Getting a Grasp on Working Memory

Recent studies are beginning to reveal how various brain areas work together, at least partly under the supervision of the frontal cortex, to produce working memory

Without it, you couldn't understand this sentence, add up a restaurant tab in your head, or even find your way home. What you would lack in this fortunately improbable scenario is working memory, an erasable mental blackboard that allows you to hold briefly in your mind and manipulate the information- whether it be words, menu prices, or a map of your surrounding -essential for comprehension, reasoning, and planning.

Working memory operates over mere seconds, but it "is a central element in the organization of behavior, language, and thinking," says Joaquin Fuster of the University of California, Los Angeles (UCLA), School of Medicine, who performed landmark studies on the cellular basis of working memory. Indeed, working memory capacity may even be what determines how intelligent a person is (see sidebar). And now, neuroscientists are beginning to identify the neural machinery underlying this critical ability in humans and animals. 'There's a boom of excitement in this area," says Jonathan Cohen, a neuroscientist at the University of Pittsburgh and Carnegie Mellon University.

The work pouring out in this boom supports a hypothesis, now more than 2 decades old, that working memory requires cooperation among scattered areas of the brain, with the precise regions depending on whether the task entails remembering objects, locations, or words. But recent findings also point to the prefrontal cortex, a part of the brain already linked to higher functions such as memory and learning, as the true orchestrator of working memory. This region not only holds data in working memory but may also coordinate the activities of the sensory regions in the service of higher reasoning. "It's like the CEO of a company who keeps track of who does what and makes sure everything gets done," says psychologist Marcel Just of Carnegie Mellon University.

Piecing together the cogs of this working-memory machine may not only help us under- stand how we think, but may also help researchers identify targets for drugs that could be used to treat the working-memory deficits common to normal aging and mental disorders such as Parkinson's and schizophrenia. "We might help folks with Parkinson's disease by giving them [the brain chemical dopamine in a way that improves frontal functioning,"predicts cognitive neurologist Murray Gross man of the Universiry of Pennsylvania Medical School. "A similar strategy could be used for the normal, healthy elderly."

Working-memory pills for the elderly are still a dream for the future. But 23 years ago, when cognitive psychologist Alan Baddeley introduced the concept of working memory as a framework for understanding what was then called short-term memory, pinpointing the brain regions involved also seemed futuristic. Baddeley, then at the Medical Research Council Applied Psychology Unit in Cambridge, U.K., "decided to step back and ask: What's the [short-term) system for?" he recalls, Based on hints from behavioral psychology experiments, he and co-worker Graham Hitch proposed that short-term memory is part of a "working-memory" system that briefly stores and processes information needed for planning and reasoning.

And to explain emerging psychological studies of normal and brain-damaged patients, they also proposed that working memory isn't a single storage depot but has multiple components: two short-term memory buffers, one for verbal and the other for visual memories, plus a "central executive, the manager that manipulates information stored in the buffers for problem-solving, planning, and organizing activities.

Although Baddeley, who is now at the University of Bristol, wasn't at all certain where the brain kept the parts of this network, electrophysiological studies from mon keys had already begun to supply hints. In 1971, Fuster, working with Garrett Alex ander at UCLA, obtained results suggesting that the prefrontal cortex, a region of the brain's surface in the forehead, stores short-term memories of an object's location. In this experiment, they first showed monkeys two identical objects -one on the right and the other on the left- and "baited" one of them with a piece of apple. The scientists then hid the objects for up to 60 seconds before showing them again to the animals, who could now reach for the previously baited object because they remembered its location.

The researchers found that neurons in a circumscribed prefrontal region became electrically active during the period when the objects were hidden and the monkey had to remember which one had the bait.

Making the connection

At the time, however, many neuroscientists failed to connect these pioneering studies with the cognitive literature on working memory. That connection wasn't clearly made until 1989, when Patricia Goldman-Rakic, Shintaro Funahashi, and Charles Bruce at Yale University School of Medicine investigated the same prefrontal cells under conditions that erased a previous concern: that the monkeys in the older experiments might have locked their eyes on the location they were supposed to remember, and that the neuronal activity was actually related to keeping the eyes on target.

The Yale researchers trained monkeys to focus on a spot in the center of a TV screen and use their peripheral vision to note the location of a square flashed briefly on the screen. After a delay of several seconds, the animals then showed that they remembered the square's location by moving their eyes to where the square had been. The team found that the same class of prefrontal cells previously identified by the UCLA and Kyoto teams became active during the delay period, showing that they were storing spatial-location information before the monkev's eves moved. What's more, different cells became active in response to different locations.

Meanwhile, the Goldman-Rakic team began finding evidence of a division of labor for different aspects of visual working memory-subdivisions, perhaps, of Baddeley's proposed visual working-memory system. In the 1980s, the researchers had traced connections between distinct regions of the prefrontal cortex and the brain's sensory regions, which presumably provide the information to be held in working memory. Then, in 1993, by measuring neuronal activity in prefrontal regions hooked to different visual areas, Goldman-Rakic and her colleagues confirmed that one part of the prefrontal cortex is involved in working memory for object identity and another in working memory for spatial locations. Says Goldman-Rakic: "I'm not sure there is a central, all-purpose, executive area" for working memory. "In my model, there are parallel systems, each with its own central processor."

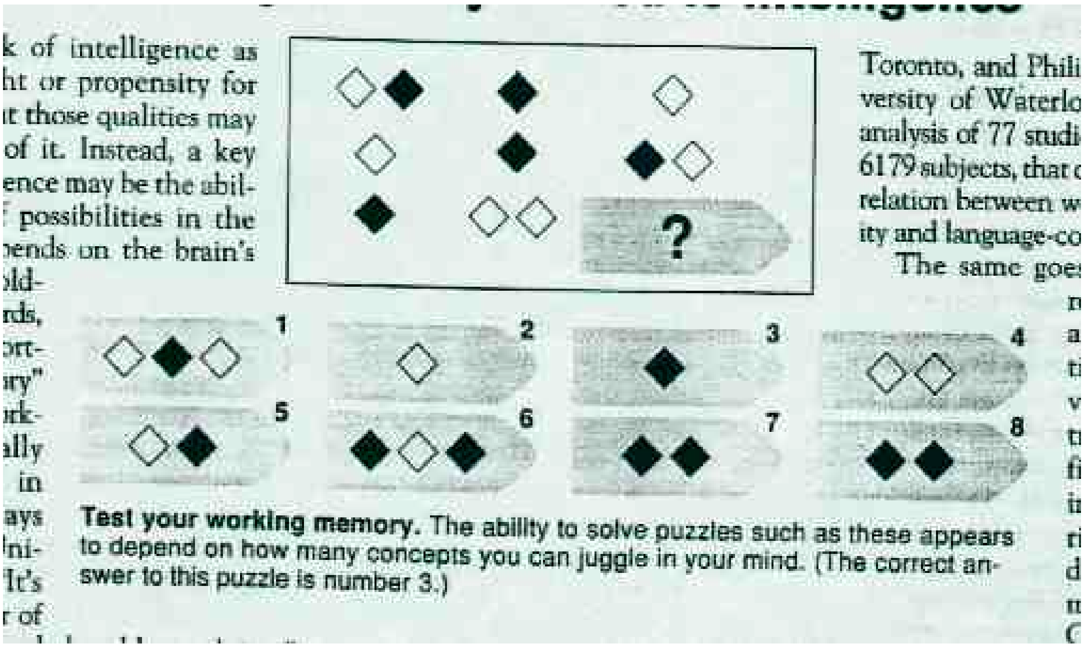
By 1996, results from neuroimaging studies of human subjects began to point to a similar division of labor in the human brain, although the prefrontal regions involved may not be identical to those in monkeys. Some of that evidence came from Susan Courtney, Leslie Ungerleider, Katrina Keil, and James Haxby at the National Institute of Mental Health (NIMH) in Bethesda, Maryland.Using positron emission tomography (PET), which maps neuronal activity b tracking the concentration of radioactive tracers in subjects' brains, they found that working memories for facial features and locations reside in separate regions of the prefrontal cortex and also in separate sensory areas.

At about the same time, John Jonides, Edward Smith, and Robert Koeppe of the University of Michigan, Ann Arbor, obtained PET evidence for a separation between spatial and verbal working

memory. The act of remembering the locations of three dots, they found, produced activity mostly on the right side of the brain -including certain regions of the prefrontal cortex and regions involved in location perception. By contrast, recalling the identity of four letters produced mostly left-hemisphere activity -including three brain regions involved in speech production an perception, two of them in the frontal cortex.

But even though there appear to be separate circuits for spatial, object, and verbal working memories in the human brain as whole, their separation within the prefrontal cortex itself may not be as absolute as the studies by Goldman-Rakic and a few others suggest. For example, Michael Petrides a McGill University believes that imaging work by his group and others strongly suggests that one prefrontal region -so-called area 46, which Goldman-Rakic found to be involved in spatial tasks only in monkeys- acts as a processor for working-memory information regardless of its type.

Working Memory Linked to Intelligence



This area, Petrides notes, is consistently activated when subjects have to keep track of choices they have made in previous trials, or juggle a number of pieces of information it their minds at once no matter what kind of information is involved -spatial, verbal, or identity. It's the area involved when, say you have 10 jobs to do at the office and must keep track of which ones have been done and which still remain to be done," he says. However, the precise role of this prefrontal region remains a matter of fierce debate.

Appointing a CEO

To help resolve this controversy some researchers have begun to focus less on how the prefrontal cortex may be subdivided and more on its overall function. One of the probable functions is, of course, online data storage, as suggested by a number of human imaging studies. That idea is further supported by more recent work showing that the degree of prefrontal activation depends on the amount of information held in working memory, as it should if the prefrontal cortex is responsible for holding data.

In work reported in the January 1997 issue of *Neuroimage,* Carnegie Mellon's Cohen, Todd Braver, and their colleagues scanned subjects' brains with functional magnetic resonance imaging

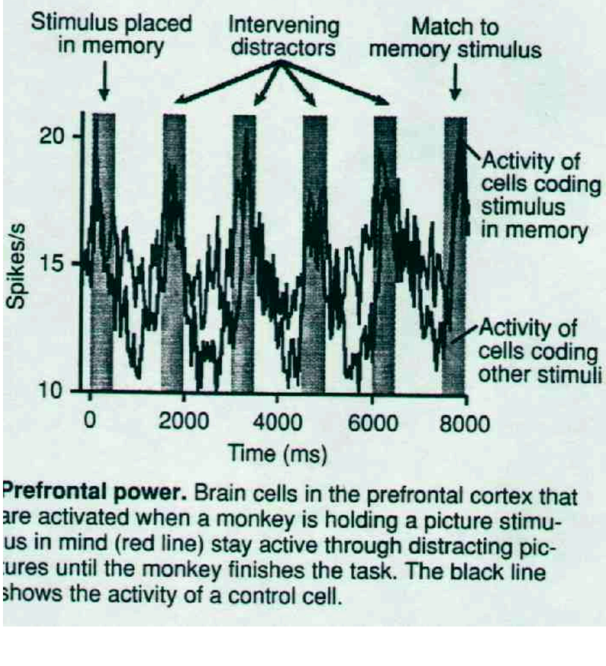
(fMRI), which gauges neuronal activity by measuring oxygen levels, while the subjects tried to remember the identity and order of a series of letters so they could find a match for a new letter. As the length of the series to be remembered increased from one to three letters, the amount of activity in prefrontal area 46 increased in parallel, indicating that this cortex is what holds the identity and order information in mind. "If you think the volume on your stereo is controlled by a particular knob," explains Cohen, "one of the things you check is whether turning that knob changes the volume." In this case, it did.

Indeed, the role of the prefrontal cortex may be even more important than that of other, more posterior areas of the brain that contribute to working memory. Evidence for this comes from Robert Desimone and Earl Miller at the NIMH, who recently measured the activity of cells in the temporal cortex, one of the posterior areas linked to working memory for object identity, while monkeys were holding a picture in mind and looking for a match in a series of test pictures. As expected, the researchers found that these cells became active after the remembered picture had disappeared from view.

Surprisingly, though, they fell silent as soon as the monkeys were shown a new, distracting picture. Because the monkeys were still able to make a match, they clearly remembered the stimulus, but apparently not as a result of activity in temporal cells. Desimone, Miller, and Cynthia Erickson then went on to find the cells responsible for this memory in the prefrontal cortex. Cells there, they discovered, showed memory- related activity that persisted while a monkey gazed at distracting pictures.

Steven Wise and Giuseppe di Pellegrino at the National Institutes of Health and Michael Stemmer: and Christos Constantinidis at Johns Hopkins University have documented a similar story for the spatial pathway. "The prefrontal activity is more like what you would expect from a memory signal: If memory persists, so should the activity," Wise says.

However, not all prefrontal activity is geared toward storage. Recent work suggests that the prefrontal cortex may be performing at least some of what psychologists have termed "executive functions" as well, an idea also suggested by studies of patients who have suffered frontal-lobe damage. These individuals often show severe difficulties in executive functions that require working memory, such as planning and organizing. They are also either easily distracted or, conversely, cannot switch their attention away from a task.



Prefrontal power. Brain cells in the prefrontal cortex that are activated when a monkey is holding a picture stimulus in mind (red line) stay active through distracting pictures until the monkey finishes the task. The black line shows the activity of a control cell.

An indication that working memory is important for one measure of intelligence, language comprehension, came in 1980. Psychologists Patricia Carpenter and Meredyth Daneman of Carnegie Mellon University in Pittsburgh had 41 college students read or listened to a set of unrelated sentences while remembering the last word of each. They found that the students' working-memory capacities, measured by the number of last words recalled, could predict their performance on the verbal Scholastic Aptitude Test, accounting for up to 36% of the variability in their scores. Given the complexity of the verbal SAT, this is "impressive," Daneman says. "It's very hard to find measures better than that."

What's more, she says, "the same general trends showed up in different variants of the [working-memory] task in different labs all over the world." Last year, Daneman, now at the University of Toronto, and Philip Merikle of the University of Waterloo completed a meta analysis of 77 studies, including a total of 6179 subjects, that confirmed the high correlation between working-memory capacity and language-comprehension ability.

But because the damage seen in such patients covers a wide swath of neural territory, researchers can't use them to trace functions to specific brain sections or cells. More recent monkey and human neuroimaging studies, however, point to part of the prefrontal cortex-area 46, in fact -as a critical engine for planning and attention, bolstering the argument that the working-memory circuits aren't completely independent in the brain.

In 1992, for instance, UCLA's Fuster and J avier Quintana found a class of neurons in area 46 of the monkey prefrontal cortex whose activity increased during the brief delay between a stimulus -a flash of colored light- and the monkeys' response to it, which was to move either to the right or left. In contrast, activity of a second group of cells in the prefrontal cortex, which responded to the stimulus color, decreased during the delay. Fuster believes the former group of cells may be the neural basis for planning, and the latter for memory of the stimulus, which should decay with time. Explains Fuster:
"There are cells that look to the future and cells that look to the past."

Imaging studies of human brains point to another executive role for the prefrontal cortex: switching attention between tasks. Mark D'Esposito and his University of Pennsylvania Medical School colleagues used fMRI to scan the brains of subjects doing two simple, non-working~memory tasks: judging whether spoken words fit a category such as "vegetable," and mentally rotating two squares to determine which matched a third square. When subjects did either task alone, the researchers saw no prefrontal activity.

But doing both tasks at once lit up area 46 in the prefrontal cortex, suggesting that it is responsible for the attention control required to switch rapidly between two tasks -an executive, working-memory duty called dual-task coordination. Says D'Esposito: "This is the first imaging study to show directly that the prefrontal cortex is involved in this executive process."

Thus, the prefrontal cortex appears to assume the lion's share of the working-memory duties, both holding relevant information on-line and performing complex processing functions. To do its job, however, this cortex must cooperate with connected sensory regions that hold and use the information for briefer periods of time. Now the race is on to determine exactly what role these posterior areas play and how that role depends on the prefrontal cortex. "Animal studies and more sophisticated imaging techniques will address this in the next few years," says Desimone.

Researchers are also scrambling to pinpoint the processing jobs performed by the prefrontal cortex-perhaps including moving information into working memory, updating what's already there, and using it to select a response and to determine whether such jobs are confined to separate

prefrontal compartments. But many processing operations happen too quickly for current imaging techniques to capture or may be separated into regions too small for them to differentiate. 'Neuroimaging is still coarse-grained for many of the processes we'd like to look at" says Cohen.

As the techniques become more refined, they will deliver more and more data for neuroscientists to incorporate into their theories. But that task may well strain researchers' own working memories, which will need some electronic assistance. "We need more complex theories, and we need computer models to test those theories in sufficient detail," says Cohen. Eventually, these studies will expand, if not our working memories, our ability to fathom them.

-Ingrid Wickelgren