Biological Level of Analysis Additional Readings

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Quan

Experiment

Definition: A formal trial undertaken to (confirm or disconfirm) a hypothesis. Experiments do the following:
1. Directly vary a condition you think might affect behavior.
2. Create two or more groups of subjects.
3. Record whether varying the condition has any effect on behavior.

IV: Conditions altered or varied by the experimenter, who sets their size, amount, or value

DV: Measure the results of the experiment

EV: Conditions that a researcher wishes to prevent from affecting the outcome of the experiment

Groups

Experiment: The group of subjects exposed to the independent variable or experimental condition

Control: The group of subjects exposed to all experimental conditions or variables except the independent variable

Positive: The experiment gives a clear statistical result

Negative: The experimenter effect (changes in behavior caused by the unintended influence of an experimenter) is a common problem in psychological research. This occurs because humans are very sensitive to hints about what is expected of them.

Example: → A PET scan detects positrons emitted by weakly radioactive glucose as it is consumed by the brain. Because the brain runs on glucose, a PET scan shows which areas are using more energy. PET scans reveal that very specific brain areas are active when you are reading a word, hearing a word, saying a word, or thinking about the meaning of a word.

objective / subjective

Double Blind

Definition: An experiment in which neither the participants nor the individuals running the study know which participants are in the control group and which are in the experimental group until after the results are tallied. This method is mostly used when dealing with drug research to see the true effects of a drug rather than the psychological effect. The most common place for this in drug research is with placebo experiments.

Positive: By having the experiments unaware of what is going on in the experiment, it eliminated any unconscious or conscious effects that the experimenters may have on the participants involved in the experiment (experimenter effect); also when collecting and analyzing the data, self-fulfilling prophecy on the part of the experimenter is also eliminated to get the most valid and most unbiased results.

Negative: → There may be an adverse effect from the experimenters not knowing all of the details of the experiment and not having complete control over the experiment, such that they may be able to control all extraneous variables or the like.

NOT

Example: (Basson et al., 2002) is an example of a placebo study in which a double-blind method was used. In the experiment, the experimenters gave half of their participants, whom were all female, Viagra and the other half a placebo. Later when asked, 41% of the women who were on Viagra reported improvement in their sex life, while 43% of women who were taking the placebo reported improvement in their sex life: this suggests that the major cause of improvement in sexual experiences is psychological and not biological.

Correlation Studies Quan

Definition: Looking for Relationships (anything measured, rated, or scored). A Positive Correlation: high value of one variable is associated to high value of the other variable. A Negative Correlation: High values of one variable is associated with low values of the other variable. +1.00: perfect positive while -1.00: perfect negative

Positive: Can be done in either natural or laboratory environment. Can make us discover relationships and make predictions

Negative: Correlation does not show causation; conclusions about causation is very tempting

Example: Bushman and Anderson, 2001
Found positive correlation between television violence and child aggression. Brings the questions:
- Did violence in television cause child aggression?
- Do aggressive children watch violent shows?

Interviews

Interviews: Qual

Definition: A common method for studying people and how they feel about things in the present. Quite a bit of personal, detailed information can be obtained with this technique. It is a research that involves studying people face to face and asking questions while noting the subjects' tones of voice, hand gestures, postures, facial expressions, body language cues, and so forth. In an unstructured interview, conversation is informal, and topics are taken up freely as they rise. In a structured interview, the interviewer obtains information by asking a planned sense of questions.

Positive: Its advantages include the facts that researcher(s) can gather information on feelings, opinions, and behavior patterns. Accordingly, researchers can obtain personal, detailed information. Also, interview can be done in a variety of settings.

Negative: Because this is face-to-face, subjects' responses may not be completely honest--trying to sort out fiction from fact (since the interviewee is going to be on his or her best behavior and will try to present information in the most favorable light) would be problematic. Also, researchers' biases can influence behavior of the subjects. All of us carry around subtle and not-so-subtle prejudices against certain types of people, age groups, modes of dress, etc. there is no doubt that these factors have an influence not only on the types of questions we ask but also on the interpretation we give to an answer (observer bias). "Halo effect," the tendency to generalize a favorable or unfavorable impression to unrelated details of personality, may arise as well (e.i. a subject is open-minded and researcher assumes the subject to be honest as well).

Example: Experiment on anorexia entitled, *"It's exercise or nothing": a qualitative analysis of exercise dependence.* Done by D. Bamber, I.M. Cockerill, S. Rodgers and D. Carroll (2000). Its objective was to explore, using qualitative methods, the concept of exercise dependence. Semistructured interviews were undertaken with subjects screened for exercise dependence and eating disorders. Remember that Mrs. Helton sent you the email to the link.

Female exercisers, four in each case, were allocated a priori to four groups: primary exercise dependent; secondary exercise dependent, where there was a coincidence of exercise dependence and an eating disorder; eating disordered; control, where there was no evidence of either exercise dependence or eating disorder. They were asked about their exercise and eating attitudes and behavior, as well as about any history of psychological distress. Their narratives were taped, transcribed, and analyzed from a social constructionist perspective (method).

Participants classified as primary exercise dependent either showed no evidence of exercise dependent attitudes and behavior or, if they exhibited features of exercise dependence, displayed symptoms of an eating disorder. Only the latter reported a history of psychological distress, similar to that exhibited by women classified as secondary exercise dependent or eating disordered. For secondary exercise dependent and eating disordered women, as well as for controls, the narratives largely confirmed the a priori classification (result).

Concluded that where exercise dependence was manifest, it was always in the context of an eating disorder, and it was this co-morbidity, in addition to eating disorders per se, that was associated with psychological distress. As such, these qualitative data support the concept of secondary, but not primary, exercise dependence.

Case Studies Qual

Definition: An in-depth focus on all aspects of a single person.

Positive: Case studies can provide special opportunities to answer interesting questions.

Negative: Case Studies lack formal control groups. This limits the conclusions that can be drawn from clinical observations.

Example: A case study was done by Dr. J.M. Harlow (1868). Phineas Gage, a foreman on a work crew, had a 13 pound steel rod pierced through the front of his brain. Amazingly, he survived the accident. Within the 2 months, Gage walked talked, and moved normally. However, Gage changed from a dependable worker to a "surly, foul-mouthed liar." Throughout the recovery, Dr. Harlow recorded and observed the behavior of Gage. This is known to be one of the first case studies done.

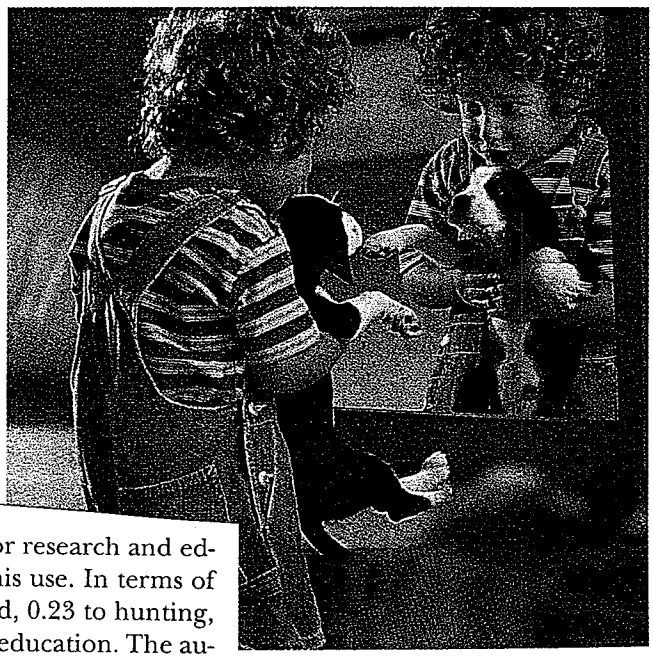
Ethical Issues in Research with Animals

Most of the research described in this book involves experimentation on living animals. Any time we use another species of animals for our own purposes, we should be sure that what we are doing is both humane and worthwhile. I believe that a good case can be made that research on the physiology of behavior qualifies on both counts. Humane treatment is a matter of procedure. We know how to maintain laboratory animals in good health in comfortable, sanitary conditions. We know how to administer anesthetics and analgesics so that animals do not suffer during or after surgery, and we know how to prevent infections with proper surgical procedures and the use of antibiotics. Most industrially developed societies have very strict regulations about the care of animals and require approval of the experimental procedures used on them. There is no excuse for mistreating animals in our care. In fact, the vast majority of laboratory animals *are* treated humanely.

We use animals for many purposes. We eat their meat and eggs, and we drink their milk; we turn their hides into leather; we extract insulin and other hormones from their organs to treat people's diseases; we train them to do useful work on farms or to entertain us. Even having a pet is a form of exploitation; it is we—not they—who decide that they will live in our homes. The fact is, we have been using other animals throughout the history of our species.

Pet-owning causes much more suffering among animals than scientific research does. As Miller (1983) notes, pet owners are not required to receive permission from a board of experts that includes a veterinarian to house their pets, nor are they subject to periodic inspections to be sure that their homes are clean and sanitary, that their pets have enough space to exercise properly, or that their pets' diets are appropriate. Scientific researchers are. Miller also notes that fifty times more dogs and cats are killed by humane societies each year because they have been abandoned by former pet owners than are used in scientific research.

If a person believes that it is wrong to use another animal in any way, regardless of the benefits to humans, there is nothing anyone can say to convince him or her of the value of scientific research with animals. For this person, the issue is closed from the very beginning. Moral absolutes cannot be settled logically; like religious beliefs, they can be accepted or rejected, but they cannot be proved or disproved. My arguments in support of scientific research with animals are based on an evaluation of the benefits the research has to humans. (We should also remember that research with animals often helps *other animals;* procedures used by veterinarians, as well as those used by physicians, come from such research.)



Before describing the advantages of research with animals, let me point out that the use of animals in research and teaching is a special target of animal rights activists. Nicholl and Russell (1990) examined twenty-one books written by such activists and counted the number of pages devoted to concern for different uses of animals. Next, they compared the relative concern the authors showed for these uses to the numbers of animals actually involved in each of these categories. The results indicate that the authors showed relatively little concern for animals used for food, hunting, or furs, or for those killed in pounds. In contrast, although only 0.3 percent of the animals are used for research and education, 63.3 percent of the pages were devoted to criticizing this use. In terms of pages per million animals used, the authors devoted 0.08 to food, 0.23 to hunting, 1.27 to furs, 1.44 to killing in pounds—and 53.2 to research and education. The authors showed 665 times more concern for research and education than for food and 231 times more than for hunting. Even the use of animals for furs (which consumes two-thirds as many animals as research and education) attracted 41.9 times less attention per animal.

3

The disproportionate amount of concern that animal rights activists show toward the use of animals in research and education is puzzling, particularly because this is the one *indispensable* use of animals. We *can* survive without eating animals, we *can* live without hunting, we *can* do without furs. But without using animals for research and for training future researchers, we *cannot* make progress in understanding and treating diseases. In not too many years, our scientists will probably have developed a vaccine that will prevent the further spread of AIDS. Some animal rights activists believe that preventing the deaths of laboratory animals in the pursuit of such a vaccine is a more worthy goal than preventing the deaths of millions of humans that will occur as a result of the disease if a vaccine is not found. Even diseases that we have already conquered would take new victims if drug companies could no longer use animals. If they were deprived of animals, these companies could no longer extract hormones used to treat human diseases, and they could not prepare many of the vaccines that we now use to prevent them.

Our species is beset by medical, mental, and behavioral problems, many of which can be solved only through biological research. Let us consider some of the major neurological disorders. Strokes, caused by bleeding or occlusion of a blood vessel within the brain, often leave people partly paralyzed, unable to read, write, or converse with their friends and family. Basic research on the means by which nerve cells communicate with each other has led to important discoveries about the causes of the death of brain cells. This research was not directed toward a specific practical goal; the potential benefits actually came as a surprise to the investigators.

Experiments based on these results have shown that if a blood vessel leading to the brain is blocked for a few minutes, the part of the brain that is nourished by that vessel will die. However, the brain damage can be prevented by first administering a drug that interferes with a particular kind of neural communication. This research is important, because it may lead to medical treatments that can help to reduce the brain damage caused by strokes. But it involves operating on a laboratory animal such as a rat and pinching off a blood vessel. (The animals are anesthetized, of course.) Some of the animals will sustain brain damage, and all will be killed so that their brains can be examined. However, you will probably agree that research like this is just as legitimate as using animals for food.

As you will learn later in this book, research with laboratory animals has produced important discoveries about the possible causes or potential treatments of neurological and mental disorders, including Parkinson's disease, schizophrenia, manic-depressive illness, anxiety disorders, obsessive-compulsive disorders, anorexia nervosa, obesity, and drug addictions. Although much progress has been made, these problems are still with us, and they cause much human suffering. Unless we continue our research with laboratory animals, the problems will not be solved. Some people have suggested that instead of using laboratory animals in our research, we could use tissue cultures or computers. Unfortunately, neither tissue cultures nor computers are substitutes for living organisms. We have no way to study behavioral problems such as addictions in tissue cultures, nor can we program a computer to simulate the workings of an animal's nervous system. (If we could, that would mean we already had all the answers.)

This book will discuss some of the many important discoveries that have helped to reduce human suffering. For example, the discovery of a vaccine for polio, a serious disease of the nervous system, involved the use of rhesus monkeys. As you will learn in Chapter 4, Parkinson's disease, an incurable, progressive neurological disorder, has been treated for years with a drug called L-DOPA, discovered through animal research. Now, because of research with rats, mice, rabbits, and monkeys, stimulated by the accidental poisoning of several young people with a contaminated batch of synthetic heroin, patients are being treated with a drug that may actually slow down the rate of brain degeneration. Researchers have hopes that a drug will be found to prevent the brain degeneration altogether.

The easiest way to justify research with animals is to point to actual and potential benefits to human health, as I have just done. However, we can also justify this research with a less practical, but perhaps equally important, argument. One of the things that characterize our species is a quest for an understanding of our world. For example, astronomers study the universe and try to uncover its mysteries. Even if their discoveries never lead to practical benefits such as better drugs or faster methods of transportation, the fact that they enrich our understanding of the beginning and the fate of our universe justifies their efforts. The pursuit of knowledge is itself a worthwhile endeavor. Surely, the attempt to understand the universe within us—our nervous system, which is responsible for all that we are or can be—is also valuable.

Scientists Spot Brain's 'Free Will' Center

August 23, 2007 08:40:46 PM PST
By Amanda Gardner
HealthDay Reporter

THURSDAY, Aug. 23 (HealthDay News) -- If you've ever been of "two minds" about doing something, a new study may explain why.

Scientists say one part of the brain is responsible for initiating action, while a totally separate area is in charge of *not* taking that action. This newly identified region, involved in an aspect of self-control, may change conceptions of human free will, the researchers said. It could also explain the basis of impulsive as well as reluctant behavior, they added. "The central issue is quite simple. If we want to do something, and we decide not to, how does that brain wire that?" said Rajesh Miranda, associate professor of neuroscience and experimental therapeutics at Texas A&M Health Science Center College of Medicine. "They showed the region in the brain that can act as a gate to suppress a plan to do something," said Miranda, who was not involved in the research.

"The big search in neuroscience is, are there general inhibiting or specific inhibiting circuits?" added another outside expert, Dr. John Hart, a spokesman for the American Academy of Neurology and a behavioral neurologist and cognitive neuroscientist at the University of Texas at Dallas. "This is another piece of the puzzle. . . . but does it generalize beyond that task to all life decisions? That has yet to be shown," he said.

This study and others like it are really in their infancy, Miranda pointed out. That's important to remember, since the findings could one day have legal and other implications. "This kind of data could have implications for legal definitions of 'diminished capacity,' " he explained. "There's a potential for informing legal definitions of mental illness and things like that." The study, which was published in the Aug. 22 issue of *The Journal of Neuroscience*, was conducted by researchers from University College London, in the United Kingdom, the Max Planck Institute in Leipzig, Germany, and Ghent University, Belgium.

Using functional magnetic resonance imaging (fMRI), the researchers studied the brain activity of participants in two situations -- when they acted out as they had planned, or when they decided *not* to follow their original intention. Fifteen right-handed individuals (seven males and eight females, average age 26) participated in a "go-no-go" exercise. They were asked to press a button on a keyboard but first to indicate what time they were going to perform this action. They were also asked to choose instances in which they stopped before actually pressing the button. When participants decided not to press the button, a specific area of the frontal lobe region of the brain lit up. When participants followed through, however, the area did not light up.
The executive-function frontal lobes, which have previously been identified with inhibition, are part of what makes humans human, neurologists say.

"These areas are the most expanded in humans as compared to animals," explained Dr. Kimford Meador, spokesman for the American Academy of Neurology and professor of neurology at the University of Florida, Gainesville. "The frontal lobe is important for initiation, for planning, personality, creativity."

"The frontal lobes distinguish us from lower-order creatures," added David Masur, director of neuropsychology in the department of neurology at Montefiore Medical Center and clinical professor of neurology at Albert Einstein College of Medicine, both in New York City. "We have larger frontal lobes, and these are what really are responsible for much of what we define as human behavior, social interaction, ability to plan, organize, some language ability, abstract reasoning or thinking."

For now, the implications of the research are esoteric but, down the line, who knows?
"Much of our society is based on the concept of not only free will but also 'free won't,' the inhibition of response," Masur explained. "The difference between us as intelligent ordered social creatures and the society that would run amok is the ability to inhibit our responses, the ability to take control if a situation calls for it, to *stop* acting in a particular way . . . Maybe down the line somebody can develop a drug or hormone or transmitter system that targets that particular area of brain which strengthens the ability to negate responses which are too impulsive."
"It's a fascinating mind-brain question about where does our free will begin and end," added Meador.

Amnesia

RELATIONAL LEARNING

So far, I have discussed relatively simple forms of learning, which can be understood as changes in circuits of neurons that detect the presence of particular stimuli or as strengthened connections between neurons that convey sensory information and those that produce responses. But most forms of learning are more complex; most memories of real objects and events are related to other memories. Seeing a photograph of an old friend may remind you of the sound of the person's name and of the movements you have to make to pronounce it. You may also be reminded of things you have done with your friend: places you have visited, conversations you have had, experiences you have shared. Each of these memories can contain a series of events, complete with sights and sounds, which you will be able to recall in the proper sequence. Obviously, the neural circuits in the inferior temporal cortex that recognize your friend's face are connected to circuits in many other parts of the brain, and these circuits are connected to many others. This section discusses research on relational learning, which includes the establishment and retrieval of memories of events and episodes.

Human Anterograde Amnesia

One of the most dramatic and intriguing phenomena caused by brain damage is *anterograde amnesia,* which, at first glance, appears to be the inability to learn new information. However, when we examine the phenomenon more carefully, we find that the

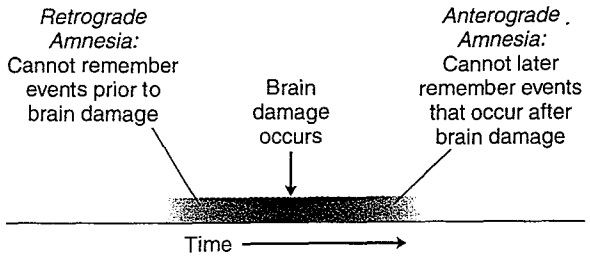


FIGURE 12.24

A schematic definition of retrograde amnesia and anterograde amnesia.

basic abilities of perceptual learning, stimulus–response learning, and motor learning are intact but that complex relational learning, of the type I just described, is gone. This section discusses the nature of anterograde amnesia in humans and its anatomical basis. The section that follows discusses related research with laboratory animals.

The term **anterograde amnesia** refers to difficulty in learning new information. A person with pure anterograde amnesia can remember events that occurred in the past, during the time before the brain damage occurred, but cannot retain information he or she encounters *after* the damage. In contrast, **retrograde amnesia** refers to the inability to remember events that happened *before* the brain damage occurred. (See ***Figure 12.24.***) As we will see, pure anterograde amnesia is rare; usually, there is also a retrograde amnesia for events that occurred for a period of time before the brain damage occurred.

In 1889, Sergei Korsakoff, a Russian physician, first described a severe memory impairment caused by brain damage, and the disorder was given his name. The most profound symptom of **Korsakoff's syndrome** is a severe anterograde amnesia: The patients appear to be unable to form new memories, although they can still remember old ones. They can converse normally and can remember events that happened long before their brain damage occurred, but they cannot remember events that happened afterward.

Korsakoff's syndrome is usually (but not always) a result of brain damage produced by chronic alcoholism. The disorder actually results from a thiamine (vitamin B_1) deficiency caused by the alcoholism (Adams, 1969; Haas, 1988). Because alcoholics receive a substantial number of calories from the alcohol they ingest, they usually eat a poor diet, and their vitamin intake is consequently low. Furthermore, alcohol interferes with intestinal absorption of thiamine. The ensuing deficiency produces brain damage.

Anterograde amnesia can also be caused by damage to the temporal lobes. Scoville and Milner (1957) reported that bilateral removal of the medial temporal lobe produced a memory impairment in humans that was apparently identical to that seen in Korsakoff's syndrome. Thirty operations had been performed on psychotic patients in an attempt to alleviate their mental disorder, but it was not until this operation was performed on patient H.M. that the anterograde amnesia was discovered. The psychotic patients' behavior was already so disturbed that their amnesia was not detected. However, patient H.M. was reasonably intelligent and was not psychotic; therefore, his postoperative deficit was discovered immediately. He had received the surgery in an attempt to treat his very severe epilepsy, which could not be controlled even by high doses of anticonvulsant medication.

The surgery successfully treated H.M.'s seizure disorder, but it became apparent that the operation had produced a serious memory impairment. Subsequently, Scoville and Milner (1957) examined eight of the psychotic patients who were coherent enough to cooperate with them. Careful testing revealed that some of these patients also had anterograde amnesia; the deficit appeared to occur only when the hippocampus was removed. They concluded that the hippocampus was the critical structure destroyed by the surgery. Once it was discovered that bilateral medial temporal lobectomy causes anterograde amnesia, neurosurgeons stopped performing them and are now careful to operate on only one temporal lobe. (Unilateral temporal lobectomy may cause minor memory problems, but nothing like what occurs after bilateral operations.)

Anterograde amnesia Amnesia for events that occur after some disturbance to the brain, such as head injury or certain degenerative brain diseases.

Retrograde amnesia Amnesia for events that preceded some disturbance to the brain, such as a head injury or electroconvulsive shock.

Korsakoff's syndrome Permanent anterograde amnesia caused by brain damage resulting from chronic alcoholism or malnutrition.

Basic Description

For you to understand more fully the nature of anterograde amnesia, I will discuss the case of patient H.M. in more detail (Milner, Corkin, and Teuber, 1968; Milner,

1970; Corkin et al., 1981). Patient H.M. has been extensively studied because his amnesia is relatively pure. His intellectual ability and his immediate verbal memory appear to be normal. He can repeat seven numbers forward and five numbers backward, and he can carry on conversations, rephrase sentences, and perform mental arithmetic. He has a retrograde amnesia for events that occurred during several years preceding the operation, but he can recall older memories very well. He showed no personality change after the operation, and he appears to be generally polite and good-natured.

However, since the operation, H.M. has been unable to learn anything new. He cannot identify by name people he has met since the operation (performed in 1953, when he was twenty-seven years old), nor can he find his way back home if he leaves his house. (His family moved to a new house after his operation, and he never learned how to get around in the new neighborhood. He now lives in a nursing home, where he can be cared for.) He is aware of his disorder and often says something like this:

> Every day is alone in itself, whatever enjoyment I've had, and whatever sorrow I've had . . . Right now, I'm wondering. Have I done or said anything amiss? You see, at this moment everything looks clear to me, but what happened just before? That's what worries me. It's like waking from a dream; I just don't remember. (Milner, 1970, p. 37)

H.M. is capable of remembering a small amount of verbal information as long as he is not distracted; constant rehearsal can keep information in his immediate memory for a long time. However, rehearsal does not appear to have any long-term effects; if he is distracted for a moment, he will completely forget whatever he had been rehearsing. He works very well at repetitive tasks. Indeed, because he so quickly forgets what previously happened, he does not easily become bored. He can endlessly reread the same magazine or laugh at the same jokes, finding them fresh and new each time. His time is typically spent solving crossword puzzles and watching television.

From these findings, Milner and her colleagues made the following conclusions:

1. *The hippocampus is not the location of long-term memories; nor is it necessary for the retrieval of long-term memories.* If it were, H.M. would not have been able to remember events from early in his life, he would not know how to talk, he would not know how to dress himself, and so on.
2. *The hippocampus is not the location of immediate (short-term) memories.* If it were, H.M. would not be able to carry on a conversation, because he would not remember what the other person said long enough to think of a reply.
3. *The hippocampus is involved in converting immediate (short-term) memories into long-term memories.* This conclusion is based on a particular hypothesis of memory function: that our immediate memory of an event is retained by neural activity and that long-term memories consist of relatively permanent biochemical or structural changes in neurons. The conclusion seems a reasonable explanation for the fact that when presented with new information, H.M. seems to understand it and remember it as long as he thinks about it but that a permanent record of the information is just never made.

As we will see, these three conclusions are too simple. Subsequent research on patients with anterograde amnesia indicates that the facts are more complicated—and more interesting—than they first appeared to be. But to appreciate the significance of the findings of more recent research, we must understand these three conclusions and remember the facts that led to them.

Many psychologists believe that learning consists of at least two stages: short-term memory and long-term memory. They conceive of short-term memory as a means of storing a limited amount of information temporarily and long-term memory as a means of storing an unlimited amount (or at least an enormously large

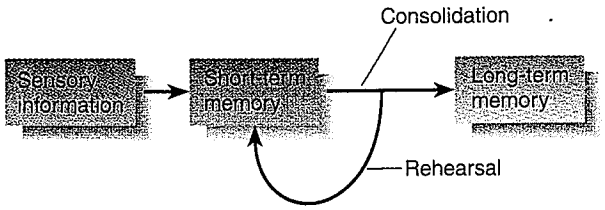


FIGURE 12.25

A simple model of the learning process.

amount) of information permanently. As we saw earlier in this chapter, short-term memory is an immediate memory for stimuli that have just been perceived. We can remember a new item of information (such as a telephone number) for as long as we want to by engaging in a particular behavior: rehearsal. However, once we stop rehearsing the information, we may or may not be able to remember it later; that is, the information may or may not get stored in **long-term memory.**

Short-term memory can hold only a limited amount of information. To demonstrate this fact, read the following numbers to yourself just once, and then close your eyes and recite them back.

1 4 9 2 3 0 7

You probably had no trouble remembering them. Now, try the following set of numbers, and go through them *only once* before you close your eyes.

7 2 5 2 3 9 1 6 5 8 4

Very few people can repeat eleven numbers; in fact, you may not have even bothered to try, once you saw how many numbers there were. Therefore, short-term memory has definite limits. But of course, if you wanted to, you could recite the numbers again and again until you had memorized them; that is, you could rehearse the information in short-term memory until it was eventually stored in long-term memory. Long-term memory has no known limits; and as its name suggests, it is relatively durable. Presumably, it is a result of changes in synaptic strength, such as the ones responsible for long-term potentiation. If we stop thinking about something we have just perceived (that is, something contained in short-term memory), we may or may not remember the information later. However, information in long-term memory need not be continuously rehearsed; once we have learned something, we can stop thinking about it until we need the information at a future time.

The simplest model of the memory process says that sensory information enters short-term memory, rehearsal keeps it there, and eventually, the information makes its way into long-term memory, where it is permanently stored. The conversion of short-term memories into long-term memories has been called **consolidation,** because the memories are "made solid," so to speak. (See ***Figure 12.25.***)

Now you can understand the original conclusions of Milner and her colleagues: If H.M.'s short-term memory is intact and if he can remember events from before his operation, then the problem must be that consolidation does not take place. Thus, the role of the hippocampal formation in memory is consolidation—converting short-term memories to long-term memories.

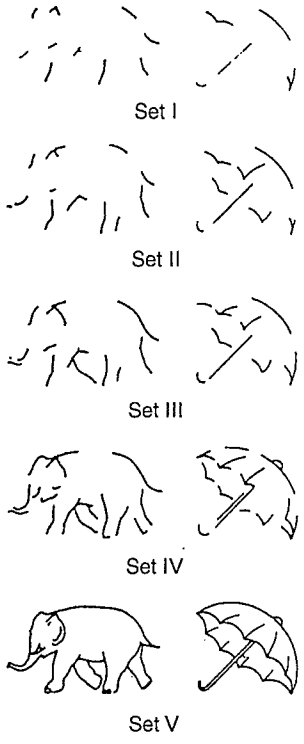


FIGURE 12.26

Examples of broken drawings.

(Reprinted with permission of author and publisher from Gollin, E.S. Developmental studies of visual recognition of incomplete objects. Perceptual and Motor Skills, *1960,* 11, *289–298.)*

Spared Learning Abilities

H.M.'s memory deficit is striking and dramatic. However, when he and other patients with anterograde amnesia are studied more carefully, it becomes apparent that the amnesia does not represent a total failure in learning ability. When the patients are appropriately trained and tested, we find that they are capable of three of the four major types of learning described in the first section of this chapter: perceptual learning, stimulus–response learning, and motor learning.

First, let's consider perceptual learning. Figure 12.26 shows two sample items from a test of the ability to recognize broken drawings; note how the drawings are successively more complete. (See ***Figure 12.26.***) Subjects are first shown the least complete set (set I) of each of twenty different drawings. If they do not recognize a figure (and most people do not recognize set I), they are shown more complete sets until they identify it. One hour later, the subjects are tested again for retention, starting with set I. H.M. was given this test and, when retested an hour later, showed con-

siderable improvement (Milner, 1970). When he was retested four months later, he *still* showed this improvement. His performance was not as good as that of normal control subjects, but he showed unmistakable evidence of long-term retention.

The incomplete drawing task is known as a **priming task.** *Priming* refers to the fact that when people perceive a particular stimulus, it becomes easier for them to perceive it again. As you will see, researchers have used several different types of priming tasks to investigate the nature of anterograde amnesia.

Johnson, Kim, and Risse (1985) found that patients with anterograde amnesia could learn to recognize faces and melodies. They played unfamiliar melodies from Korean songs to amnesic patients and found that when they were tested later, the patients preferred these melodies to ones they had not heard before. The experimenters also presented photographs of two men along with stories of their lives: One man was dishonest, mean, and vicious, and the other was nice enough to invite home to dinner. Twenty days later, the amnesic patients said they liked the picture of the "nice" man better than that of the "nasty" one.

Investigators have also succeeded in demonstrating stimulus–response learning by H.M. and other amnesic subjects. For example, Woodruff-Pak (1993) found that H.M. and another patient with anterograde amnesia could acquire a classically conditioned eyeblink response. H.M. even showed retention of the task two years later: He acquired the response again in one-tenth the number of trials that were needed previously. Sidman, Stoddard, and Mohr (1968) successfully trained patient H.M. on an instrumental conditioning task—a visual discrimination task in which pennies were given for correct responses.

Finally, Milner (1965) demonstrated motor learning. She and her colleagues presented H.M. with a mirror-drawing task. This procedure requires the subject to trace the outline of a figure (in this case, a star) with a pencil while looking at the figure in a mirror. (See ***Figure 12.27.***) The task may seem simple, but it is actually rather difficult and requires some practice to perform well. With practice, H.M. became proficient at mirror drawing; his errors were reduced considerably during the first session, and his improvement was retained on subsequent days of testing. He also learned a pursuit rotor task, which required him to try to keep a pointer placed above a spot of light moving in a circular path. Thus, several different forms of long-term memory can certainly be established in patients with anterograde amnesia.

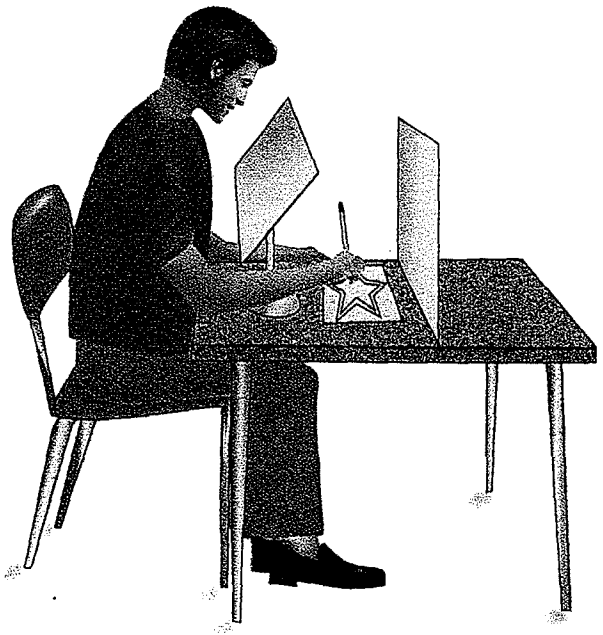
Long-term memory Relatively stable memory of events that occurred in the more distant past, as opposed to short-term memory.

Consolidation The process by which short-term memories are converted into long-term memories.

Priming task A phenomenon in which exposure to a particular stimulus automatically facilitates perception of that stimulus or related stimuli.

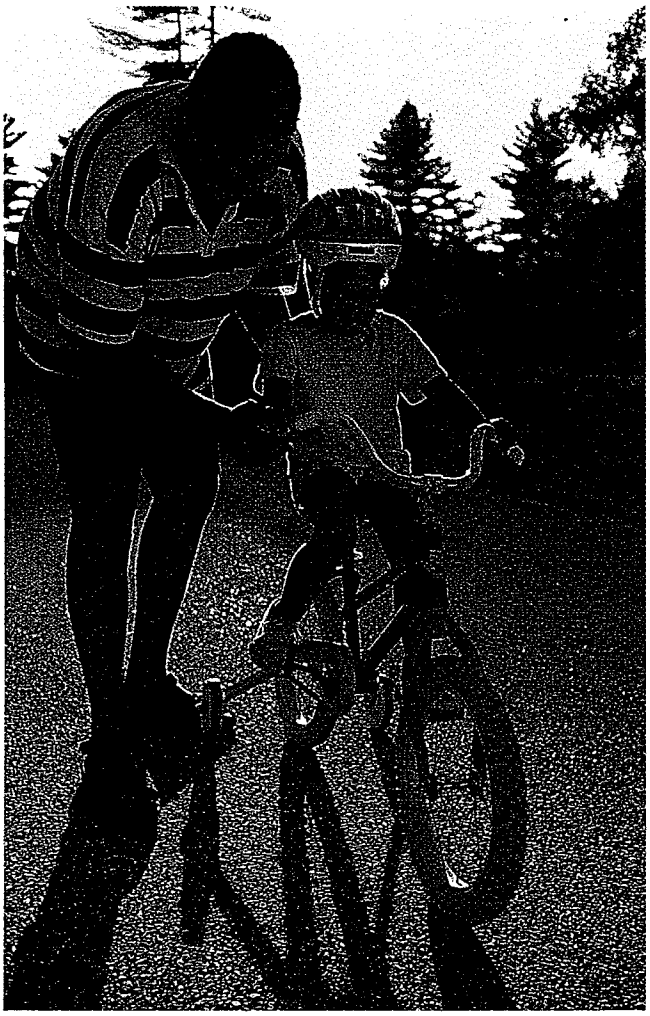
FIGURE 12.27

The mirror-drawing task.



Declarative and Nondeclarative Memories

If amnesic patients can learn tasks like these, you might ask, why do we call them *amnesic*? The answer is this: Although the patients can learn to perform these tasks, they do not remember anything about having learned them. They do not remember the experimenters, the room in which the training took place, the apparatus that was used, or any events that occurred during the training. Although H.M. learned to recognize the broken drawings, he denied that he had ever seen them before. Although the amnesic patients in the study by Johnson, Kim, and Risse learned to like some melodies better, they did not recognize that they had heard them before; nor did they remember having seen the pictures of the two young men. Although H.M. successfully acquired a classically conditioned eyeblink response, he did not remember the experimenter, the apparatus, or the headband he wore that held the device that delivered a puff of air to his eye. Similarly, in the experiment by Sidman, Stoddard, and Mohr, although H.M. learned to make the correct response (press a



Learning to ride a bicycle is a combination of stimulus-response learning and motor learning, both of which are nondeclarative in nature. Remembering when we learned to ride a bicycle is an episodic memory, a form of relational learning.

panel with a picture of a circle on it), he was unable to recall having done so. In fact, once H.M. had learned the task, the experimenters interrupted him, had him count his pennies (to distract him for a little while), and then asked him to say what he was supposed to do. He seemed puzzled by the question; he had absolutely no idea. But when they turned on the stimuli again, he immediately made the correct response.

The distinction between what people with anterograde amnesia can and cannot learn is obviously important, because it reflects the basic organization of the learning process. Clearly, there are at least two major categories of memories. Psychologists have given them several different names. For example, some investigators (Eichenbaum, Otto, and Cohen, 1992; Squire, 1992) suggest that patients with anterograde amnesia are unable to form **declarative memories,** which have been defined as those that are "explicitly available to conscious recollection as facts, events, or specific stimuli" (Squire, Shimamura, and Amaral, 1989, p. 218). The term *declarative* obviously comes from *declare,* which means "to proclaim; to announce." The term reflects the fact that patients with anterograde amnesia cannot talk about experiences that they have had since the time of their brain damage. And note that the definition refers specifically to *stimuli.* Thus, according to Squire and his colleagues, declarative memory is a form of *perceptual memory*—specifically, memory of events that we can think and talk about.

The other category of memories, often called **nondeclarative memories,** includes instances of perceptual, stimulus–response, and motor learning that we are not necessarily conscious of. (Some psychologists refer to these two categories as *explicit* and *implicit* memories, respectively.) Nondeclarative memories appear to operate automatically. They do not require deliberate attempts on the part of the learner to memorize something. They do not seem to include facts; instead, they control behaviors. For example, suppose we learn to ride a bicycle. We do so quite consciously and develop declarative memories about our attempts: who helped us learn, where we rode, how we felt, how many times we fell, and so on. But we also form nondeclarative stimulus–response and motor memories; *we learn to ride.* We learn to make automatic adjustments with our hands and bodies that keep our center of gravity above the wheels.

A particularly interesting experiment by Squire et al. (1992) showed that the priming task that I described earlier does not involve the hippocampus but that a test of declarative memory does. Normal subjects were given lists of words to study. Then they were placed in a PET scanner that recorded regional brain activation. They were shown the first three letters of the words and were asked either to say the first word that came to mind (*priming task*) or to use the letter sequences as cues and try to remember the words they had seen on the list (*declarative memory task*). Note that the stimuli were the same in both cases; only the instructions were different.

When the subjects performed the declarative memory task, increased activity was seen in the right hippocampus and right prefrontal cortex. When they performed the priming task, changes were seen in a region of the visual association cortex, but no changes were seen in the hippocampus. (See ***Figure 12.28.***)

Table 12.1 lists the declarative and nondeclarative memory tasks that I have described so far. (See ***Table 12.1.***)

Declarative memory Memory that can be verbally expressed, such as memory for events in a person's past.

Nondeclarative memory Memory whose formation does not depend on the hippocampal formation; a collective term for perceptual, stimulus–response, and motor memory.

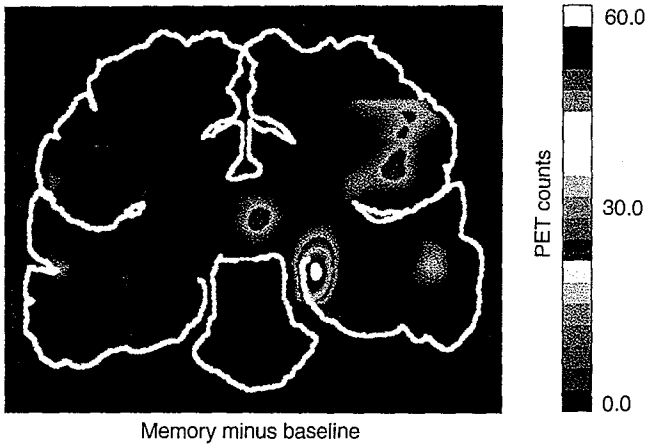


FIGURE 12.28

PET scan of regional cerebral blood flow. The image represents the difference between blood flow during the baseline condition and during performance of the memory task, averaged across fourteen normal subjects. The peak activity (white center ringed by red, yellow, green, and blue) is located in the region of the hippocampal formation and parahippocampal gyrus.

(From Squire, L.R., Ojemann, J.G., Miezin, F.M., Petersen, S.E., Videen, T.O., and Raichle, M.E. Proceedings of the National Academy of Sciences, *1992, 89, 1837–1841. Reprinted with permission.)*

Anterograde Amnesia: Failure of Relational Learning

As we have seen, anterograde amnesia appears to be a loss of the ability to establish new declarative memories; the ability to establish new nondeclarative memories (perceptual, stimulus–response, or motor learning) is intact. What, exactly, are declarative memories? Are they *verbal* memories? Is it simply that people with anterograde amnesia cannot learn new verbal information?

The answer seems to be "no". Declarative memories are not necessarily verbal memories; they are recollections of things or events we have previously experienced. Let's consider the most complex forms of declarative memories: memories of particular episodes. Episodic memories consist of collections of perceptions of events organized in time and identified by a particular context. For example, consider my memory of this morning's breakfast. I put on my robe and slippers, walked downstairs, made coffee, drank some orange juice, made waffle batter, baked a waffle,

TABLE 12.1 Examples of Declarative and Nondeclarative Memory Tasks

DECLARATIVE MEMORY TASKS	
Remembering past experiences	
Learning new works	
Recalling words (DEF___)	
NONDECLARATIVE MEMORY TASKS	**TYPE OF LEARNING**
Broken drawings	Perceptual
Recognizing faces	Perceptual (and stimulus–response?)
Recognizing melodies	Perceptual
Classical conditioning (eyeblink)	Stimulus–response
Instrumental conditioning (choose circle)	Stimulus–response
Mirror drawing	Motor
Pursuit rotor	Motor
Word completion (DEF___)	Stimulus–response

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and ate it at the table next to the window. If I wanted to (and if I thought you were interested), I could give you many more details. The point is that the memory contains many events, organized in time. But would we say that my memory is a *verbal* memory? Clearly not; what I remember about my experience this morning is perceptions of a series of *events*, not a series of *words*. I remember not words but perceptions: the sight of the snow falling outside, the feel of the cold floor replaced by the comfortable warmth of my slippers, the smell of the coffee beans as I opened the container, the rasping sound made by the coffee grinder, and so on.

Obviously, memories must be organized. If you asked me about this morning's breakfast, your words would bring to mind a *set* of perceptual memories—memories of events that occurred at a particular time and place. What does the hippocampal formation have to do with that ability? The most likely explanation is that during the original experience, it somehow ties together a series of perceptions in such a way that their memories, too, are linked. The hippocampal formation enables us to learn the *relation* between the stimuli that were present at the time—the *context* in which the episode occurred—and the events themselves. As we saw, people with anterograde amnesia can form perceptual memories. As the priming studies have shown, once they see something, they are more likely to recognize it later. But their perceptual memories are isolated; the memories of individual objects and events are not tied together or to the context in which they occurred. Thus, seeing a particular person does not remind them of other times they have seen that person or of the things they have done together. Anterograde amnesia appears to be a loss of the ability to learn about the relations among stimuli, including the time and place in which they occurred and the order of their occurrence.

Anatomy of Anterograde Amnesia

The phenomenon of anterograde amnesia and its implications for the nature of relational learning has led investigators to study this phenomenon in laboratory animals. But before I review this research (which has provided some very interesting results), we should examine the brain damage that produces anterograde amnesia. One fact is clear: Damage to the hippocampus, or to regions that supply its inputs and receive its outputs, causes anterograde amnesia.

As we saw earlier in this chapter, the most important input to the hippocampal formation comes from the entorhinal cortex. The entorhinal cortex receives its inputs from the cingulate cortex and all regions of the association cortex, either directly or via two adjacent regions of limbic cortex: the **perirhinal cortex** and the **parahippocampal cortex.** (See ***Figure 12.29.***) It also receives information from the amygdala, which may be responsible for the role that emotions play in memories. The outputs of the hippocampal system are relayed back through the entorhinal, perirhinal, and parahippocampal to the same regions that provide inputs: the cingulate cortex and all regions of the association cortex.

Perirhinal cortex A region of limbic cortex adjacent to the hippocampal formation that, along with the parahippocampal cortex, relays information between the entorhinal cortex and other regions of the brain.

Parahippocampal cortex A region of limbic cortex adjacent to the hippocampal formation that, along with the perirhinal cortex, relays information between the entorhinal cortex and other regions of the brain.

The hippocampal formation also receives input from subcortical regions via the fornix. As far as we know, these inputs select and modulate the functions of the hippocampal formation, but they do not supply it with specific information. (An analogy may make this distinction clearer. An antenna supplies a radio with information that is being broadcast, whereas the on–off switch, the volume control, and the station selector control the radio's functions.) The fornix carries dopaminergic axons from the ventral tegmental area, noradrenergic axons from the locus coeruleus, serotonergic axons from the raphe nuclei, and acetylcholinergic axons from the medial septum.

The clearest evidence that damage to the hippocampal formation produces anterograde amnesia came from a case studied by Zola-Morgan, Squire, and Amaral (1986). Patient R.B., a 52-year-old man with a history of heart trouble, sustained a cardiac arrest. Although his heart was successfully restarted, the period of anoxia caused by the temporary halt in blood flow resulted in brain damage. The primary

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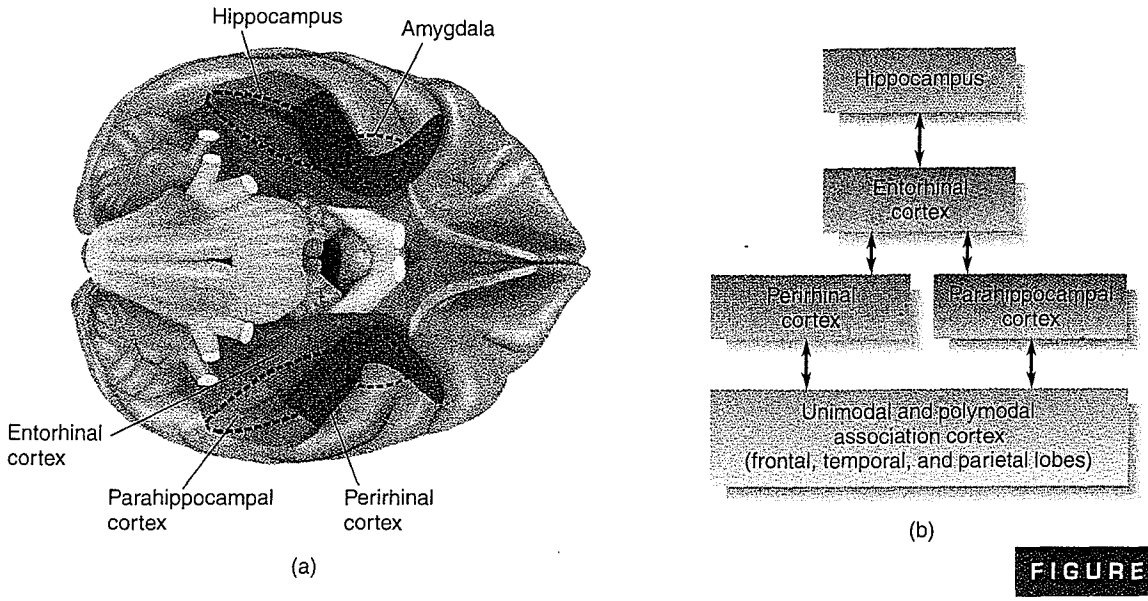

FIGURE 12.29

Cortical connections of the hippocampal formation. (a) A view of the base of a monkey's brain. (b) Connections with the cerebral cortex.

(Adapted from Squire, L.R. Psychological Review, *1992, 99, 195–231.)*

symptom of this brain damage was a permanent anterograde amnesia, which Zola-Morgan and his colleagues carefully documented. Five years after the onset of the amnesia, R.B. died of heart failure. His family gave permission for histological examination of his brain.

The investigators discovered that field CA1 of the hippocampal formation was gone; its neurons had completely degenerated. Subsequent studies reported other patients with anterograde amnesia caused by CA1 damage (Victor and Agamonolis, 1990; Kartsounis, Rudge, and Stevens, 1995; Rempel-Clower et al., 1996). (See ***Figure 12.30.***) In addition, several studies have found that a period of anoxia causes damage to field CA1 in monkeys and in rats and that the damage causes anterograde amnesia in these species, too (Auer, Jensen, and Whishaw, 1989; Zola-Morgan et al., 1992).

Relational Learning in Laboratory Animals

The discovery that hippocampal lesions produced anterograde amnesia in humans stimulated interest in the exact role that this structure plays in the learning process. To pursue this interest, many investigators turned to

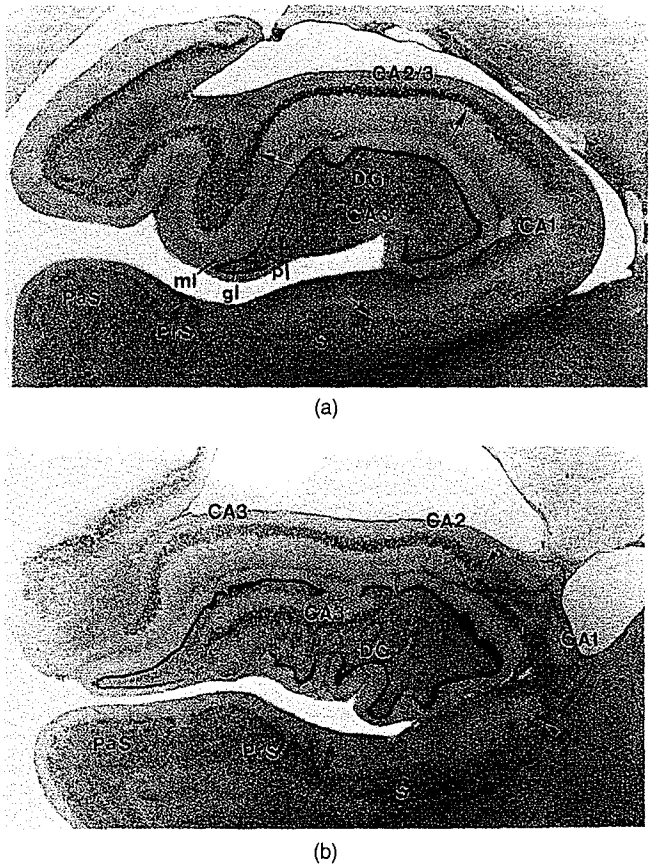

FIGURE 12.30

Damage to field CA1 caused by anoxia. (a) Section through a normal hippocampus. (b) Section through the hippocampus of patient G.D. The pyramidal cells of field CA1 (between the two arrowheads) have degenerated. (DG = dentate gyrus; gl, ml, pl = layers of the dentate gyrus; PaS = parasubiculum; PrS = presubiculum; S = subiculum; F = fornix).

(From Rempel-Clower, N.L., Zola, S.M., Squire, L.R., and Amaral, D.G. Journal of Neuroscience, *1996,* 16, *5233–5255. Reprinted with permission.)*

Circadian Rhythms

BIOLOGICAL CLOCKS

Much of our behavior follows regular rhythms. For example, we saw that the stages of sleep are organized around a 90-minute cycle of REM and slow-wave sleep. The same rhythm continues during the day as the basic rest-activity cycle (BRAC). And, of course, our daily pattern of sleep and waking follows a 24-hour cycle. Finally, many animals display seasonal breeding rhythms in which reproductive behaviors and hormone levels show yearly fluctuations. In recent years, investigators have learned much about the neural mechanisms that are responsible for these rhythms.

Circadian rhythm (*sur kay dee un* or *sur ka dee un*) A daily rhythmical change in behavior or physiological process.

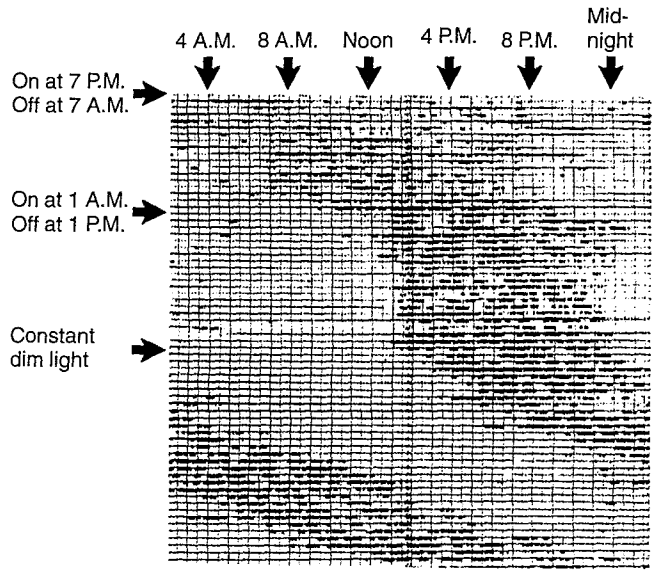

FIGURE 8.21

Wheel-running activity of a rat. Note that the animal's activity occurs at "night" (that is, during the 12 hours the light is off) and that the active period is reset when the light period is changed. When the animal is maintained in constant dim illumination, it displays a free-running activity cycle of approximately 25 hours.

(From Groblewski, T.A., Nuñez, A., and Gold, R.M. Paper presented at the meeting of the Eastern Psychological Association, April 1980.)

Circadian Rhythms and Zeitgebers

Daily rhythms in behavior and physiological processes are found throughout the plant and animal world. These cycles are generally called **circadian rhythms.** (*Circa* means "about," and *dies* means "day"; therefore, a circadian rhythm is one that varies on a cycle of approximately 24 hours.) Some of these rhythms are passive responses to changes in illumination. However, other rhythms are controlled by mechanisms within the organism—by "internal clocks." For example, Figure 8.21 shows the activity of a rat during various conditions of illumination. Each horizontal line represents 24 hours. Vertical tick marks represent the animal's activity in a running wheel. The upper portion of the figure shows the activity of the rat during a normal day–night cycle, with alternating 12-hour periods of light and dark. Notice that the animal is active during the night, which is normal for a rat. (See ***Figure 8.21.***)

Next, the dark–light cycle was shifted by 6 hours; the animal's activity cycle quickly followed the change. (See ***Figure 8.21.***) Finally, dim lights were left on continuously. The cyclical pattern in the rat's activity remained. Because there were no cycles of light and dark in the rat's environment, the source of rhythmicity must be located within the animal; that is, the animal must possess an internal, biological clock. You can see that the rat's clock

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was not set precisely to 24 hours; when the illumination was held constant, the clock ran a bit slow. The animal began its bout of activity almost one hour later each day. (See *Figure 8.21.*)

The phenomenon illustrated in Figure 8.21 is typical of the circadian rhythms shown by many species. A free-running clock, with a cycle a little longer than 24 hours, controls some biological functions—in this case, motor activity. Regular daily variation in the level of illumination (that is, sunlight and darkness) normally keeps the clock adjusted to 24 hours. Light serves as a **zeitgeber** (German for "time giver"); it synchronizes the endogenous rhythm. Studies with many species of animals have shown that if they are maintained in constant darkness (or constant dim light), a brief period of bright light will reset their internal clock, advancing or retarding it, depending upon when the light flash occurs (Aschoff, 1979). For example, if an animal is exposed to bright light soon after dusk, the biological clock is set back to an earlier time—as if dusk had not yet arrived. On the other hand, if the light occurs late at night, the biological clock is set ahead to a later time—as if dawn had already come.

Like other animals, humans exhibit circadian rhythms. Our normal period of inactivity begins several hours after the start of the dark portion of the day–night cycle and persists for a variable amount of time into the light portion. Without the benefits of modern civilization we would probably go to sleep earlier and get up earlier than we do; we use artificial lights to delay our bedtime and window shades to extend our time for sleep. Under constant illumination our biological clocks will run free, gaining or losing time like a watch that runs too slow or too fast. Different people have different cycle lengths, but most people in that situation will begin to live a "day" that is approximately 25 hours long. This works out quite well, because the morning light, acting as a zeitgeber, simply resets the clock.

Zeitgeber (*tsite gay ber*) A stimulus (usually the light of dawn) that resets the biological clock responsible for circadian rhythms.

Suprachiasmatic nucleus (SCN) (*soo pra ky az mat ik*) A nucleus situated atop the optic chiasm. It contains a biological clock responsible for organizing many of the body's circadian rhythms.

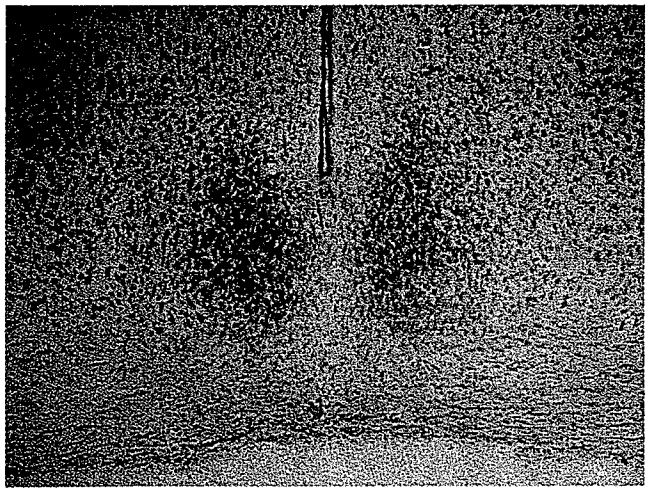
Role of the Suprachiasmatic Nucleus

Researchers working independently in two laboratories (Moore and Eichler, 1972; Stephan and Zucker, 1972) discovered that the primary biological clock of the rat is located in the **suprachiasmatic nucleus (SCN)** of the hypothalamus; they found that lesions disrupted circadian rhythms of wheel running, drinking, and hormonal secretion. The SCN also provides the primary control over the timing of sleep cycles. Rats are nocturnal animals; they sleep during the day and forage and feed at night. Lesions of the SCN abolish this pattern; sleep occurs in bouts that are randomly dispersed throughout both day and night (Ibuka and Kawamura, 1975; Stephan and Nuñez, 1977). However, rats with SCN lesions still obtain the same amount of sleep that normal animals do. The lesions disrupt the circadian pattern but do not affect the total amount of sleep.

FIGURE 8.22

A cross section through a rat brain, showing the location and appearance of the suprachiasmatic nuclei. Cresyl violet stain.

(Courtesy of Geert DeVries, University of Massachusetts.)



Anatomy and Connections

Figure 8.22 shows the suprachiasmatic nuclei in a cross section through the hypothalamus of a rat; they appear as two clusters of dark-staining neurons at the base of the brain, just above the optic chiasm. (See *Figure 8.22.*) The suprachiasmatic nuclei of the rat consist of approximately 10,000 small neurons, tightly packed into a volume of between 0.1 and 0.3 mm^3 (Meijer and Rietveld, 1989). The dendrites of these neurons form synapses with one another—a phenomenon that is found only in this part of the hypothalamus and that probably relates to the special function of these nuclei. A group of neurons is found clustered around the capillaries that serve the SCN. These neurons contain a large amount of rough en-

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doplasmic reticulum, which suggests that they may be neurosecretory cells (Card, Riley, and Moore, 1980; Moore, Card, and Riley, 1980). Thus, some of the control that the SCN exerts over other parts of the brain may be accomplished by the secretion of neuromodulators.

Because light is the primary zeitgeber for most mammals' activity cycles, we would expect that the SCN receives fibers from the visual system. Indeed, anatomical studies have revealed a direct projection of fibers from the retina to the SCN: the *retinohypothalamic pathway* (Hendrickson, Wagoner, and Cowan, 1972; Aronson et al., 1993). If you look carefully at Figure 8.22, you can see small dark spots within the optic chiasm, just ventral and medial to the base of the SCN; these are cell bodies of oligodendrocytes that serve axons that enter the SCN and provide information from the retina. (See ***Figure 8.22.***)

Pulses of light that reset an animal's circadian rhythm trigger the production of Fos protein in the SCN, which indicates that the light initiates a period of neural activity in this nucleus (Rusak et al., 1990, 1992). (The significance of the Fos protein as an indicator of neural activation was discussed in Chapter 5.)

How does the SCN control drinking, eating, sleep cycles, and hormone secretion? Although neurons of the SCN project to several parts of the brain, transplantation studies suggest that the SCN controls some functions by releasing chemical signals. Lehman et al. (1987) destroyed the SCN and then transplanted in their place a new set of suprachiasmatic nuclei obtained from donor animals. The grafts succeeded in reestablishing circadian rhythms, even though very few efferent connections were observed between the graft and the recipient's brain. Even more convincing evidence comes from a transplantation study by Silver et al. (1996). Silver and her colleagues first destroyed the SCN in a group of hamsters, abolishing their circadian rhythms. Then, a few weeks later, they removed SCN tissue from donor animals and placed it in very small semipermeable capsules, which they then implanted in the animals' third ventricles. Nutrients and other chemicals could pass through the walls of the capsules, keeping the SCN tissue alive, but the neurons inside the capsules were not able to establish synaptic connections with the surrounding tissue. Nevertheless, the transplants reestablished circadian rhythms in the recipient animals.

The Nature of the Clock

All clocks must have a time base. Mechanical clocks use flywheels or pendulums; electronic clocks use quartz crystals. The SCN, too, must contain a physiological mechanism that parses time into units. After years of research, investigators are finally beginning to discover the nature of the biological clock in the SCN.

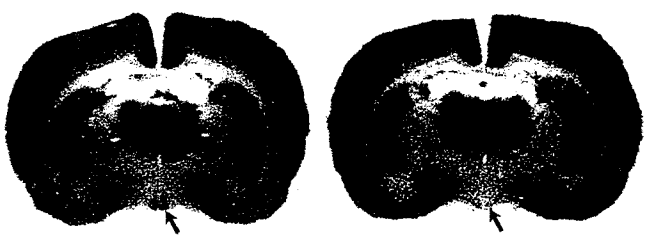
Several studies have demonstrated daily activity rhythms in the SCN, which indicates that the circadian clock is located there. A study by Schwartz and Gainer (1977) nicely demonstrated day–night fluctuations in the activity of the SCN. These investigators injected rats with radioactive 2-deoxyglucose (2-DG). As you will recall from Chapter 5, this chemical is structurally similar to ordinary glucose; thus, it is taken up by cells that are metabolically active. However, it cannot be utilized, nor can it leave the cell. Therefore, metabolically active cells will accumulate radioactivity.

Schwartz and Gainer injected some rats with radioactive 2-DG during the day and injected others at night. The animals were then killed, and autoradiographs of cross sections through the brain were prepared. Figure 8.23 shows photographs of two of these cross sections. Note the evidence of radioactivity (and hence a high metabolic rate) in the SCN of the brain that was injected during the day (*left*). (See ***Figure 8.23.***)

FIGURE 8.23

Autoradiographs of cross sections through the brains of rats that had been injected with carbon-14-labeled 2-deoxyglucose during the day (*left*) and the night (*right*). The dark region at the base of the brain (*arrows*) indicates increased metabolic activity of the suprachiasmatic nuclei.

(From Schwartz, W.J., and Gainer, H. Science, 1977, 197, 1089–1091. Reprinted with permission. Copyright 1977 by the American Association for the Advancement of Science.)



The "ticking" of the biological clock within the SCN could involve interactions of circuits of neurons, or it could be intrinsic to individual neurons themselves. Evidence suggests the latter—that each neuron contains a clock. For example, Welsh et al. (1995) removed tissue

from the rat SCN and dissolved the connections between the cells with papain, an enzyme that is sometimes used as a meat tenderizer. They kept the cells alive in a culture medium. Recordings from an array of microelectrodes showed that the neurons displayed individual, independent circadian rhythms in activity. Figure 8.24 shows the activity cycles of four neurons. As you can see, all showed circadian rhythms, but their periods of peak activity occurred at different times of day. (In an intact brain, of course, something synchronizes the activity of the SCN neurons.) (See ***Figure 8.24.***)

What causes SCN neurons to "tick"? Researchers have uncovered some of the details of one mechanism so far—that of the circadian clock of *Drosophila melanogaster*, the common fruit fly (Hunterensor, Ousley, and Sehgal, 1996; Lee et al., 1996; Myers et al., 1996; Zeng et al., 1996). It appears that in this species, circadian rhythms are produced by the production of two proteins, PER and TIM, that inhibit their own production when they reach a certain level in the cell. As a result, the levels of the proteins decline, which removes the inhibition and starts the production cycle again. One of these proteins, TIM, may be involved in mediating the effects of a zeitgeber.

What about the mammalian clock? Is this mechanism peculiar to insects, or do cells in the SCN work this way, too? Although it is too early to say, it does appear that a PER-like protein is produced in the rat SCN (Rosewell, Siwicki, and Wise, 1994). We will have to await the results of further research.

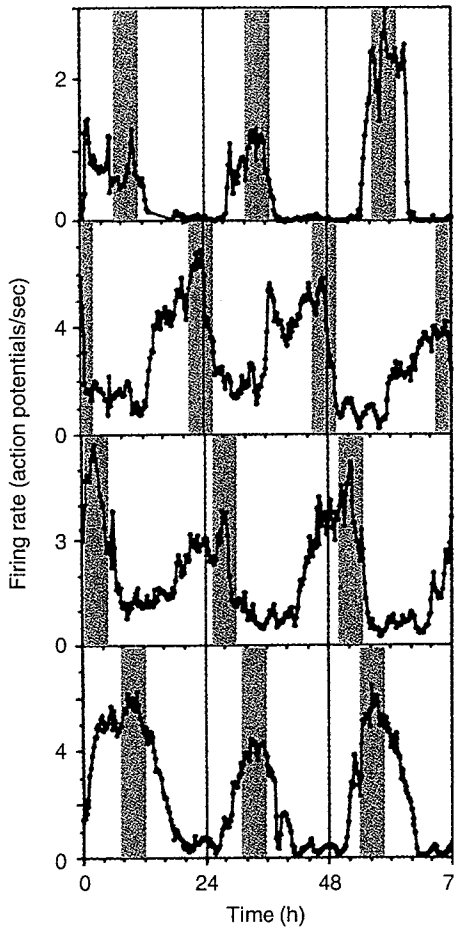


FIGURE 8.24

Firing rate of individual SCN neurons in a tissue culture. Color bars have been added to emphasize the daily peaks. Note that although each neuron has a period of approximately one day, their activity cycles are not synchronized.

(From Welsh, D.K., Logothetis, D.E., Meister, M., and Reppert, S.M. Neuron, *1995, 14, 697–706. Copyright 1995 Cell Press. Reprinted by permission.)*

Control of Seasonal Rhythms: The Pineal Gland and Melatonin

Although the SCN has an intrinsic rhythm of approximately 24 hours, it plays a role in much longer rhythms. (We could say that it is involved in a biological calendar as well as a biological clock.) Male hamsters show annual rhythms of testosterone secretion, which appear to be based on the amount of light that occurs each day. Their breeding season begins as the day length increases and ends when it decreases. Lesions of the SCN abolish these annual breeding cycles; the animals' testes then secrete testosterone all year (Rusak and Morin, 1976). Possibly, the lesions disrupt these annual cycles because they destroy the 24-hour clock against which the daily light period is measured to determine the season. That is, if the light period is considerably shorter than 12 hours, the season is winter; if it is considerably longer than 12 hours, the season is summer.

The control of seasonal rhythms involves another part of the brain: the **pineal gland** (Bartness et al., 1993; Moore, 1995). This structure sits on top of the midbrain, just in front of the cerebellum. (See ***Figure 8.25.***) The pineal gland secretes a hormone called **melatonin,** so named because it has the ability in certain animals (primarily fish, reptiles, and amphibians) to turn the skin temporarily dark. (The dark color is produced by a chemical known as *melanin.*) In mammals, melatonin controls seasonal rhythms. Neurons in the SCN make synaptic connections with neurons in the *paraventricular nucleus of the hypothalamus* (the PVN). The axons of these neurons travel all the way to the spinal cord, where they form synapses with preganglionic neurons of the sympathetic nervous system. The postganglionic neurons innervate the pineal gland and control the secretion of melatonin.

In response to input from the SCN, the pineal gland secretes melatonin during the night. This melatonin acts back on various structures in the brain (including the SCN, whose cells contain melatonin receptors) and controls hormones, physiological processes, and behaviors that show seasonal variations. During long nights a large amount of melatonin is secreted, and the animals go into the winter phase of their cycle. Lesions of the SCN, the paraventricular nucleus (PVN), or the pineal gland

Pineal gland (*py nee ul*) A gland attached to the dorsal tectum; produces melatonin and plays a role in circadian and seasonal rhythms.

Melatonin (*mell a tone in*) A hormone secreted during the night by the pineal body; plays a role in circadian and seasonal rhythms.

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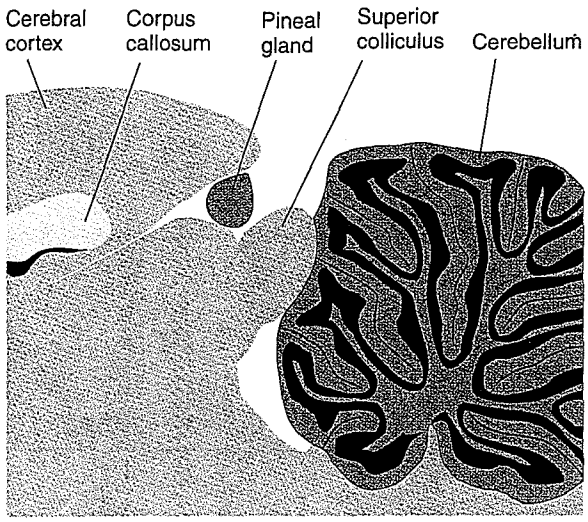


FIGURE 8.25

The pineal gland, located on the dorsal surface of the midbrain.

(Adapted from Paxinos, G., and Watson, C. The Rat Brain in Stereotaxic Coordinates. *Sydney: Academic Press, 1982.)*

disrupt seasonal rhythms that are controlled by day length—and so do knife cuts that interrupt the neural connection between the SCN and the PVN, which indicates that this is one function of the SCN that is mediated through its neural connections with another structure. Furthermore, although transplants of fetal suprachiasmatic nuclei will restore circadian rhythms, they will not restore seasonal rhythms, because the transplanted tissue does not establish neural connections with the PVN (Ralph and Lehman, 1991).

Changes in Circadian Rhythms: Shift Work and Jet Lag

When people abruptly change their daily rhythms of activity, their internal circadian rhythms, controlled by the SCN, become desynchronized with those in the external environment. For example, if a person who normally works on the day shift begins working on a night shift or if someone travels east or west across several time zones, his or her SCN will signal the rest of the brain that it is time to sleep during the work shift (or the middle of the day, in the case of jet travel). This disparity between internal rhythms and the external environment results in sleep disturbances and mood changes and interferes with people's ability to function during waking hours.

Jet lag is a temporary phenomenon; after several days, people who have crossed several time zones find it easier to fall asleep at the appropriate time, and their daytime alertness improves. Shift work can present a more enduring problem when people are required to change shifts frequently. Obviously, the solution to jet lag and to the problems caused by shift work is to get the internal clock synchronized with the external environment as quickly as possible. The most obvious way to start is to try to provide strong zeitgebers at the appropriate time. If a person is exposed to bright light before the low point in the daily rhythm of body temperature (which occurs an hour or two before the person usually awakens), the person's circadian rhythm is delayed. If the exposure to bright light occurs after the low point, the circadian rhythm is advanced (Dijk et al., 1995). In fact, several studies have shown that exposure to bright lights at the appropriate time helps to ease the transition (Boulos et al., 1995). Houpt, Boulos, and Moore-Ede (1996) have even developed a computer program that helps to determine the optimal pattern of light exposure to minimize the effects of jet travel between various parts of the world. Similarly, people adapt to shift work more rapidly if artificial light is kept at a brighter level and if their bedroom is kept as dark as possible (Eastman et al., 1995).

As we saw in the previous subsection, the role of melatonin in seasonal rhythms is well established. Studies in recent years suggest that melatonin may also be involved in circadian rhythms. As we saw, melatonin is secreted during the night, which, for diurnal mammals such as ourselves, is the period during which we sleep. But although our species lacks strong seasonal rhythms, the daily rhythm of melatonin secretion persists. Thus, melatonin must have some functions besides regulation of seasonal rhythms.

Recent studies have found that melatonin, acting on receptors in the SCN, can affect the sensitivity of SCN neurons to zeitgebers and can itself alter circadian rhythms (Gillette and McArthur, 1995; Starkey et al., 1995). Researchers do not yet understand exactly what role melatonin plays in the control of circadian rhythms, but they have already discovered practical applications. Melatonin secretion normally reaches its highest levels early in the night, at around bedtime. Investigators have found that the administration of melatonin at the appropriate time (in most cases, just before going to bed) significantly reduces the adverse effects of both jet lag and shifts in work sched-

Researchers are beginning to understand the role of the suprachiasmatic nucleus and the pineal gland in phenomena such as jet lag.

ules (Arendt et al., 1995; Deacon and Arendt, 1996). Bedtime melatonin has even helped to synchronize circadian rhythms and improved the sleep of blind people for whom light cannot serve as a zeitgeber (Skene, Deacon, and Arendt, 1996).

INTERIM SUMMARY

Our daily lives are characterized by cycles in physical activity, sleep, body temperature, secretion of hormones, and many other physiological changes. Circadian rhythms—those with a period of approximately one day—are controlled by biological clocks in the brain. The principal biological clock appears to be located in the suprachiasmatic nuclei of the hypothalamus; lesions of these nuclei disrupt most circadian rhythms, and the activity of neurons located there correlates with the day–night cycle. Light serves as a zeitgeber for most circadian rhythms. That is, the biological clocks tend to run a bit slow, with a period of approximately 25 hours. The sight of sunlight in the morning is conveyed from the retina to the SCN—directly and via the IGL of the lateral geniculate nucleus. The effect of the light is to reset the clock to the start of a new cycle.

Individual neurons, rather than circuits of neurons, are responsible for the "ticks." Studies with tissue cultures suggest that synchronization of the firing patterns of individual neurons is accomplished by means of chemical communication between cells, perhaps involving astrocytes. In the fruit fly, two genes, *tim* and *per*, are responsible for circadian rhythms. These genes' proteins (TIM and PER) bind, travel to the nucleus, and inhibit further protein synthesis until they disintegrate and the cycle begins again.

The SCN and the pineal gland control annual rhythms. During the night the SCN signals the pineal gland to secrete melatonin. Prolonged melatonin secretion, which occurs during winter, causes the animals to enter the winter phase of their annual cycle. Melatonin also appears to be involved in synchronizing circadian rhythms: The hormone can help people to adjust to the effects of shift work or jet lag and even synchronize the daily rhythms of blind people for whom light cannot serve as a zeitgeber.

IN HORMONES WE TRUST

Experiments show oxytocin stimulates trusting behavior.

By JOSEPH B. VERRENGIA
THE ASSOCIATED PRESS

It sounds like the plot for another Batman sequel: The villain sprays Gotham City with a trust hormone and people rush to give him all their money. Banks, the stock market and even governments collapse.

Farfetched? Swiss and American scientists demonstrate in new experiments how a squirt of the hormone oxytocin stimulates trusting behavior in humans, and they acknowledge that the possibility of abuse can't be ignored.

"Of course, this finding could be misused," said Ernst Fehr of the University of Zurich, the senior researcher in the study, which appears in today's issue of the journal Nature. "I don't think we currently have such abuses."

Other scientists say the new research raises important questions about oxytocin's therapeutic potential for conditions such as autism, in which trust is diminished. Or perhaps the hormone's activity could be reduced to treat more rare diseases, such as Williams syndrome, in which children approach strangers fearlessly.

Oxytocin is secreted in brain tissue and synthesized by the hypothalamus. This small-but-crucial feature located deep in the brain controls biological reactions such as hunger, thirst and body temperature, as well as visceral fight-or-flight reactions associated with powerful, basic emotions such as fear and anger.

For years oxytocin was considered to be a straightforward reproductive hormone found in both sexes. In both humans and animals, this chemical messenger stimulates uterine contractions in labor and induces milk production. In both women and men, oxytocin is released during sex, too.

Then, elevated concentrations of the hormone also were found in cerebrospinal fluid during and after birth. Experiments showed it was involved in the biochemistry of attachment. It's a sensible conclusion, given that babies require years of care and the body needs to motivate mothers for the demanding task of child-rearing.

In recent years, scientists have wondered whether oxytocin also is generally involved with other aspects of bonding behavior – and specifically whether it stimulates trust.

Trust is the glue of society and human interactions. Erase it, and you compromise everything from love to trade and political order.

"I once likened trust to a love potion," Damasio writes in Nature. "Add trust to the mix, for without trust there is no love."

In the experiments, the researchers tried to manipulate people's trust by adding more oxytocin to their brains. They used a synthetic version in a nasal spray that was absorbed by mucous membranes and crossed the blood-brain barrier. Researchers say the dose was harmless and altered oxytocin levels only temporarily.

A total of 178 male students from universities in Zurich took part in a pair of experiments. All the volunteers were in their 20s. They got the oxytocin or a placebo.

In the first experiment, they played a game in which an "investor" could choose to hand over to a "trustee" up to 12 units of money that are each equal to .40 Swiss franc, or about 32 cents. The trustee triples the investor's money, then gets to decide how much of the proceeds to share.

Of 29 subjects who got oxytocin, 45 percent invested the maximum amount of 12 monetary units and, according to the researchers, showed "maximal trust." Only 21 percent had a lower trust level in which they invested fewer than 8 monetary units.

In contrast, the placebo group's trust behavior was reversed. Only 21 percent of the placebo subjects invested the maximum, while 45 percent invested at low levels.

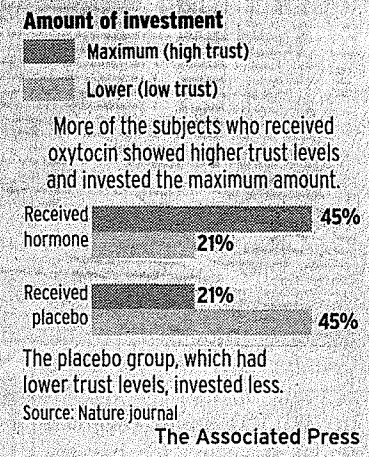
Overall, those who got oxytocin invested 17 percent more than investors who received a placebo.

"Oxytocin causes a substantial increase in trusting behavior," Fehr and his colleagues reported.

Researchers said they are performing a new round of experiments using brain imaging. "Now that we know that oxytocin has behavioral effects," Fehr said, "we want to know the brain circuits behind these effects."

A test of trust

In experiments with a nasal spray containing the hormone oxytocin, human subjects were significantly more trusting and willing to invest money.



The placebo group, which had lower trust levels, invested less.

Source: Nature journal

The Associated Press

Orange County Register
June 2, 2006

Menopause in a Mayan Village

Because menopause is both a physiological and a psychological event, its impact on a woman reflects an interplay of biological processes and personal expectations (Robinson, 1996). Women who expect menopause to be very distressing tend to have more symptoms (Matthews, 1992), and many of these expectations depend on culture. Indeed, the experience of menopause differs substantially across cultures.

One researcher studied 100 pre-, peri- (that is, during), and postmenopausal women in a rural Mayan Indian village in Yucatan, Mexico (Beyenne, 1986). Mayan women marry and begin having children in their teens. They are frequently grandmothers in their 30s, and the onset of menopause typically occurs in the 30s or early 40s. As in many traditional societies, old age is a period of power and respect, particularly for women, who become the head of the extended family households of their married sons.

The Mayans believe that menstruating women carry danger. Women therefore stay home during their menstrual periods to avoid contaminating other people, particularly newborn babies. Not surprisingly, Mayan women are glad when menopause lifts the restrictions and taboos. Premenopausal women reported looking forward to menopause and did not expect any adverse physical or psychological effects. Peri- and postmenopausal women, like others in the community, were unfamiliar with the concept of hot flashes, and local physicians, midwives, and healers reported that they had never treated any women of the village for menopause-related symptoms.

The absence of a common physical symptom of menopause, hot flashes, could be attributed to many causes, from the psychological to the physical (such as bearing a large number of babies and early onset of menopause). Cross-cultural research suggests that the presence of hot flashes varies tremendously from culture to culture. Fifty to 80 percent of European and North American women report hot flashes, whereas these experiences are unusual in Japan and India (Hulka & Meirik, 1996; Robinson, 1996). The experience of menopause among the Mayans underscores the role of culture in shaping what may at first seem strictly a matter of biological maturation.

Midlife Changes in Men

The term *male menopause* is part of the American vernacular, although male reproductive ability does not undergo any specific or dramatic period of physical change. Healthy men can produce sperm and engage in sexual activity as long as they live, although male sexuality does change gradually with age. Sexual desire from the 40s to the 70s shows substantial declines as testosterone levels drop (Schiavi et al., 1990; see also Module 24). The ability to sense touch and vibration in the penis also diminishes with age and is correlated with reduced sexual activity (see Johnson & Murray, 1992).

As with women, however, individual differences are substantial, and men can enjoy sexuality through their 90s if they live that long and have an available partner. (In fact, men in retirement communities often report very active sex lives because the ratio of women to men in old age is so high!) Contrary to youthful stereotypes, masturbation is also a lifelong affair for many men and women (Gibson, 1996).

The New York Times

September 12, 2011

In Study, Fatherhood Leads to Drop in Testosterone

By PAM BELLUCK

This is probably not the news most fathers want to hear. Testosterone, that most male of hormones, takes a dive after a man becomes a parent. And the more he gets involved in caring for his children — changing diapers, jiggling the boy or girl on his knee, reading "Goodnight Moon" for the umpteenth time — the lower his testosterone drops.

So says the first large study measuring testosterone in men when they were single and childless and several years after they had children. Experts say the research has implications for understanding the biology of fatherhood, hormone roles in men and even health issues like prostate cancer.

"The real take-home message," said Peter Ellison, a professor of human evolutionary biology at Harvard who was not involved in the study, is that "male parental care is important. It's important enough that it's actually shaped the physiology of men."

"Unfortunately," Dr. Ellison added, "I think American males have been brainwashed" to believe lower testosterone means that "maybe you're a wimp, that it's because you're not really a man. "My hope would be that this kind of research has an impact on the American male. It would make them realize that we're meant to be active fathers and participate in the care of our offspring."

The study, experts say, suggests that men's bodies evolved hormonal systems that helped them commit to their families once children were born. It also suggests that men's behavior can affect hormonal signals their bodies send, not just that hormones influence behavior. And, experts say, it underscores that mothers were meant to have child care help.

"This is part of the guy being invested in the marriage," said Carol Worthman, an anthropologist at Emory University who also was not involved in the study. Lower testosterone, she said, is the father's way of saying, " 'I'm here, I'm not looking around, I'm really toning things down so I can have good relationships.' What's great about this study is it lays it on the table that more is not always better. Faster, bigger, stronger — no, not always."

Experts said the study was a significant contribution to hormone research because it tested men before and after becoming fathers and involved many participants: 600 men in the Cebu Province of the Philippines who are participating in a larger, well-respected health study following babies who were born in 1983 and 1984.

Testosterone was measured when the men were 21 and single, and again nearly five years later. Although testosterone naturally decreases with age, men who became fathers showed much greater declines, more than double that of the childless men. And men who spent more than three hours a day caring for children — playing, feeding, bathing, toileting, reading or dressing them — had the lowest testosterone.

"It could almost be demonized, like, 'Oh my God, fathers, don't take care of your kids because your testosterone will drop way down,' " said Lee Gettler, an anthropologist at Northwestern University and co-author of the study, published in The Proceedings of the National Academy of Sciences. "But this should be viewed as, 'Oh it's great, women aren't the only ones biologically adapted to be parents.'

"Humans give birth to incredibly dependent infants. Historically, the idea that men were out clubbing large animals and women were staying behind with babies has been largely discredited. The only way mothers could have highly needy offspring every couple of years is if they were getting help."

Smaller studies, measuring just snapshots in time, found fathers have lower testosterone, but they could not establish whether fatherhood brought testosterone down or lower-testosterone men were just more likely to become fathers. In the new study, said Christopher Kuzawa, a co-author and Northwestern anthropologist, having higher testosterone to start with "actually predicted that they're more likely to become fathers," possibly because men with higher testosterone were more assertive in competing for women or appeared healthier and more attractive. But regardless of initial testosterone level, after having children, the hormone plummeted.

Scientists say this suggests a biological trade-off, with high testosterone helping secure a mate, but reduced testosterone better for sustaining family life.

"A dad with lower testosterone is maybe a little more sensitive to cues from his child, and maybe he's a little less sensitive to cues from a woman he meets at a restaurant," said Peter Gray, an anthropologist at the University of Nevada, Las Vegas, who has conducted unrelated research on testosterone in fathers.

The study did not examine specific effects on men's behavior, like whether those with smaller drops in testosterone were more likely to be neglectful or aggressive. It also did not examine the roles played by other hormones or whether factors like stress or sleeplessness contributed to a decline in testosterone.

Other studies have suggested, though not as definitively, that behavior and relationships affect testosterone levels. A study of Air Force veterans showed that testosterone climbed back up after men were divorced. A study of Harvard Business School students found that those in committed romantic relationships had lower testosterone than those who were not. Another study found that fathers in a Tanzanian group known for involved parenting had low testosterone, while those from a neighboring culture without active fathering did not.

Similar results have been found in birds and in mammals like marmosets, said Toni Ziegler, a senior scientist at the Wisconsin National Primate Research Center.

Experts say the new testosterone study could offer insight into men's medical conditions, particularly prostate cancer. Higher lifetime testosterone levels increase the risk of prostate cancer, just as higher estrogen exposure increases breast cancer risk.

"Fathers who spend a lot of time in fathering roles might have lower long-term exposure to testosterone," reducing their risk, Dr. Ellison said.

Many questions remain. Does testosterone, which appeared to decline most steeply in fathers during their child's first month, rebound as children become older and less dependent? How often do levels fluctuate?

They did not change before and after a play session with children, researchers found. But do they rise when fathers are at work and decrease on weekends? And are only biological fathers affected, or would similar results occur "if you have an uncle or brother or stepfather living in the household and they care for the baby?" asked Sarah B. Hrdy, the primatologist and author of "Mothers and Others."

The lowering of their testosterone did not prevent the men in the study from having more children. "You don't need a lot of testosterone to have libido," Dr. Kuzawa said.

"If guys are worried about basically, 'Am I going to remain a guy?' " Dr. Worthman said, "we're not talking about changes that are going to take testosterone outside the range of having hairy chests, deep voices and big muscles and sperm counts. These are more subtle effects."

And, as Dr. Gray wrote in a commentary accompanying the study, "The descent of a man's testosterone may even be welcomed by some, perhaps his progeny."

BEHAVIORAL CHANGES accompany motherhood in virtually all female mammals. New research suggests that hormone-induced alterations of the female brain may make mothers more vigilant, nurturing and attuned to the needs of their young, as well as improve their spatial memory and learning.

THE MATERNAL BRAIN

Pregnancy and motherhood change the structure of the female mammal's brain, making mothers attentive to their young and better at caring for them

By CRAIG HOWARD KINSLEY and KELLY G. LAMBERT

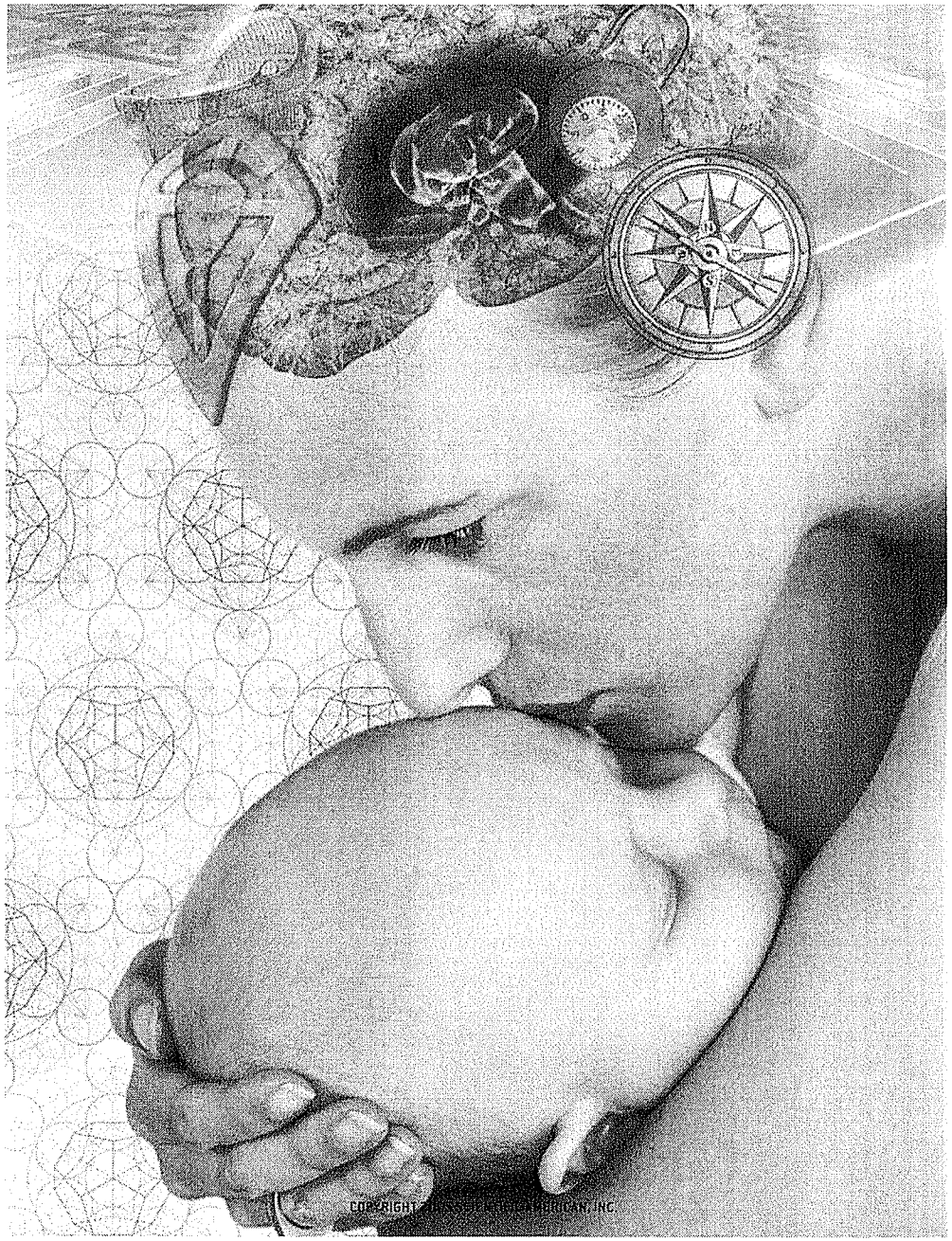
Mothers are made, not born. Virtually all female mammals, from rats to monkeys to humans, undergo fundamental behavioral changes during pregnancy and motherhood. What was once a largely self-directed organism devoted to its own needs and survival becomes one focused on the care and well-being of its offspring. Although scientists have long observed and marveled at this transition, only now are they beginning to understand what causes it. New research indicates that the dramatic hormonal fluctuations that occur during pregnancy, birth and lactation may remodel the female brain, increasing the size of neurons in some regions and producing structural changes in others.

Some of these sites are involved in regulating maternal behaviors such as building nests, grooming young and protecting them from predators. Other affected regions, though, control memory, learning, and responses to fear and stress. Recent experiments have shown that mother rats outperform virgins in navigating mazes and capturing prey. In addition to motivating females toward caring for their offspring, the hormone-induced brain changes may enhance a mother rat's foraging abilities, giving her pups a better chance of survival. What is more, the cognitive benefits appear to be long-lasting, persisting until the mother rats enter old age.

Although studies of this phenomenon have so far focused on rodents, it is likely that human females also gain long-lasting mental benefits from motherhood. Most mammals share similar maternal behaviors, which are probably controlled by the same brain regions in both humans and rats. In fact, some researchers have suggested that the development of maternal behavior was one of the main drivers for the evolution of the mammalian brain. As mammals arose from their reptile forebears, their reproductive strategy shifted from drop-the-eggs-and-flee to defend-the-nest, and the selective advantages of the latter approach may have favored the emergence of hormonal brain changes and the resulting beneficial behaviors. The hand—or paw—that rocks the cradle indeed rules the world.

Awash in Hormones

HALF A CENTURY AGO scientists found the first hints that the hormones of pregnancy spur a female mammal's ardor for



JUSTINE COOPER

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its offspring. Starting in the 1940s, Frank A. Beach of Yale University showed that estrogen and progesterone, the female reproductive hormones, regulate responses such as aggression and sexuality in rats, hamsters, cats and dogs. Further pioneering work by Daniel S. Lehrman and Jay S. Rosenblatt, then at the Institute of Animal Behavior at Rutgers University, demonstrated that the same hormones were required for the display of maternal behavior in rats. In 1984 Robert S. Bridges, now at the Tufts Cummings School of Veterinary Medicine, reported that the production of estrogen and progesterone increased at certain points during pregnancy and that the appearance of maternal behavior depended on the interplay of the hormones and their eventual decrease. Bridges and his colleagues went on to show that prolactin, the lactation-inducing hormone, stimulated maternal behavior in female rats already primed with progesterone and estrogen.

Besides hormones, other chemicals affecting the nervous system appear to play a role in triggering motherly impulses. In 1980 Alan R. Gintzler of the State University of New York Downstate Medical Center reported increases in endorphins—painkilling proteins produced by the pituitary gland and the brain region called the hypothalamus—over the course of a rat's pregnancy, especially just before birth. In addition to preparing the mother for the discomfort of birth, the endorphins may initiate maternal behavior. Taken together, the data demonstrate that the regulation of this behavior requires the coordination of many hormonal and neurochemical systems and that the female brain is exquisitely responsive to the changes that occur with pregnancy.

Scientists have also identified the brain regions that govern maternal behavior. Michael Numan and Marilyn Numan of Boston College have shown that a part of the hypothalamus in the female brain, the medial preoptic area (mPOA), is largely responsible for this activity; creating a lesion in the mPOA or injecting morphine into the region will disrupt the characteristic behavior of mother rats. But other areas of the brain are also involved [*see box on opposite page*], and each of these sites is rife with receptors for hormones and other neurochemicals. Noted neuroscientist Paul MacLean of the National Institute of Mental Health has proposed that the neural pathways from the thalamus, the brain's relay station, to the cingulate cortex, which regulates emotions, are an important part of the maternal behavior system. Damaging the cingulate cortex in mother rats eliminates their maternal behavior. In his 1990 book *The Triune Brain in Evolution*, MacLean hypothesized that the development of these pathways helped to shape the mammalian brain as it evolved from the simpler reptilian brain.

Interestingly, once the reproductive hormones initiate the maternal response, the brain's dependency on them seems to diminish, and the offspring alone can stimulate maternal behavior. Although a newly born mammal is a demanding little creature, unappealing on many levels—it is smelly, helpless and sleeps only intermittently—the mother's devotion to it is the most motivated of all animal displays, exceeding even sexual behavior and feeding. Joan I. Morrell of Rutgers has suggested that the offspring themselves may be the reward that reinforces maternal behavior. When given the choice between cocaine and newly born pups, mother rats choose pups.

Craig Ferris of the University of Massachusetts Medical School recently studied the brains of lactating mother rats using functional magnetic resonance imaging (fMRI), a noninvasive technique that tracks changes in brain activity. Ferris found that activity in the mother's nucleus accumbens, a site that is integral to reinforcement and reward, increased significantly when she nursed her pups. And Ronald J. Gandelman of Rutgers has shown that when a mother mouse is given the opportunity to receive foster pups—the mouse presses a bar in her cage, causing the pups to slide down a chute—the mother will keep pressing the bar until her cage fills with the squirming, pink objects.

Several researchers have hypothesized that as suckling pups attach to their mother's nipples, they may release tiny amounts of endorphins in the mother's body. These natural painkillers may act somewhat like an opiate drug, drawing the mother again and again to contact with her pups. Suckling and pup contact also release the hormone oxytocin, which may have a similar effect on the mother. Lower mammalian species such as mice and rats, which most likely lack the lofty principles and motivations of humans, may care for their pups for the simple reason that it feels good to do so.

But what about the motivations of the human mother? Jeffrey P. Lorberbaum of the Medical University of South Carolina has used fMRI to examine the brains of human moms as they listened to their babies cry. The patterns of activity were similar to those of the rodent mothers, with the mPOA region of the hypothalamus and the prefrontal and orbitofrontal cortices all lighting up. Furthermore, Andreas Bartels and Semir Zeki of University College London found that the brain areas that regulate reward became activated when human moms merely gazed at their children. The similarity between the human and rodent responses suggests the existence of a general maternal circuit in the mammalian brain.

When given the choice between cocaine and newly born pups, mother rats choose pups.

Overview/*Mother Wit*

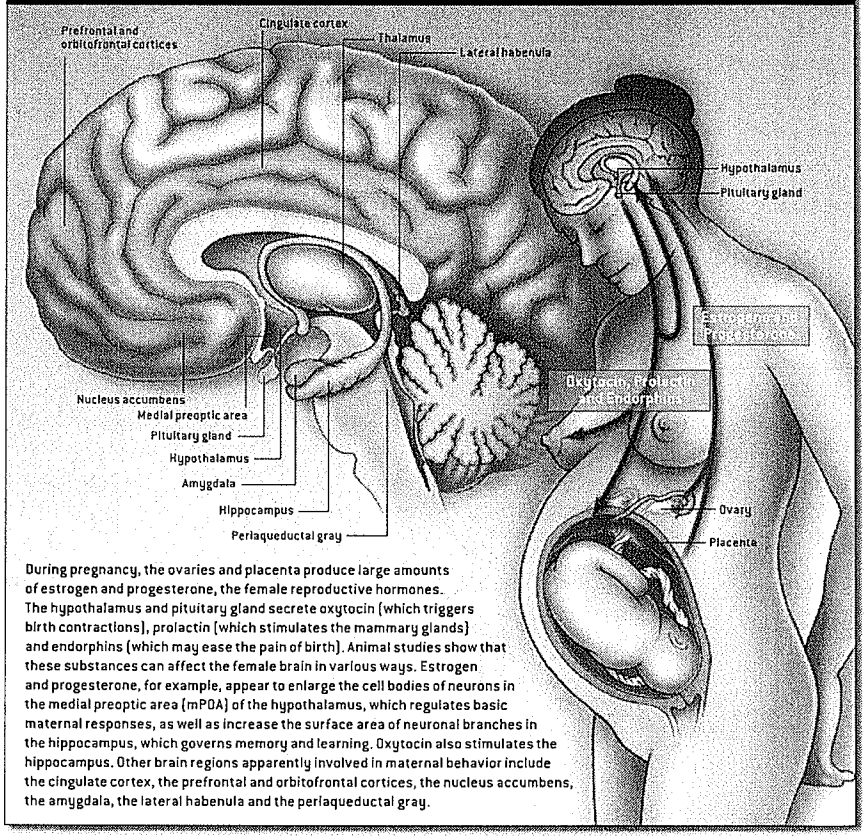
- Studies of rodents have shown that the hormones of pregnancy trigger changes not only in the brain regions governing maternal behavior but also in areas that regulate memory and learning.
- These brain changes may explain why mother rats are better than virgins at navigating mazes and capturing prey.
- Researchers are now investigating whether human females also gain mental benefits from motherhood.

Brain Changes

TO UNDERSTAND THE WORKINGS of this circuit, researchers have studied how the female brain changes at different reproductive stages. In the 1970s Marian C. Diamond of the University of California, Berkeley, provided some of the earliest evidence while investigating the cortices of pregnant rats. The outermost layer of the brain, the cortex receives and processes sensory information and also controls voluntary movements. Rats raised in enriched sensory environments, surrounded by wheels, toys and tunnels, typically develop more intricately folded cortices than rats housed in bare cages. Diamond, however, found that the cortices of pregnant rats from impoverished environments were just as complex as those of the female rats from enriched settings. She concluded that some combination of hormones and fetus-related factors were most likely stimulating the pregnant rats' brains.

Two decades later, after studies demonstrated the importance of the mPOA to maternal behavior, investigators began

THINKING FOR TWO



During pregnancy, the ovaries and placenta produce large amounts of estrogen and progesterone, the female reproductive hormones. The hypothalamus and pituitary gland secrete oxytocin (which triggers birth contractions), prolactin (which stimulates the mammary glands) and endorphins (which may ease the pain of birth). Animal studies show that these substances can affect the female brain in various ways. Estrogen and progesterone, for example, appear to enlarge the cell bodies of neurons in the medial preoptic area (mPOA) of the hypothalamus, which regulates basic maternal responses, as well as increase the surface area of neuronal branches in the hippocampus, which governs memory and learning. Oxytocin also stimulates the hippocampus. Other brain regions apparently involved in maternal behavior include the cingulate cortex, the prefrontal and orbitofrontal cortices, the nucleus accumbens, the amygdala, the lateral habenula and the periaqueductal gray.

TAMI TOLPA

looking for changes to that brain region. In the mid-1990s Lori Keyser, a researcher in one of our laboratories (Kinsley's) at the University of Richmond, showed that the cell bodies of the neurons in the mPOA of pregnant rats increase in volume. What is more, the length and number of dendrites (the signal-receiving branches extending from the cell body) in mPOA neurons increase as the pregnancy progresses. The same changes were also observed in female rats treated with a pregnancy-mimicking regimen of progesterone and estradiol, the most powerful of the natural estrogens. These neuronal alterations typically accompany a rise in protein synthesis and activity. In essence, the hormones of pregnancy "rev up" the mPOA neurons in anticipation of birth and the demands of motherhood. The nerve cells are like thoroughbreds straining at the starting gate, awaiting their release for the race. After birth, the mPOA neurons direct the mother's attention and motivation to her offspring, enabling her to care for, protect and nurture her progeny with the panoply of behaviors known collectively as maternal.

Maternal behavior encompasses many facets beyond the direct care of offspring, however, so it occurred to us that other brain regions might also undergo changes. For instance, a mother rat has to take risks to tend her nest and young. She must frequently leave the relative safety of the nest to forage for food, making herself and her helpless offspring more vulnerable to predators, because if she stays in the nest, she and her brood will slowly starve. We can predict two cognitive changes that would improve the mother rat's cost-benefit ratio. First, an enhancement of her foraging skills—for example, the spatial ability used for navigating her environment—would minimize the amount of time she is away from the nest. Second, a diminution of the rat's fear and anxiety would make it easier for her to leave the nest, allow her to forage faster, and steel her for confrontations with her hostile surroundings.

Are other features of the mothers' hunting skills also enhanced? Recent work by undergraduates Naomi Hester, Natalie Karp and Angela Orthmeyer in Kinsley's lab has shown that mother rats are faster than virgins at capturing prey. Slightly food-deprived mother and virgin rats were each placed in a five-foot-square enclosure bedded with wood chips, in which a cricket was hidden. The virgins took an average of nearly 270 seconds to find the cricket and eat it, compared with just more than 50 seconds for the lactating females. Even when the virgin females were made hungrier or when the sounds of the crickets were masked, the mother rats were still able to get to the prey more quickly.

Regarding the second prediction, Inga Neumann of the University of Regensburg in Germany has repeatedly documented that pregnant and lactating rats suffer less fear and anxiety (as measured by levels of stress hormones in their blood) than virgin rats when confronted with challenges such as forced swimming. Jennifer Wartella, while in Kinsley's lab, confirmed and extended these results by examining rat behavior in the five-foot-square enclosure; she found that mother rats were more likely to investigate the space and less likely to freeze up, two hallmarks of boldness. In addition, we found a reduction in neuronal activity in the CA3 region of the hippocampus and the basolateral amygdala, two areas of the brain that regulate stress and emotion. The resulting mitigation of fear and stress responses, combined with the enhancements in spatial ability, ensures that the mother rat is able to leave the security of the nest, forage efficiently and return home quickly to care for her vulnerable offspring.

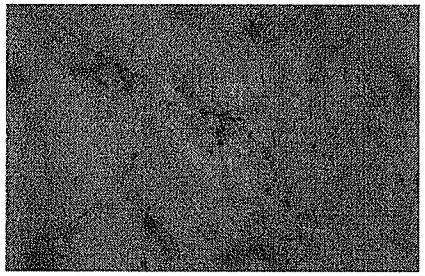
It appears that hormonal fluctuations ramp up neural activity during pregnancy.

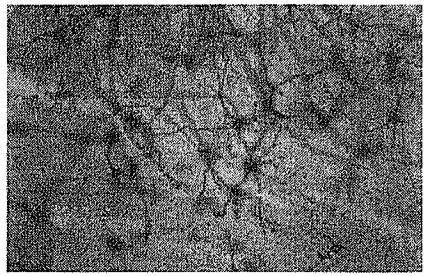
Alterations of the hippocampus, which regulates memory and learning as well as emotions, appear to play a major role in causing these behavioral changes. Some fascinating work by Catherine Woolley and Bruce McEwen of the Rockefeller University showed ebb-and-flow variations in the CA1 region of the hippocampus during a female rat's estrous cycle (the equivalent of the human menstrual cycle). The density of dendritic spines—tiny, thornlike projections that provide more surface area for the reception of nerve signals—increased in this region as the female's levels of estrogen rose. If the relatively brief hormonal fluctuations of the estrous cycle produced such striking structural changes, we wondered, what would happen to the hippocampus during pregnancy, when estrogen and progesterone levels remain high for an extended period? Graciela Stafisso-Sandoz, Regina Trainer and Princy Quadros in Kinsley's lab examined the brains of rats in the late stages of pregnancy, as well as females treated with pregnancy hormones, and found the concentrations of CA1 spines to be denser than normal. Because these spines direct input to their associated neurons, the big rise in density during pregnancy may contribute to the enhanced ability of the mothers to navigate mazes and capture prey.

Oxytocin, the hormone that triggers birth contractions and milk release, also appears to have effects on the hippocampus that improve memory and learning. Kazuhito Tomizawa and his colleagues at Okayama University in Japan have reported that oxytocin promotes the establishment of long-lasting connections between neurons in the hippocampus. Injections of oxytocin into the brains of virgin female mice improved their long-term memory, presumably by increasing enzyme activity that strengthened the neuronal connections. Conversely, injecting oxytocin inhibitors into the brains of mother rats impaired their performance on memory-related tasks.

Other researchers have focused on motherhood's effects on glial cells, the connective tissue of the central nervous system. Gordon W. Gifford and student collaborators in Kinsley's lab have examined astrocytes, star-shaped glial cells that provide nutrients and structural support for neurons. They found that the astrocytes in the mPOA and hippocampus of late-pregnant, lactating and hormone-treated female rats were significantly more complex and numerous than those in virgin rats. Again, it appears that hormonal fluctuations ramp up neural activity during pregnancy, modifying neurons and glial cells in critical brain regions to enhance learning and spatial memory.

Do any of these cognitive benefits extend beyond the lactational period? Jessica D. Gatewood, working with other students in Kinsley's lab, has reported that mother rats up to two years old—equivalent to human females older than 60—learn spatial tasks significantly faster than age-matched virgin rats and exhibit less steep memory declines. At every age tested (six, 12, 18 and 24 months), the mothers were better than the virgins at remembering the locations of food rewards in mazes. And when we examined the brains of the mother rats at the conclusion of testing, we found fewer deposits of amyloid precursor proteins—which seem to play a role in the degeneration of the aging nervous system—in two parts of the hippocampus, the CA1 region and the dentate gyrus.





CELL BODIES of neurons from the mPOA of a virgin female rat (*left*) are much smaller than those from a pregnant rat (*right*). The hormones of pregnancy appear to "rev up" the mPOA neurons, boosting their protein synthesis and activity in anticipation of the demands of motherhood.

FROM "ALTERATIONS OF MEDIAL PREOPTIC AREA NEURONS FOLLOWING PREGNANCY AND PREGNANCY-LIKE STEROIDAL TREATMENT IN THE RAT," BY L. KEYSER-MARCUS ET AL., IN *BRAIN RESEARCH BULLETIN*, VOL. 55, 15 2001; WITH PERMISSION FROM ELSEVIER

Recent work by Gennifer Love, Ilan M. McNamara and Melissa Morgan in our other lab (Lambert's), employing a different strain of rat and testing conditions, has confirmed that long-term spatial learning is enhanced in older mother rats. What is more, the investigators gauged the boldness of the rats using a maze shaped like a plus sign, with two open arms that rodents typically avoid because they are elevated and exposed, offering no hiding places [*see bottom illustration in box on next page*]. At most of the ages through 22 months that were tested, the mother rats spent more time in the fear-evoking open arms of the maze than the virgin rats did. When the brains of the mother rats were examined, researchers found fewer degenerating cells in the cingulate, frontal and parietal cortices, regions that receive considerable sensory input. These results suggest that the repeated inundation of the female brain with the hormones of pregnancy, coupled with the enriching sensory environment of the nest, may mitigate some of the effects of aging on cognition.

The Human Connection

DO HUMAN FEMALES RECEIVE any similar cognitive benefits from pregnancy and motherhood? Recent studies indicate that the human brain may undergo changes in sensory regulatory systems that parallel the alterations in other animals. Alison Fleming of the University of Toronto at Mississauga has shown that human mothers are capable of recognizing many of their infants' odors and sounds, possibly because of enhanced sensory abilities. She and her colleagues found that mothers with high postbirth levels of the hormone cortisol were more attracted to and motivated by their babies' scents and were better able to recognize their infants' cries. The results indicate that cortisol, which typically rises with stress and

THE AUTHORS

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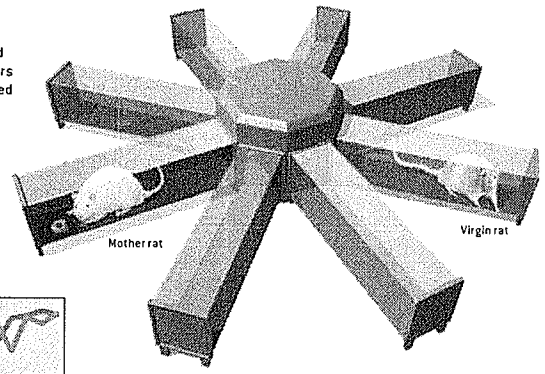
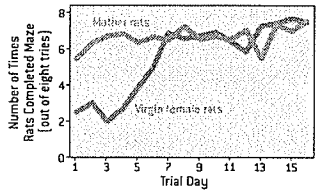
MOTHER KNOWS BEST

Recent experiments indicate that reproductive experience enhances spatial learning and memory in rats while alleviating fear and stress. These behavioral changes can improve a mother rat's foraging abilities, giving her pups a better chance of survival.

EIGHT-ARM RADIAL MAZE

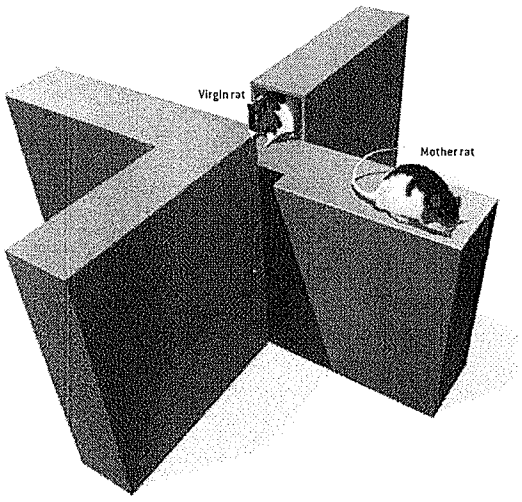
First the researchers familiarized the rats with a radial maze in which food baits were initially placed in all eight arms, then in only four, then in two, and finally in just one. Then the investigators measured how well the rats remembered which arm remained baited. Mother rats who had experienced two or more pregnancies were mostly successful in completing the maze (that is, finding the bait within three minutes) from the first day of testing; the virgin female rats did not match their success until the seventh day.

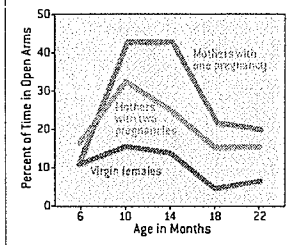




ELEVATED PLUS MAZE

In this maze, which was shaped like a plus sign and raised four feet above the floor, researchers measured how much time the rats spent in the two open arms, which rodents tend to avoid because they are elevated and exposed (unlike the maze's two closed arms). At nearly every age, the mother rats were bolder than the virgins, spending more time in the fear-evoking open arms.





SLIM FILMS

can have a negative impact on health, may have a positive effect in new mothers. By raising cortisol levels, the stress of parenting may boost attention, vigilance and sensitivity, strengthening the mother-infant bond.

Other studies have pointed to a possible long-term effect of motherhood. As part of the New England Centenarian Study, Thomas Perls and his colleagues at Boston University found that women who had been pregnant at or after the age of 40 were four times more likely to survive to 100 than women who had been pregnant earlier in life. Perls interpreted the data to suggest that women who became pregnant naturally in their 40s were probably aging at a slower pace. We would add, however, that pregnancy and the subsequent maternal experience may have enhanced the women's brains at a crucial period when the menopause-induced decline in reproductive hormones was just starting. The cognitive benefits of motherhood may have helped offset the loss of the memory-protecting hormones, leading to better neural health and increased longevity.

Is it possible that motherhood provides an edge to women as they compete with others for limited resources? Unfortunately, scientists have conducted little research comparing the learning or spatial memory abilities of human mothers and nonmothers. A 1999 study led by J. Galen Buckwalter of the University of Southern California showed that pregnant women had below-normal results on several verbal memory tests but that their scores rebounded soon after they gave birth. This study, however, was small (only 19 subjects) and found no significant changes in general intelligence. In her book *The Mommy Brain*, journalist Katherine Ellison documents many instances wherein the skills acquired through parenting might also aid women in the workplace. Successful leadership requires sensitivity to employee needs and a sustained vigilance of impending challenges and threats. But can these skills transfer from the nursery to the boardroom?

Investigators have begun to focus on one skill that is traditionally associated with motherhood: the ability to multitask. Do changes in the maternal brain allow mothers to balance competing demands—child care, work, social obligations and so on—better than nonmothers? Scientists do not yet know the answer, but studies indicate that the human brain is remarkably plastic: its structure and activity can change when a person is confronted with a challenge. Arne May and colleagues at the University of Regensburg found structural changes in the brains of young women and men who had learned how to juggle three balls in the air; the regions devoted to perception and the prediction of movement expanded after the subjects learned how to juggle, then contracted after they stopped practicing. Likewise, perhaps alterations occurring in the maternal brain enable the mother to juggle the demands of parenthood successfully.

Animal studies show that mother rats are particularly good at multitasking. Experiments in Lambert's lab have demonstrated that mother rats nearly always beat virgins in competitions that involve simultaneously monitoring sights, sounds, odors and other animals. In a race to find a preferred food (Froot Loops), rats who had experienced two or more pregnancies were the first to attain the treat 60 percent of the time. Rats who had given birth just once won the prize 33 percent of the time, compared with only 7 percent for the virgin rats.

Finally, what about the paternal brain? Do fathers who care for offspring gain any mental benefits? Studies of the common marmoset, a small Brazilian monkey, may provide some insights. Marmosets are monogamous, and both parents participate in the care of their offspring. In collaboration with Sian Evans and V. Jessica Capri of Monkey Jungle in Miami, Fla., Anne Garrett from Lambert's lab tested mother and father marmosets on a "foraging tree" in which the monkeys had to learn which containers held the most food. Parents—both mothers and fathers—outperformed nonparents in the test. This result supported earlier studies that examined a mouse species (*Peromyscus californicus*) in which the male contributes significantly to parental care. In Lambert's lab, Erica Glasper and other students found that father mice, like mothers, had an advantage in the dry-land maze; Ashley Everette and Kelly Tu showed that the fathers were quicker to investigate novel stimuli, such as Lego blocks, than their bachelor counterparts were.

In summary, reproductive experience appears to promote changes in the mammalian brain that alter skills and behavior, particularly among females. For the female, the greatest challenge from an evolutionary perspective is to ensure that her genetic investment flourishes. Maternal behaviors have evolved to increase the female's chances of success. This does not mean that mothers are better than their virgin counterparts at every task; in all likelihood, only the behaviors affecting the survival of their offspring would be enhanced. Still, many benefits seem to emerge from motherhood as the maternal brain rises to the reproductive challenge placed before it. In other words, when the going gets tough, the brain gets going. ■

Mother rats nearly always beat virgins in competitions that involve multitasking.

MORE TO EXPLORE

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Twin research

Two of a kind

Aug 12th 2004 | TWINSBURG, OHIO
From The Economist print edition

Researchers have descended on a small town in Ohio for two frenzied days of work. Twin research has never been so popular

IN THE first weekend of every August, the town of Twinsburg, Ohio, holds a parade. Decorated floats, cars and lorries roll slowly past neat, white houses and clipped lawns, while thousands of onlookers clap and wave flags in the sunshine. The scene is a perfect little slice of America. There is, though, something rather strange about the participants: they all seem to come in pairs. Identical twins of all colours, shapes, ages and sizes are assembling for the world's largest annual gathering of their kind.

The Twinsburg meeting is of interest to more people than just the twins themselves. Every year, the festival attracts dozens of scientists who come to prod, swab, sample and question the participants. For identical twins are natural clones: the odd mutation aside, they share 100% of their genes. That means studying them can cast light on the relative importance of genetics and environment in shaping particular human characteristics.

In the past, such research has been controversial. Josef Mengele, a Nazi doctor working at the Auschwitz extermination camp during the second world war, was fascinated by twins. He sought them out among arrivals at the camp and preserved them from the gas-chambers for a series of brutal experiments. After the war, Cyril Burt, a British psychologist who worked on the heredity of intelligence, tainted twin research with results that appear, in retrospect, to have been rather too good. Some of his data on identical twins who had been reared apart were probably faked. In any case, the prevailing ideology in the social sciences after the war was Marxist, and disliked suggestions that differences in human potential might have underlying genetic causes. Twin studies were thus viewed with suspicion.

Womb mates

The ideological pendulum has swung back, however, as the human genome project and its aftermath have turned genes from abstract concepts to real pieces of DNA. The role of genes in sensitive areas such as intelligence is acknowledged by all but a few die-hards. The interesting questions now concern how nature and nurture interact to produce particular bits of biology, rather than which of the two is more important (see article). Twin studies, which are a good way to ask these questions, are back in fashion, and many twins are enthusiastic participants in this research. Laura and Linda Seber, for example, are identical twins from Sheffield Village, Ohio. They have been coming to Twinsburg for decades. Over the years, they have taken part in around 50 experiments. They have had their reactions measured, been deprived of sleep for a night and had electrodes attached to their brains. Like many other twins, they do it because they find the tests interesting and want to help science.

Research at the Twinsburg festival began in a small way, with a single stand in 1979. Gradually, news spread, and more scientists began turning up. This year, half a dozen groups of researchers were lodged in a specially pitched research tent.

In one corner of this tent, Paul Breslin, who works at the Monell Institute in Philadelphia, watched over several tables where twins sat sipping clear liquids from cups and making notes. It was the team's third year at Twinsburg. Dr Breslin and his colleagues want to find out how genes influence human perception, particularly the senses of smell and taste and those (warmth, cold, pain, tingle, itch and so on) that result from stimulation of the skin. Perception is an example of something that is probably influenced by both genes and experience. Even before birth, people are exposed to flavours such as chocolate, garlic, mint and vanilla that pass intact into the bloodstream, and thus to the fetus. Though it is not yet clear whether such pre-natal exposure shapes taste-perception, there is evidence that it shapes preferences for foods encountered later in life.

However, there are clearly genetic influences at work, as well—for example in the ability to taste quinine. Some people experience this as intensely bitter, even when it is present at very low levels. Others, whose genetic endowment is different, are less bothered by it. Twin studies make this extremely clear. Within a pair of identical twins, either both, or neither, will find quinine hard to swallow. Non-identical twins will agree less frequently.

On the other side of the tent Dennis Drayna, from the National Institute on Deafness and Other Communication Disorders, in Maryland, was studying hearing. He wants to know

what happens to sounds after they reach the ear. It is not clear, he says, whether sound is processed into sensation mostly in the ear or in the brain. Dr Drayna has already been involved in a twin study which revealed that the perception of musical pitch is highly heritable. At Twinsburg, he is playing different words, or parts of words, into the left and right ears of his twinned volunteers. The composite of the two sounds that an individual reports hearing depends on how he processes this diverse information and that, Dr Drayna believes, may well be influenced by genetics.

Elsewhere in the marquee, Peter Miraldi, of Kent State University in Ohio, was trying to find out whether genes affect an individual's motivation to communicate with others. A number of twin studies have shown that personality and sociability are heritable, so he thinks this is fertile ground. And next to Mr Miraldi was a team of dermatologists from Case Western Reserve University in Cleveland. They are looking at the development of skin diseases and male-pattern baldness. The goal of the latter piece of research is to find the genes responsible for making men's hair fall out.

The busiest part of the tent, however, was the queue for forensic-science research into fingerprints. The origins of this study are shrouded in mystery. For many months, the festival's organisers have been convinced that the Secret Service—the American government agency responsible for, among other things, the safety of the president—is behind it. When *The Economist* contacted the Secret Service for more information, we were referred to Steve Nash, who is chairman of the International Association for Identification (IAI), and is also a detective in the scientific investigations section of the Marin County Sheriff's Office in California. The IAI, based in Minnesota, is an organisation of forensic scientists from around the world. Among other things, it publishes the *Journal of Forensic Identification*.

Mr Nash insists that the work on twins is being sponsored by the IAI, and has nothing to do with the Secret Service. He says the organisation collects sets of similar finger and palm prints so that improvements can be made in the ability to distinguish ordinary sets of prints. Although identical twins tend to share whorls, loops and arches in their fingerprints because of their common heredity, the precise patterns of their prints are not the same.

Just who will benefit from this research is unclear. Although the IAI is an international organisation, not everyone in it will have access to the twin data. Deciding who does will have "a lot of parameters", according to Mr Nash. He says that the work is being assisted by the American government at the county, state and federal level, and that government agencies will have access to the data for their research. He takes pains to stress that this will be for research purposes, and says none of the data will be included in any criminal databases. But this cloak-and-dagger approach suggests that, while twin studies have come a long way, they have not shaken off their controversial past quite yet. If they are truly to do so, a little more openness from the Feds would be nice.