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Deep in the Heart of Memory: Factoring Fear

By Dennis Meredith

Neuroscientists are discovering how a small chunk of circuitry in the brain indelibly imprints our most emotionally charged recollections.

Take a journey back into the most vivid memories of your life. For me, there's the terrifying childhood attack by a deranged rooster; the gut-roiling public embarrassment of a forgotten speech; and, ah yes, the sweet, transporting taste of my first kiss. Such memories don't just benignly percolate up in our minds, like the mundane recall that we need to buy bread at the market. Rather, they envelop our consciousness in a nerve-tingling fog of sensory remembrance.

It's no surprise, then, that memories packing an emotional punch are not imprinted on the brain using routine memory circuits. Rather, our terrifying traumas and our delicious delights spark activity in a small but potent almond-shaped structure called the amygdala, buried deep in our neural gelatin. This little neural nugget abets our very survival--charging memories with an emotional force that compels us to avoid lunatic fowl, practice our speeches, and look for love in all the right places.

But this little clump of brain tissue also can smother our lives in the torment of post-traumatic stress disorder (PTSD), the corrosive dread of phobias, or the black dog of depression. The medical impact of traumatic disorders is immense. One in six soldiers in Iraq reports that his or her experience has produced major depression, anxiety, or PTSD, according to a study by the U.S. Army. Some mental-health experts estimate that at least 100,000 veterans of that war will need mental-health treatment. Here at home, our efforts to escape the anxiety provoked by the stresses of daily life have been prodigious, as evidenced by the 142-million prescriptions written in this country in 2003 for Prozac, Paxil, Zoloft, and other antidepressants.

The profound importance of emotional memory has impelled Duke neuroscientists Kevin LaBar and Roberto Cabeza to make it their scientific mission to understand the complexities of its neural machinery. In a wide variety of experiments, they expose volunteer subjects to stimuli designed to provoke an emotional response--tear-jerking scenes from movies, for example, or mild shocks to the wrist. Then, using magnetic resonance imaging (MRI), they examine how and, more important, where the brain responds when the subjects are asked to recall what happened. Their efforts will not only contribute to better treatments for anxiety disorders, but also could yield a deeper understanding of how emotional memories influence, and sometimes rule, our lives.

Routine memories are stored in the brain with the aid of the wishbone-shaped hippocampus, which filters the stream of sensory data flooding into our brains and helps imprint that data as lingering memories. But a jolt of danger--and the accompanying blast of adrenalin into our bloodstream--activates both of the amygdalae attached to the tips of the hippocampus. These structures somehow stamp the indelible imprint of emotion on the resulting memories. The scientific mystery being tackled by LaBar and Cabeza is how the amygdalae blaze such permanent and vivid memory pathways in the brain's circuitry.

Getting into people's heads, particularly into the brain's depths where the amygdalae nestle, has been among the biggest challenges for researchers like LaBar and Cabeza, both of whom are on the faculties of Duke's Center for Cognitive Neuroscience and the department of psychological and brain sciences.

Neuroscientists first explored emotional memory by studying patients with specific damage to the amygdalae or surrounding structures from accident or disease. "But studies of such patients are very difficult, given that the locations of the lesions are not always clear; and finding patients with lesions in particular brain areas is a matter of chance," says Cabeza. Even if

neuroscientists did find the right patients, he says, "the brain undergoes adaptive changes to such lesions. So it's difficult to know whether any changes we measure are due to the lesion itself or adaptation of the brain to the lesion."

Finally, he says, brain lesions might not directly affect a structure such as the amygdala that is critical to a particular function. Instead, they might only block a neural pathway serving that structure--just as blocking a highway might not directly affect the operation of a roadside hamburger stand, but only block the pathway by which hungry customers can reach it. So, scientists studying the effects of such a lesion--or diners looking for a hamburger--could be misled by a lack of activity in the structure to think it's closed for business.

The real revolution in exploring brain function came with the development of functional magnetic resonance imaging (fMRI), which allows researchers to direct harmless magnetic fields and radio waves into the brain to produce detailed scans of brain activity while the subject is performing a specified mental task. These scans can reveal differences in magnetic properties between oxygenated blood and deoxygenated blood. Because regions of the brain that are in heavy use during mental tasks trigger influxes of oxygenated blood into the region, they can be readily distinguished on fMRI scans.

Thus, researchers can get an invaluable, albeit indirect, measure of brain activity in specific regions such as the amygdalae. "Some people compare the impact of brain imaging on cognitive neuroscience to the impact of the telescope on astronomy," says Cabeza. "In both cases, a new instrument has allowed scientists to see things they couldn't see before."

Seeing things they couldn't see before has led Cabeza and LaBar to ingenious new ways of exploring and monitoring brain activity. Their latest experiments, reported in the June 2004 issue of the journal *Neuron*, revealed for the first time that the brain's emotional centers affect or "modulate" the function of the memory centers as memories of emotion-laden events are being formed.

In the experiments, they slid volunteers into MRI machines and scanned their brains while showing them pictures that evoked both positive (romantic scenes, sports victories) and negative (aggressive acts, injured people) emotions. They also showed neutral pictures of buildings or scenes of routine shopping. After the scanning sessions, the researchers measured the emotional impact of the images by testing how well the participants remembered them. In their subsequent analysis of the brain scans, Cabeza and LaBar found that the emotional and memory regions interacted more during the formation of emotional than of neutral memories. The findings provide firm evidence that the amygdala modulates the function of the hippocampus and other memory regions, Cabeza said in the report. "Other studies have focused on the general enhancing effects of emotion on memory," he wrote. "But this study provides the first direct evidence for the modulation hypothesis in humans."

In an earlier discovery, published in the *Proceedings of the National Academy of Sciences* in 2002, LaBar and other colleagues used fMRI studies to show that fear-producing stimuli travel along separate brain pathways from tasks, such as driving, that require concentration. The two streams join in the prefrontal cortex--the higher processing area of the brain--and at that point can interfere with each other. "These findings are important because diseases that involve distractibility, from Alzheimer's to attention-deficit disorder, always seem to involve the prefrontal cortex," says Gregory McCarthy, director of the Duke-UNC Brain Imaging and Analysis Center (BIAC). "Understanding the biology of this will speed efforts to develop drugs or therapies that may influence these systems."

In ongoing experiments, the researchers are studying the effects of "fear-conditioning." In one study, LaBar and his colleagues teach subjects to associate the image of a particular type of square with a mild shock to the wrist. Then the scientists add some type of social stress, such as asking the subjects to deliver a public speech. The following day, they bring the subjects back into the laboratory and test their physiological response to the square--increased perspiration caused by stress--to determine how well they have retained the fear response. "In psychiatry, it's known that stress can impair learning and memory," says LaBar. "This experimental approach gives us a way to study the role that the amygdala plays in mediating stress responses and how stress can aid or impair learning and memory."

Phobias constitute a far more general fear of specific situations, and LaBar has invented a way to mimic in the laboratory the development of these fears, which are what researchers call "context-dependent." In this case, the researchers use a specific setting to create the context. They place subjects in a small room where they teach them to associate the image of a square of a certain size and color with a mild shock. Keeping the subjects in that same room, the researchers proceed to "extinguish" the association by showing the square without administering the shock.

The researchers then remove the subjects from the "shock" room and, after a short period, either return them to it or place

them in an entirely different room. They then test how quickly the subjects recover the unpleasant association of the square with the shock--a measure of their created "phobia" of the room.

"We've found that the person only recovers this 'phobia' if the shock happens in the same room," says LaBar. If the shock happens in a different room, he says, the subject is no longer fearful. "This context-specific recovery of fear is thought to be important for phobias."

As anyone knows who has ever tried to get through a workday while in a blue funk, mood can also affect mental functioning. So, LaBar and his colleagues have also devised experiments to test how mood affects emotional, as well as cognitive, processing. First, the researchers establish a mood by showing subjects scenes from a happy or a sad movie--Bambi, Titanic, Shadowlands, and Death of a Salesman, among others. Then, while scanning the subjects' brains, the researchers give them a counting task, at the same time presenting them with emotional "distractors"--glimpses of sad clips that elicit an emotion, or neutral clips as a control. "We know little about how longer-lasting mood states can modulate the fast response to emotional stimuli in the amygdala," says LaBar. "In this study, we're looking at amygdala activation, as well as at how people perform cognitively in such situations." Studies like this can give important insights into how mood can affect cognitive function, and thus how people might be expected to perform tasks when they are under the added burden of sadness, he says.

Within his broader studies of memory's intricate machinery, Cabeza is also zeroing in on the processing of emotion, studying, for example, its function in depressed people. "There is some evidence that, while depressed people don't have a general memory deficit, they have difficulty remembering pleasant events and a better memory for negative events," says Cabeza. This tendency could help feed their depression, he adds. Cabeza is collaborating with Duke psychologist Timothy Strauman and his colleagues to investigate how well people who are depressed remember pictures depicting sad events, in comparison with people who are not depressed.

The researchers show their subjects pictures depicting sad events, while at the same time scanning their brains to measure differences in activity in the amygdala and connected memory structures. "A particularly exciting possibility is that we'll be able to combine drug treatments with such studies, to measure how effectively they change brain activity associated with depression," says Cabeza. "We might even be able to detect changes in the brain before they show up in behavior."

Aging also alters the processing of emotion, says Cabeza, and so he and his colleagues are planning fMRI studies of brains of elderly people to explore the activity of their emotional circuitry. "There is some evidence that regions critical to emotional processing might be affected in forms of pathological aging such as Alzheimer's disease," he says. "So, it may be possible to analyze activity in these regions using fMRI to detect early signs of Alzheimer's."

As LaBar and Cabeza learn more about the amygdala and its associated circuitry, they are coming to appreciate the subtle complexity of the modest little structure. "When we started this work, it was thought that the amygdala was a specialized fear modulator," says LaBar. "We do still believe that, but we're also finding that it influences maternal and sexual behaviors. We know very little about its role in such reward-based behaviors." Nor, says LaBar, do researchers understand how the amygdala might affect unconscious learning, such as skills or habits.

An especially fascinating question arising from studies of emotional memory is whether scientists could ever invent a "magical memory pill" to alleviate PTSD or traumatic memories. Some preliminary clinical studies around the world have raised the possibility. A handful of subjects in the U.S. and France are participating in studies in which they were given the drug propranolol immediately after a terrorizing experience such as an attempted rape. The drug blocks the action of stress hormones, including adrenalin, that activate the amygdala to imprint emotion-charged memories on the brain.

So far, the studies have only given early hints that the drugs might reduce the disturbing intensity of such memories, and research is continuing. Says LaBar, "While there could be designer drugs to either enhance or suppress emotional memories, there are huge problems in terms of ethics and specificity." He says the new appreciation of the amygdala's complex role in making memories means that "designing drugs to target specific emotions within the amygdala is going to be a major challenge." And how about the likelihood of a drug or treatment to erase specific memories, as depicted in the movie *Eternal Sunshine of the Spotless Mind*, in which a woman deletes memories of her ex-boyfriend? Never going to happen, assert the researchers: Recalling even the most specific memories involves the entire landscape of the brain.

Nevertheless, they say, future studies will likely provide additional insights into the neural circuitry of memory, including emotional memory--revealing more, for example, about how genes control the formation of such neural circuitry, as well as

its function in influencing behavior. A prime example of the far-reaching implications of those studies was a discovery--reported in the December 2004 issue of *Neuron* by Duke cell biologist Marc Caron and his colleagues--of the first genetic defect specifically linked to depression and resistance to antidepressive drugs.

Cabeza emphasizes that among the most important advances required to understand the brain will be correcting the mental biases of brain scientists themselves. "We need to break free from the taxonomy of cognitive processes we inherited from the last century," he says. "We've all been trained to think of cognitive abilities in terms of discrete functions such as memory, attention, perception, imagery, and so forth. However, we now realize that the same brain regions are activated by a variety of functions. So, it's a bit funny that when you read a scientific paper, if the paper is about memory, the authors say activity in a given region is due to memory. And if you read a paper about language, the authors say the same region is involved in language. But we're now at a point where it's obvious we cannot keep attributing a brain region to our favorite process."

"We have to find new ways to explain activation of regions that can accommodate many processes and get beyond this rigid classification," says Cabeza. "We need to build bridges between the two different worlds of studies of cognition--the psychological tradition and the neuroanatomical tradition. It's a big challenge, but it offers great promise for understanding the brain and its disorders."

The impact of deeper knowledge of emotional processing will be profound. Understanding our own neural demons might mean, ironically, not only trying to vanquish them, but also, ultimately, embracing them. After all, we are the culmination of all our memories, those of rampaging roosters--and of tender kisses.

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