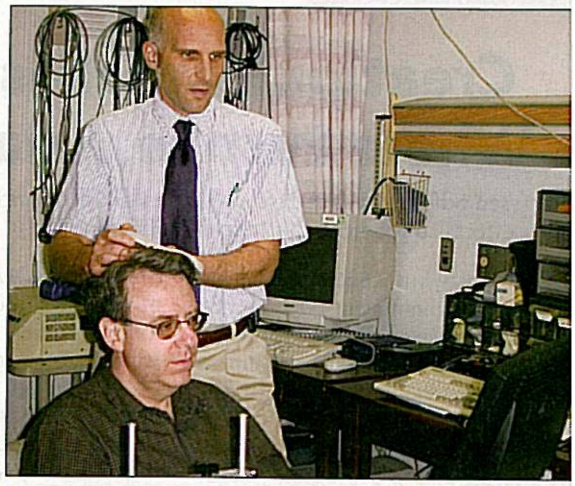
Faster thinking with rTMS?

Neurological and psychiatric disorders aren't the only brain processes that affect wide-ranging neural circuits. Speaking, seeing, and problem solving, along with most mental tasks, activate some tissue deep in the brain and other bits at the surface. Once researchers showed that rTMS could alter mood, the logical next step was to see whether "we could do the same thing for any process stored in the brain," says cognitive neuroscientist Jordan Grafman of NINDS.

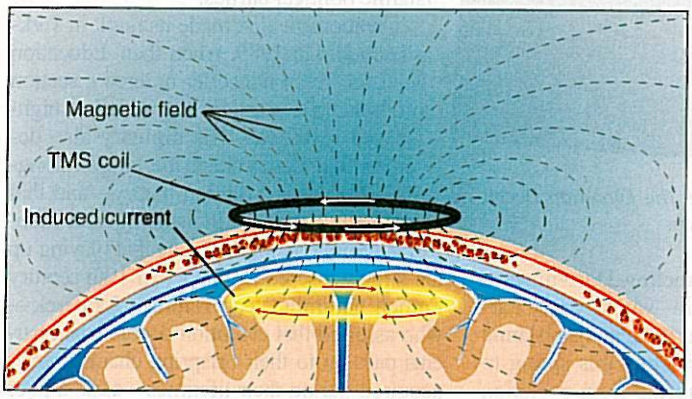
In the past few years, for instance, researchers have found that delivering rTMS to speech of the brain can take the words right someone's mouth; specifically, people pictures faster after the treatment. And applied to motor areas facilitates ligh fast movements. Grafman's group has its attention to more abstract brain pro as they reported in *Neurology* this year asked people to solve analogy puzz which they had to figure out the relati among a group of colored geometric s and then pick out the analogous patte other sets of shapes. Positron emissio mography (PET) studies show that the frontal cortex, among other areas, ligh when people perform such a task. S stimulation or rTMS to other areas o brain shortly before presenting the pu didn't help people solve them, but rTM the prefrontal cortex speeded subject sights. So far, no studies have answere how rTMS might facilitate thinking, man says. He suggests that rTMS m raise the baseline level of neural activity region just enough so that neurons have to work as hard to retrieve a memo a problem-solving strategy.

One of the barriers to figuring out neurons respond to rTMS is the lack of mal models, says George. Whereas searchers can easily dilute a drug t strength, they can't yet make an effe miniature rTMS coil. At smaller sizes coil can't create a magnetic field st enough to induce a current in the r monkey brain that's as strong as the cu induced by a full-size coil. "It's a real m rials science problem," says George.

In addition to neurobiology, Wasserm notes, plenty of other effects of rTMS a well understood. The procedure appea be safe at the mild intensities used in lab, and rTMS passed all its safety stu shortly after it was introduced. But it



Modern version. Eric Wassermann demonstrates rTMS tech on Jordan Grafman.



Indirect stimulation. With rTMS, researchers can induce a shadow current in the brain a few centimeters below the coil.

CREDITS: (TOP TO BOTTOM) ERIC WASSERMANN; ILLUSTRATION: C. SLAYDEN

technique is powerful enough to ease depression and have other possibly long-lasting clinical effects, researchers should be more diligent about including safety studies whenever they use it, Wassermann cautions: "Anything that works well can cause significant side effects."

But if researchers can live with a certain amount of neurobiological ambiguity and are willing to test the safety of the technique as they go, rTMS is a fairly affordable and therefore democratic tool—especially for neuroscience hardware. A complete setup runs $30,000 to $40,000, compared to $1.5 million and up for functional magnetic resonance imaging. It's still a young field with plenty of unanswered questions and wide-open neural territory to explore. But if the words "brain stimulation" a sive" bring improper thoughts warned: Those neurons that someone takes euphoria-induc eats ice cream are buried deep beyond the reach of rTMS. "V jokes George, "but there's no pleasure-center stimulation witl technology." –LAU

SCIENCE EDUCATION

Creationism Takes Root Where Europe, Asia Meet

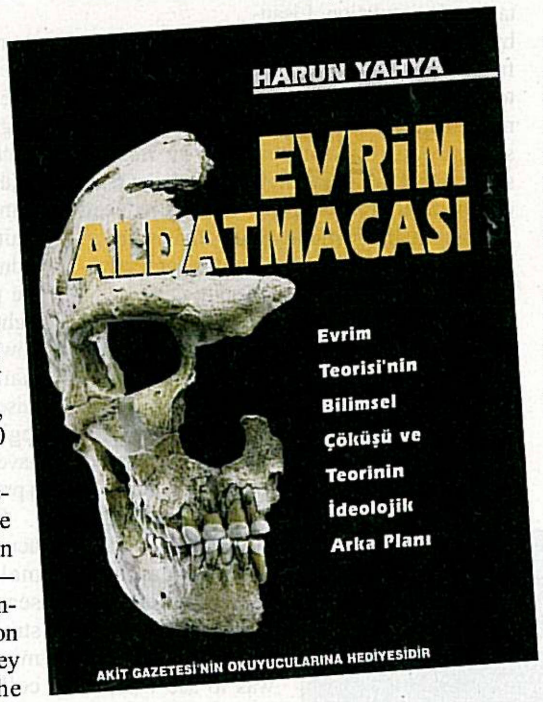
Harassed but hard-headed, some gutsy Turkish scientists are stepping up their efforts to promote the teaching of evolution

ANKARA—When Aykut Kence opened his mail one November morning in 1998, he was startled to find his face on the front page of a newsletter next to the stern visage of Chinese Communist leader Mao Zedong. After reading the article, which denounced the Turkish biologist as a leftist supporter of Darwinism, his wife Meral, also a biologist, joked: "Aykut, I've known you for 30 years, and you never told me that you were a Maoist." Kence chuckled: He subscribes to Darwin's theories, but hardly to Mao's.

It was no joke, however, when Kence and five other Turkish scientists became targets in a campaign to promote creationism and discredit Darwinism spearheaded by the Istanbul-based Bilim Arastirma Vakfi (BAV), which translates as the innocuous-sounding "Science Research Foundation." After being "outed" as Darwinists, Kence, a professor at Middle East Technical University here, and his colleagues began receiving anonymous threats, and they responded by suing BAV for defamation. They won: In 1999, Ankara Civil Court awarded them $4000 each in damages.

Although heartened by that legal victory, many scientists here fear they are losing ground to Turkish creationists in the wider court of public opinion—especially in provinces where Islamic fundamentalism is strongest. The defamation case and an unrelated investigation of key BAV members have not stopped the group's vigorous crusade—experts call it the best organized and financed in the Islamic world—to discredit the teaching of evolution. The group's few hundred active members, mostly volunteers, have developed a Web site and enlisted speakers from U.S.-based creationist organizations to appear at antievolution events across Turkey. They've also swamped the country with sophisticated books such as *The Evolution Deceit* and *The Dark Face of Darwinism* (both published under the pseudonym Harun Yahya), which some scientists complain have become more influential than textbooks in certain parts of the country.

Nor is BAV the only face of Turkish creationism. A medical professor and member of parliament, Ali Gören, recently launched a legislative drive to drop the teaching of Darwin's evolution theory in secondary schools. Labeling Darwinism a "scientific fraud," Gören—whose Virtue Party, the third-largest in parliament, has Islamic ties—urged fellow legislators this spring to protect high-school students from evolution theory's "adverse affects," which he claims encourages "atheism and separatism."



Creating a stir. Books like *The Evolution Deceit* appear to be gaining readership.

Although many scientists de initiative as doomed to fail in the liament, they worry that Turkey economic woes could give right- alist and Islamic fundamentali both of which tend to support cre boost in the next elections. "The have access to lots of money, and situation is in turmoil," says con ologist C. Can Bilgin of Middle cal University. "We can't take granted." Echoing his concern geneticist Isik Bökesoy of Ankar —who has been lambasted in fu publications for her defense o theory—and Kence, who receive mous e-mail last month sugges "enjoy [his] final days."

Such venom has only serve the researchers' resolve to protec status of evolutionary theory schools. They are organizing pul tions and have rallied the Turkis of Sciences to their cause. "I wo silence me," Kence says. "If kn people keep quiet, it only helps spread nonsense."

An evolving mindset

The debate over evolution and is a microcosm of a wider battle- gle between secularism and Isla raged ever since Kemal Atatürk secular Turkish Republic in 19 the emphasis on creationism i has waxed and waned with the Islamic political parties.

Creationism first made its m ish schools in 1985, when ther Minister Vehbi Dincerier order on "scientific creationism" ad school textbooks. His minist creed that Lamarckism be ta side Darwin's evolution theor the texts include criticisms o ries. Some biologists argue tha the largely discredited theory of French naturalist Jean-Baptiste who asserted that evolution occur ents pass on to their offspring ch acquired during their lifetimes— light on evolutionary science in ge

Over the next decade, Kence