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

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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.

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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.

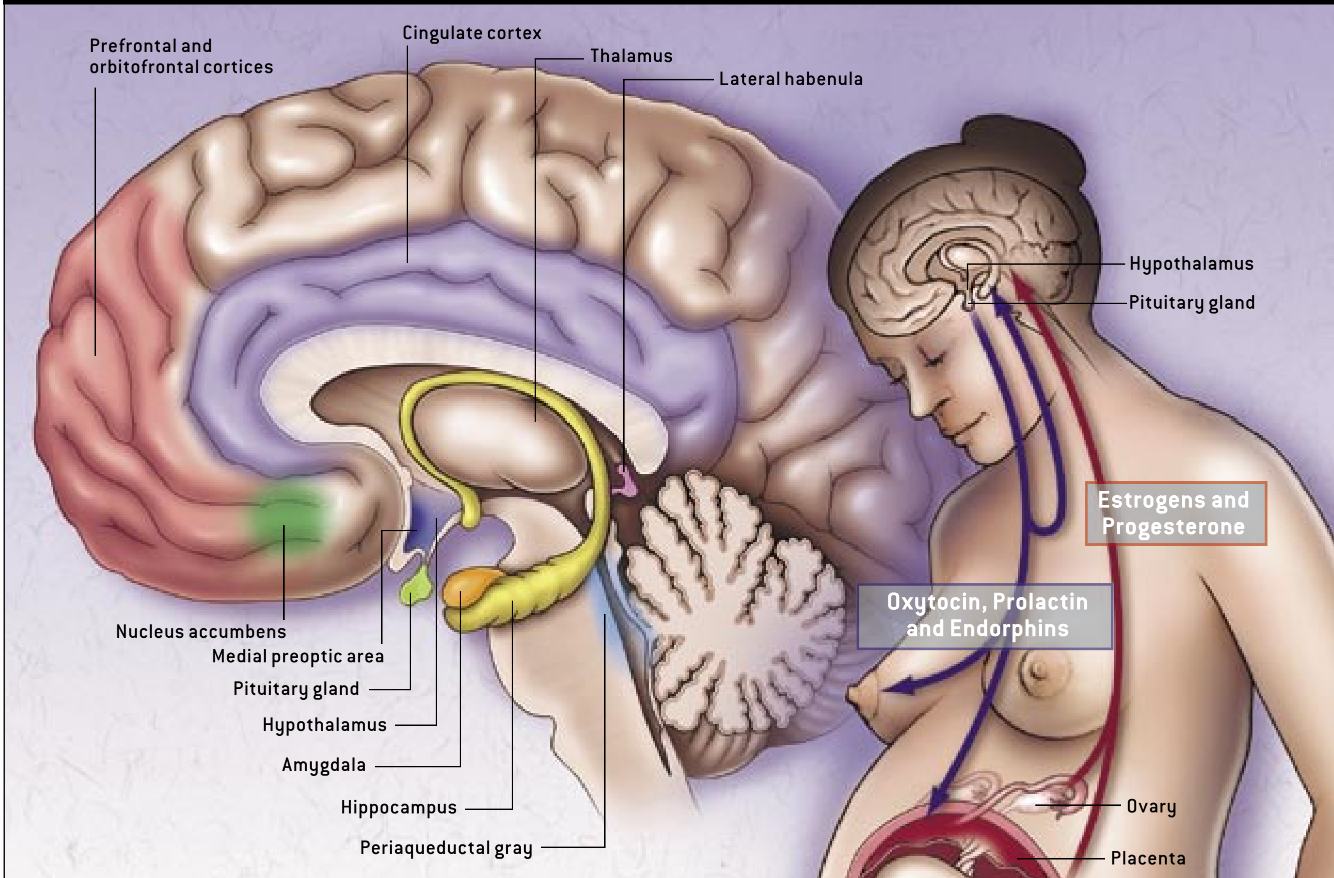
Several researchers have hypothesized that as suckling pups attach to their mother's nipples, they may release tiny amounts of endorphins in the mother's body. These natural painkillers may act somewhat like an opiate drug, drawing the mother again and again to contact with her pups. Suckling and pup 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

## 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.

## 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.

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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.

## 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 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.

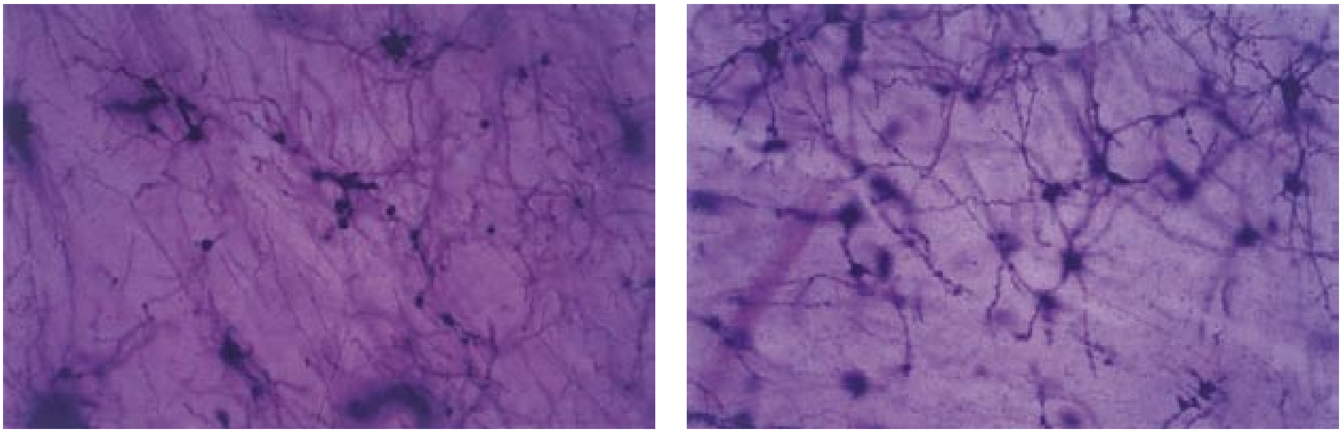
In 1999 we found support for the first prediction by showing that reproductive experience enhanced spatial learning and memory in rats. Young females that had experienced one or two pregnancies were much better than age-matched virgin rats at remembering the location of a food reward in two different kinds of mazes: an eight-arm radial maze [*see top illustration in box on page 78*] and a dry-land version of the Morris water maze, a large, circular enclosure with nine baited food wells. The improved foraging abilities were observed in both lactating females and mothers at least two weeks removed from weaning their young. Furthermore, virgin females provided with foster young performed similarly to lactating females. This result suggests that simply the presence of offspring can provide a boost to spatial memory, perhaps by stimulating brain activities that alter neuronal structures or by prompting the secretion of oxytocin.

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



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.



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.

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

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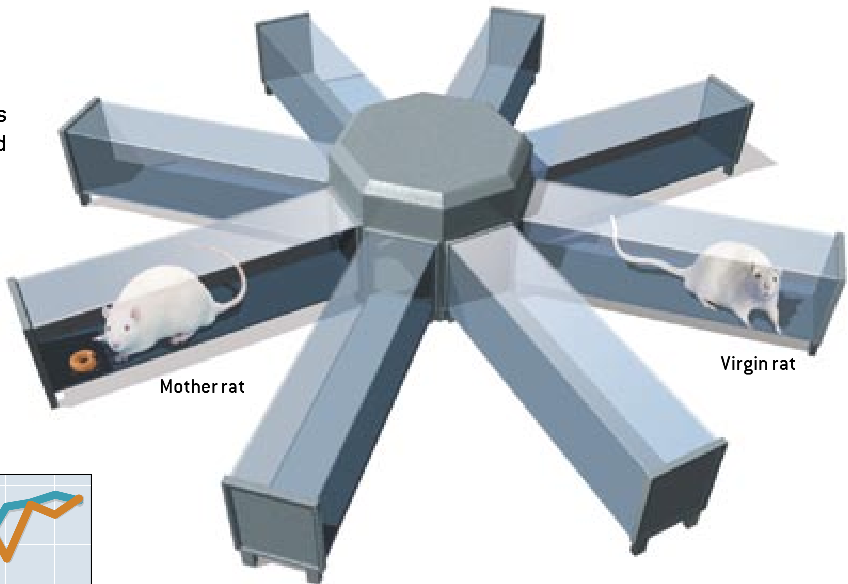
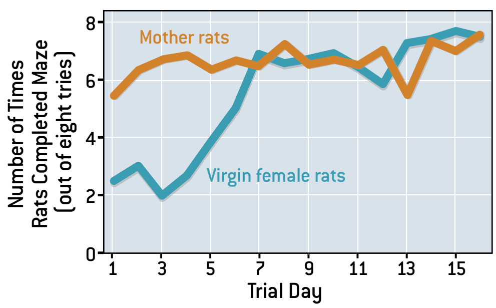
## MOTHER KNOWS BEST

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

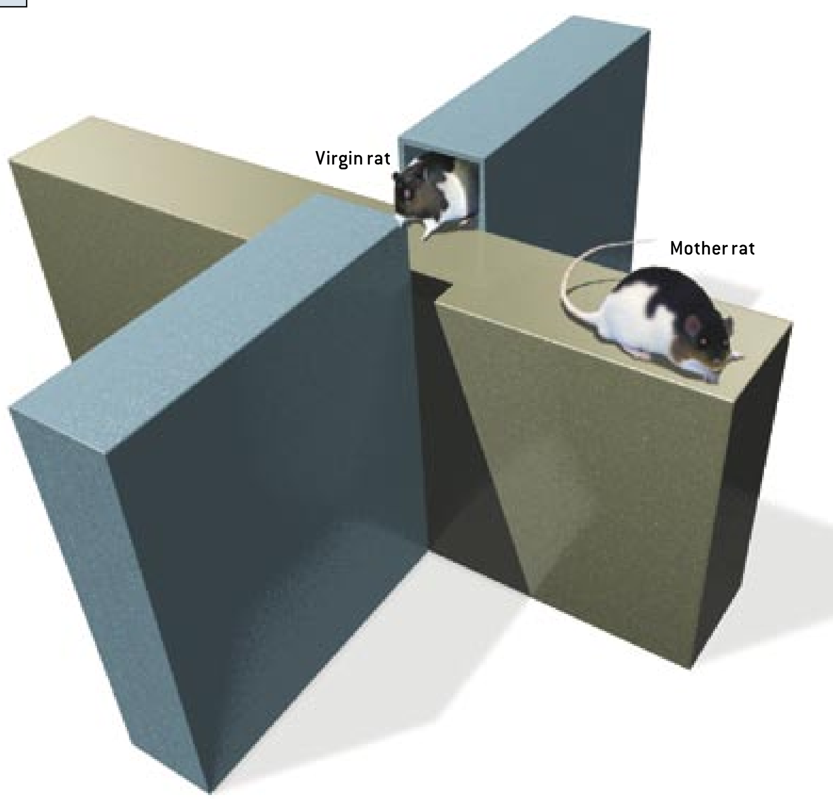
First the researchers familiarized the rats with a radial maze in which food baits were initially placed in all eight arms, then in only four, then in two, and finally in just one. Then the investigators measured how well the rats remembered which arm remained baited. Mother rats who had experienced 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.

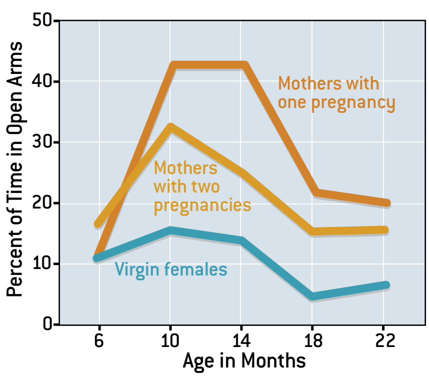



### ELEVATED PLUS MAZE

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. SA

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

## MORE TO EXPLORE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