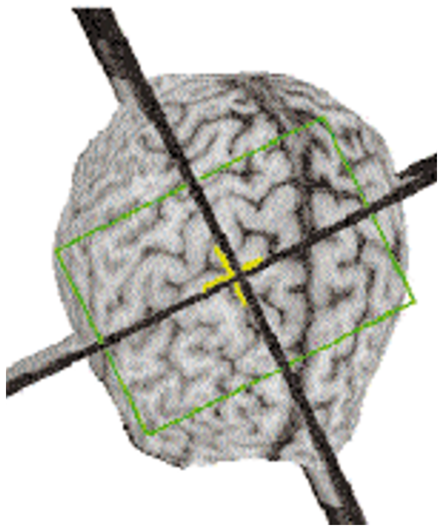
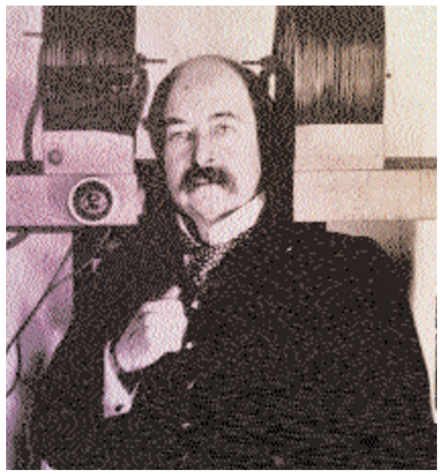
Magnetic mind games

Using short magnetic pulses, neuroscientists are reaching into the human skull and temporarily altering volunteers' brain activity. Marina Chicurel takes an induction course.



T. PAUS

A century-old dream to influence brain activity with magnets (below), is now a reality using powerful coils (left) and imaging (above).



Studying the human brain can be a frustrating business. Although sophisticated imaging techniques can offer snapshots of activity, direct intervention in the brains of humans is ethically off-limits. It is no wonder that neuroscientists sometimes feel like visitors to a museum — they can look but not touch.

But things are beginning to change. Neuroscientists studying human cognitive processes are now making tentative use of a technique that can temporarily alter their subjects' brain activity. Insights into everything from language to conscious awareness are emerging, as well as hints that the technique could help treat some mental disorders. "There are just some extraordinary things coming out," says Michael Gazzaniga of Dartmouth College in Hanover, New Hampshire, editor-in-chief of the *Journal of Cognitive Neuroscience*.

Before technology for imaging the human brain emerged, neuroscientists interested in cognitive functions were mostly limited to studying patients with brain lesions — damage to specific areas of the brain. By looking for links between the patients' symptoms and the site of the damage, researchers pinpointed brain areas involved in abilities such as language, learning and memory.

Anthony Barker used magnets to control movement.

During the 1980s and 1990s, techniques such as functional magnetic resonance imaging (fMRI), which tracks brain activity by monitoring blood flow, allowed neuroscientists to see which areas of the brain were active during specific tasks. A flood of information about the functions of different brain areas followed.

But such techniques have their limits. "There's no causality in it," complains Tomáš Paus, a neuroscientist at McGill University in Montreal, Canada. "You can never say whether one brain region is influencing another, or whether they are active together because some third region is driving both." Rather than just passively observing the brain, researchers would like to manipulate it directly.

Polar explorers

Scientists had long suspected that magnetic fields might allow them to do this. Brain cells send electrical signals along the fibres that make up their communication networks. Because changing magnetic fields can induce current in electrical conductors, researchers thought that a magnetic pulse might stimulate currents in brain cells, and so alter brain activity. Early attempts to do this date back to the nineteenth century, but it wasn't until 1985 that devices capable of producing the short, intense pulses needed to stimulate the brain were developed.

The breakthrough was made by Anthony Barker, a medical physicist at the Royal Hallamshire Hospital in Sheffield, UK. Barker used a 2-tesla magnetic pulse about 1 millisecond long to stimulate the brain area that controls finger movement. Unintentionally, the volunteer's fingers twitched[1]. "It caused a good deal of excitement," recalls Barker.

The technique, known as transcranial magnetic stimulation (TMS), remains similar today. There are hints that the intensity and frequency of the induced current can influence whether the stimulation increases or damps down brain activity[2,3]. But TMS cannot, at present, exert precise control over the brain. It puts in "random neural noise", explains Vincent Walsh of the University of Oxford, UK, who has used TMS to study cognitive functions such as visual awareness.

Single pulses affect brain function for just a few milliseconds. But a train of pulses, typically delivered at rates of about one per second, can disrupt brain activity for tens of minutes. This technique, known as repetitive TMS (rTMS), creates 'virtual' lesions for neuroscientists to experiment on.

Last year, for example, Alfonso Caramazza and colleagues at Harvard University used rTMS to reveal how our brains seem to use different regions to handle verbs and nouns. Caramazza was studying the left prefrontal cortex, an area thought to be involved in the ability to conjugate verbs. Previous lesion studies had proved inconclusive, partly because the damage often extended beyond the area of interest. And, as with other studies of brain damage, it was impossible to gauge the extent to which other parts of the patients' brains had compensated for the damage.

"With brain-damaged patients we're at the mercy of nature," says Caramazza. "That's why I became a TMS convert." When Caramazza applied rTMS to the left prefrontal cortex he found that his subjects had difficulty conju-

A. PASCUAL-LEONE/H. THEORET

Moving story: Alvaro Pascual-Leone believes TMS holds the key to unravelling many mental processes.

gating verbs[4]. But their ability to give singular and plural forms of nouns was unchanged.

In the past few years, rTMS has been used to investigate a number of thought processes. In 1999, for instance, Stephen Kosslyn, together with Alvaro Pascual-Leone of the Beth Israel Deaconess Medical Center in Boston, led a team that examined the long-standing hypothesis that when we visualize a scene in our mind's eye, we generate mental 'images' that recreate the relative distances between objects in the real scene. Support for the idea came from studies of a brain region known as V1. When we view a real scene, the pattern of active neurons in V1 forms a kind of 'map' of the scene, and some studies indicated that the same area was active during visualizations[5].

But other experiments had failed to confirm this. It was also unclear whether the activation was intimately involved in visualization, or was simply a by-product of activity in other brain regions. Kosslyn asked volunteers to memorize a pattern of stripes, and then close their eyes and answer questions about the pattern. Applying TMS to V1 increased the time the subjects took to answer[6], supporting the idea that our mind's eye conjures up lifelike images.

Other researchers have recently used TMS to study visual attention[7], the storage and retrieval of memories[8], and how we recognize our own face[9] or the angry expressions of others[10]. As interest in the technique grows, researchers are exploring ways of using it in conjunction with imaging technology.

Image conscious

Some groups are combining TMS with fMRI. A reflective tag, which can be tracked by an optical sensor, is attached to the coil, allowing the coil's position to be displayed on the MRI scan. This and similar methods should allow the neural connections within the brain to be mapped out. Paus, for example, is interested in probing changes associated with disease, and plans to examine connectivity in the frontal cortex of schizophrenic patients, which some researchers believe may be abnormal. Other experiments, which are in their early stages, have been designed to investigate how tasks such as learning change neural connections.

TMS can also be used to probe the function and timing of the signals that travel along neural pathways. Last year, Walsh and Pascual-Leone examined connections between V1 and another area in the visual cortex known as V5. Visual information from our eyes arrives at V1 and is relayed to V5, which plays a specialized role in the perception of motion. V5 also sends signals back to V1, and some researchers believe that this connection makes us aware of the motion detected in V5.

Earlier work had shown that magnetic stimulation of V5 caused subjects to see moving spots of light. So Pascual-Leone and Walsh stimulated V5 and then used a less intense pulse to disrupt activity in V1. Stimulating both areas simultaneously had no effect on what subjects reported seeing. But the appearance of the moving spots was greatly impaired if the V1 pulse was delivered between 5 and 45 milliseconds after the V5 stimulation[11]. The results show that the link from V5 back to V1 plays a role in motion awareness, as well as demonstrating that this link operates very quickly.

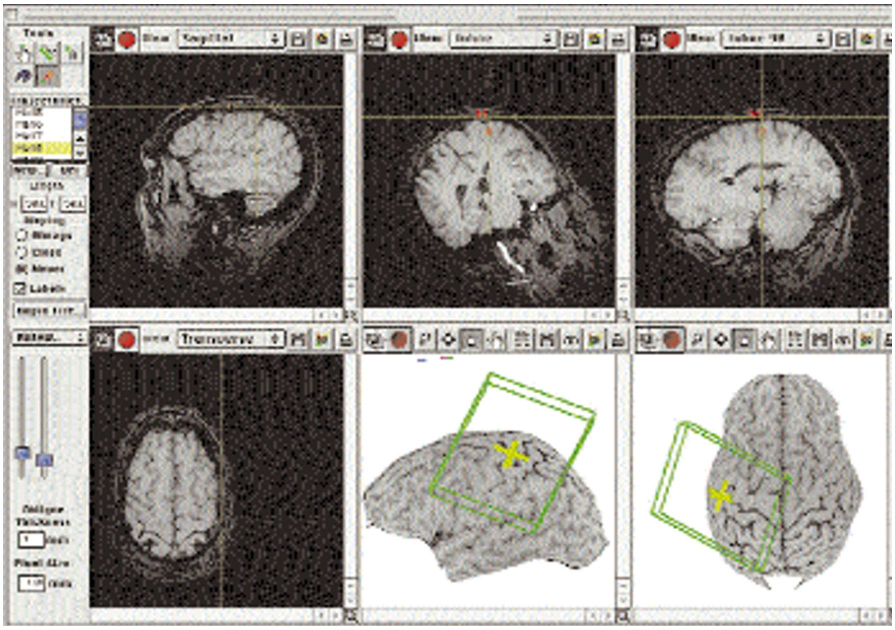
Slow headway

Walsh says that many more timing issues could be probed using similar studies. "It's amazing how many easy experiments haven't yet been exploited," he says. But TMS is taking a long time to be adopted by cognitive scientists. One factor may be the relatively poor communication between cognitive neuroscientists and those studying movement — the first group to embrace the technique. Some researchers also worry about the spatial resolution of TMS. The technique is thought to stimulate about one cubic centimetre of brain, but factors such as coil position and pulse intensity influence the affected volume in a way that is not clearly understood.

But some may have been deterred by fears that TMS could be harmful. "A concern is how virtual is the virtual lesion, especially in subjects who may have some unidentified vulnerabilities, such as an undiagnosed tendency to have seizures," says Douglas Rothman, a medical-imaging expert at Yale University in New Haven, Connecticut.

But TMS does have a good safety record. Current guidelines for the length and intensity of the stimuli were drafted in 1998 following a consensus reached at an international workshop two years earlier[12]. Some subjects have suffered single episodes of rTMS-induced seizures. But, according to Pascual-Leone, only seven such cases have been reported, none of which occurred when the published guidelines were followed.

Pascual-Leone also notes that most researchers give their subjects cognitive tests to make sure that they are back to normal before they leave the lab. But Jordan Grafman



ROGUE RESEARCH

Precise picture: imaging techniques allow the magnetic stimulus to be applied in a specific position.

of the National Institute of Neurological Disorders and Stroke in Bethesda, Maryland, thinks that these evaluations should be standardized to ensure that they pick up subtle effects. "You might want to have people stay longer, you might want to have additional testing," he says. "There have been very few studies considering this."

Despite these questions, most agree that isolated sessions of rTMS, such as those experienced by volunteers in cognitive studies, do not induce permanent changes. But repeated bouts of rTMS can have long-lived effects, and some hope to harness them to treat mental disorders. In 1995, for example, after noticing that depressed patients had low levels of activity in their left prefrontal cortices, Mark George, a psychiatrist at the Medical University of South Carolina in Charleston, tried boosting activity in that region using rTMS[13]. George says that his patients improved, but similar studies conducted since have proved to be less clear-cut.

A team led by Tal Burt, a psychiatrist at Columbia University in New York, has recently collated the results of 25 such studies[14]. The group concludes that rTMS has a modest antidepressant effect, of uncertain clinical value, but which could improve as researchers refine their methods. Factors such as coil placement, stimulation frequency and the influence of patient variability now need to be investigated. George is planning large-scale trials. "The questions now are: how big is that effect, can it be made to last, is it clinically useful, what are the use parameters that maximize the effect?" he says.

Vincent Walsh believes that there are many easy experiments involving TMS waiting to be done.

Virtual surgery

Other disorders are also being tackled with rTMS. Last year, Massimiliano Oliveri, a neuroscientist at the University of Palermo in Italy, working with colleagues at the University of Turin, showed how the technique can be used to treat hemispatial neglect, a condition in which patients have difficulty paying attention to objects on one side of their visual field.

The condition is often caused by damage to parts of the brain called the parietal cortex. Under normal circumstances, the left and right sides of this area inhibit each other. But when one side is damaged, the other becomes hyperactive. Although, to a degree, the brain may compensate for this, Oliveri reasoned that he might be able to balance the activity by creating a virtual lesion in the undamaged side. Initial results were promising, with the patients showing improved awareness during stimulation[15], and Oliveri is now using stimuli designed to produce longer-lived changes —1 Hz for 10 minutes every day for five days. The eight patients he has treated, and followed for a month so far, have improved 40% faster than non-treated controls, he says.

TMS may also be able to go one step further, and enhance normal peoples' thought processes. Last year, Grafman applied rTMS to normal volunteers while they solved a reasoning puzzle[16]. "We decided to see if we could actually make people faster," he says. By applying rTMS to the prefrontal cortex, an area that is active when people solve certain types of visual puzzle, Grafman reduced the time taken by subjects to solve a problem involving geometric shapes.

But it is unclear why such experiments work. Walsh says that noise can boost performance when it is used to block an inhibiting area, such as in Oliveri's studies of neglect, but it is difficult to see how it could enhance a circuit's precisely tuned pattern of activity. Grafman acknowledges this apparent paradox, but points out that noise can, in some systems, aid a change from one state to another — a phenomenon known as stochastic resonance.

Some scientists are uneasy about this area of research. Pascual-Leone believes it might be possible to use TMS to enhance a wealth of mental skills. "But those experiments shouldn't be done without a very serious debate," he says. "And who is to decide what behaviour should be modified, and by whom, and for what purpose?"

Others do not see an ethical dilemma in such experiments. George has been funded by the US Department of Defense to study whether TMS can help to improve memory. He argues that such methods are no different from accepted means of boosting performance. "We do things all the time to try to enhance our performance," says George. "We exercise, we practice. The idea of using a physical stimulation to do that doesn't seem to me to broach any new ground."

Whether or not such controversial projects succeed, TMS enthusiasts see a bright future for the technique. After more than a decade of relative obscurity, they say TMS is beginning to take its place in the toolboxes of cognitive neuroscientists. "People have started realizing how many unique opportunities magnetic stimulation offers," says Pascual-Leone. "I think they've started to get it." ■

Marina Chicurel is a writer in Santa Cruz, California.

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