

ON THE BRAIN

THE HARVARD MAHONEY NEUROSCIENCE INSTITUTE LETTER

Remembering Dreams

WHY IS IT that some people can vividly remember their dreams, while others have difficulty recalling even fragments of these shut-eye stories? The field of sleep science has taught us a lot about why we sleep, when we dream, and even what those dreams might mean. Now, researchers in this field are getting a clearer picture of the biological differences between those who remember their dreams and those who do not.

Until the 1950s, many people thought sleep was a passive part of daily life, a period during which our brains rested from the day's events. In 1953, however, scientists discovered a stage of sleep called REM, which is characterized by rapid eye movement, irregular breathing, and involuntary muscle jerks, and came to understand that our brains are very active during sleep. Part of that activity involves dreaming.

The period during which humans sleep can be divided into five stages. Stages one and two are periods of light sleep. Stage three is a transitional

period between light sleep and the deeper, more restorative sleep achieved in stage four. The fifth stage is REM sleep, which accounts for about 20 percent of our sleep each night. We typically go through this sleep cycle several times a night, each lasting about 90 minutes.

When we switch into REM, we undergo a number of physiological changes, including increased heart rate and blood pressure, shallow breathing, and a temporary paralysis of the muscles in our limbs. As we prepare to wake up, we emerge from REM sleep; it is during this period that many people dream. And how we awaken, according to Robert Stickgold, an HMS associate professor of medicine and director of the Center for Sleep and Cognition at Beth Israel Deaconess Medical Center, will determine whether we will recall our dreams.

"It's really not about remembering," says Stickgold. "It's about waking at the right time."

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Stickgold says several things must occur for us to remember a dream. If we fall asleep slowly, we enter a hypnagogic state as we enter stage one of our slumber. Hypnagogia is marked by dreamlike visual, auditory, and physical hallucinations that occur just at the onset of sleep. When we awaken, during or at the end of the sleep period, recall is facilitated if we awaken slowly and with little movement. According to Stickgold, the most usual time for this awakening is late in the REM stage when we tend to be calm and ready to slip back into sleep. Finally, and most importantly, we should allow ourselves to “float back and remember our dream” before getting up. Alarm clocks usually don’t allow this luxury.

Deirdre Barrett, an HMS assistant clinical professor of psychology and author of *The Committee of Sleep*, explains. “When you first wake up,” she says, “don’t jump up or even turn your attention to something other than your dream. Even if you

don’t think you can remember your dream, a whole dream can sometimes come flooding back if you just take just a minute to register any feeling or image you had as you were waking up.”

Two recent studies may help characterize the biological divide between those who remember their dreams and those who do not. In one, a 2014 study in *Neuropsychopharmacology*, researchers had participants undergo PET scans while awake and while sleeping. The scans showed that participants who showed more spontaneous brain activity in the medial prefrontal cortex and the temporoparietal junction (TPJ), both when they were asleep and awake, were more likely to recall their dreams than were participants whose scans did not show such activity. The TPJ collects and processes information both from within and from outside the body, and it plays a role in emotional processing.

The other study, published in 2013 in *Frontiers of Consciousness Research*, found that people who recall their dreams on a regular basis wake more often during sleep than do people who can’t remember their dreams. In addition, electroencephalographs of the brains of those who could recall their dreams showed greater neurological responses to stimuli, in particular, to the mention of their name, during sleep and wakefulness.

“These studies seem to have identified several characteristics that differ between so-called low- and high-dream recallers,” says Barrett. “These data don’t override some of the basic differences we’ve known of for several decades, such as hours of sleep and awakening from REM, specifically, but they provide an interesting new dimension.”

In the end, the HMS researchers say, the biological reasons we do or do not remember our dreams are one thing; whether our dreams guide us in our efforts to live rewarding lives is another one completely.

“Dreams can be interesting and you may get valuable insights from them,” says Stickgold, “but I wouldn’t marry or divorce or accept or turn down a job based on a dream.” ♥

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Marijuana and the Brain

This article is part of a series on the internal and external forces that affect the brain.

ACCORDING TO THE National Institute on Drug Abuse, marijuana use, after a decade or so of decline, is on the rise across the United States. The 2013 National Survey on Drug Use and Health reports that, in the United States, some 18.9 million people over age 12 used marijuana monthly, up from 14.5 million in 2007.

This increase, coupled with efforts in states to decriminalize marijuana use or to legalize its use for medicinal purposes, concerns some public health experts and specialists who study the effects of the drug on the brain, especially on the developing brains of young users.



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"Cannabinoid receptors and the binding sites for marijuana are all over the brain," says J. Wesley

Boyd, an assistant clinical professor of psychiatry at Harvard Medical School who works at Cambridge Health Alliance. Boyd studies the long-term effects of heavy marijuana use on the adolescent brain. "These receptors are in the cerebellum, which controls movement," he says. "They're in the hippocampus, where we form memories, and in the amygdala, which is part of the reward system."

In addition, these receptors are plentiful in the prefrontal cortex, which influences executive functioning, everything from decision making and problem solving to behavior regulation and social control.

Changing form and function

The human brain matures from back to front. Scientists say the maturation of the forward regions, particularly the frontal lobe, which is responsible for cognitive processes such as reasoning, planning, and judgment, may continue up to age 30.

In a study of chronic marijuana smokers presented at the 2010 annual meeting of the Society for Neuroscience, Staci Gruber, an HMS associate professor of psychiatry and director of McLean Hospital's Cognitive and Clinical Imaging Core, reported that cognitive deficits were greater in those who started smoking marijuana at a young age compared to those who started later in life. Youngsters who first used marijuana before age 16 performed worse on executive function tests than those who began using the drug after age 16. According to Gruber, early-onset users, who smoked more marijuana more frequently than later-onset users, made repeated errors on the tests and showed a greater inability to maintain focus.

"Our data suggest that the earlier you begin smoking, the more marijuana you smoke, and the more frequently you smoke," said Gruber following the release of the study, "have a direct effect on executive function. The earlier you begin using it, the more you use of it, the more significant that effect."

More recently, Duke University scientists looked at the effects of marijuana use on IQ. In 2012 in the *Proceedings of the National Academy of Sciences*, researchers reported on 1,037 heavy marijuana users from New Zealand who, after being given an IQ test at age 13, were monitored for their marijuana use through age 38, when

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they were again administered an IQ test. At the beginning of the study, none of the participants had used marijuana, but by the end of the investigation, some had developed a dependence on the drug. In their analysis of the data, the researchers showed that heavy users had an eight-point decline in IQ and performed worse than nonusers did on memory, processing speed, and executive function tests.

Although a decrease of eight points could spell trouble for individuals who achieve borderline scores on an IQ test (average being 85–115), Boyd says this type of decrease may be negligible for most people. “Practically speaking, on a day-to-day level, does that drop make any difference in a person’s ability to hold a job or function in a family setting? I doubt, it,” he says.

Although a decrease of eight points could spell trouble for individuals who achieve borderline scores on an IQ test, Boyd says this type of decrease may be negligible for most people. “Practically speaking, does that drop make any difference in a person’s ability to hold a job or function in a family setting? I doubt, it.”

Teenagers who smoke marijuana daily over an extended period of time also may have changes in brain structures related to working memory, which is the ability to remember and process information in the moment and, if necessary, transfer it to long-term memory. Researchers at Northwestern University discovered that memory-related structures in the brains of these individuals appeared to “shrink and collapse inward,” and speculate the change is the result of a loss of neurons in these areas. The study, published in 2013 in the *Schizophrenia Bulletin*, examined deep regions of the region, including the striatum, the globus pallidus, and the thalamus, which are critical for working memory.

The findings bolster Gruber’s work on the effects of early-onset drug use. The younger the individuals were when they started smoking marijuana, the more abnormally shaped these

brain regions became, suggesting that these areas of the brain may be more susceptible to the drug if abuse starts at an earlier age.

Recreational effects

Most studies on the brain abnormalities associated with marijuana use have focused on chronic users of the drug, with few studies observing the effects on recreational users.

In a study believed to be the first of its kind, Gruber and colleagues at Northwestern discovered abnormalities in areas of the brain related to emotion, motivation, and reward in those who only occasionally smoke marijuana. In their study of 40 college students, half of the participants reported smoking marijuana at least once a week, while the other participants used the drug fewer than five times in their life and not at all in the year before the study.

Previous animal studies have found that THC causes abnormal changes in cell structure within the nucleus accumbens, an area of the brain that is involved in reward and addiction. Other studies have found structural changes in the emotional processing centers of the brains of heavy users. Gruber’s study looked at whether similar abnormalities occurred in young, recreational users and whether the amount of marijuana smoked made a difference. The study was published in April 2014 in the *Journal of Neuroscience*.

Structural MRIs showed that the nucleus accumbens was larger in marijuana smokers than in nonusers, and also showed structural changes in the shape and volume of the amygdala. The changes were even more pronounced in users who reported smoking marijuana more frequently and smoking more of it on those occasions. The abnormalities, Gruber says, are dose dependent; in other words, they were more pronounced in those who used greater amounts of marijuana.

In 2014, Maryland joined 17 other states in decriminalizing marijuana, which decreases the penalties associated with possession of a small amount of the substance for personal use; use of the drug is fully legalized in Colorado and Washington state. Boyd advocates a cautionary approach to those who might feel that legalizing marijuana means there is no danger in using it. ♥

Marilyn Albert and Guy McKhann Receive 2014 David Mahoney Prize

THE 11TH BIENNIAL David Mahoney Symposium and Prize, held in New York City on May 14, honored Marilyn Albert, professor of neurology and psychiatry and director of the Division of Cognitive Neuroscience at Johns Hopkins School of Medicine, and Guy McKhann, professor of neurology and neuroscience and founding chairman of the Department of Neurology at Johns Hopkins.



Edward Rover, chairman and president of the Dana Foundation and Harvard Mahoney Neuroscience Institute council member, moderated the "Memory and Aging" symposium, which featured 2014 David Mahoney Prize recipients Guy McKhann, MD, and Marilyn Albert, PhD.

The event's symposium, "Memory and Aging," was moderated by Edward Rover, chairman and president of the Dana Foundation and member of the Harvard Mahoney Neuroscience Institute (HMNI) council. It featured presentations by Albert and McKhann, which were followed by questions from the more than 125 attendees. The symposium was followed by a dinner that featured a keynote address, "Looking for the cure: The future of neurobiology," delivered by Sandeep "Bob" Datta, an assistant professor of neurobiology at Harvard Medical School.

Albert, a former member of the faculty of Harvard Medical School, once directed the Gerontology Research Unit at the Massachusetts General Hospital and, from 1999 to 2003, had served as director of HMNI. In addition to McKhann's involvement in a number of scientific organizations, he has served as president of the American Neurological Association, the leading academic neurology society. Each recipient has published more than 200 peer-reviewed papers and together authored the book *Keep your Brain Young*. ♥



Ann and Tom Korologos and Gail (Mrs. John) Hilson



Bruce Gelb and Gail (Mrs. Richard) Bockman



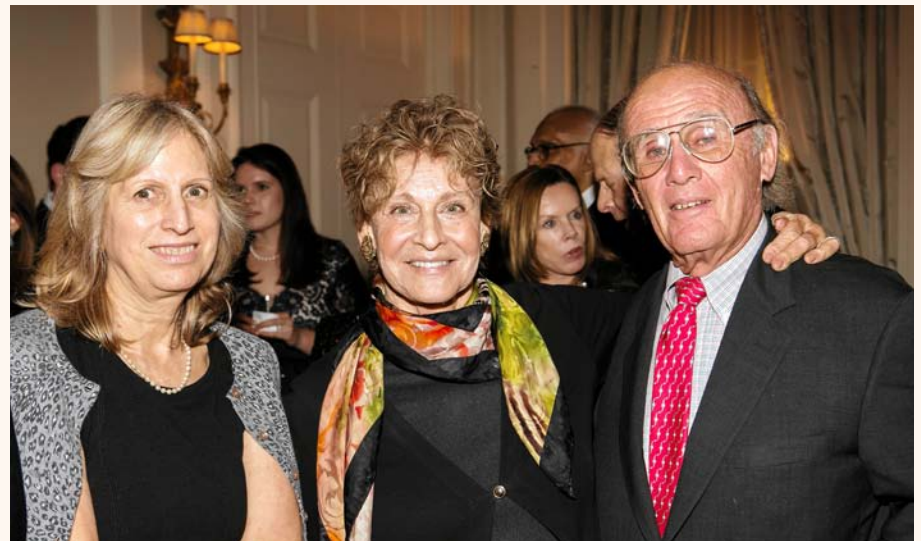
Edward Rover, Charles and Emily Grace, and Guy McKhann II, MD, the Florence Irving Associate Professor of Neurological Surgery at Columbia University Medical Center



Keynote speaker Sandeep "Bob" Datta, MD, PhD, an assistant professor of neurobiology at Harvard Medical School



Hildegard Mahoney, chairman of the Harvard Mahoney Neuroscience Institute, and grandson David Mahoney IV



Louise Mirrer, president of the New York Historical Society; Ellen (Mrs. Arthur) Liman; and Walter Liebmann



LaSalle Leffall Jr, MD, the Charles R. Drew Professor of Surgery at Howard University College of Medicine; Kathy (Mrs. Ted) Stevens; John Pinto; and Ruth (Mrs. LeSalle) Leffall



Ambassador Alan Blinken and Suzanne and William McDonough



Maureen (Mrs. Edward) Rover and Peter Nadosy



Marilyn Albert, PhD, accepts 2014 David Mahoney Prize from Hildegarde Mahoney



Myriam (Mrs. Alan) Magdovitz and Issac Shapiro



Melinda (Mrs. Alan) Blinken and Jeff Tarr



Mai (Mrs. Ridgley) Harrison and John Herman, MD, an associate professor of psychiatry at Harvard Medical School and associate chief in the Department of Psychiatry at Massachusetts General Hospital



Hildegarde Mahoney presents Guy McKhann, MD, with 2014 David Mahoney Prize

Unlocking the Secrets of Coma

WE COMMONLY USE the term coma to refer to a deep, numbing sleep in which we feel, see, and hear nothing. Kurt Vonnegut famously drew upon this definition when, in *Slaughterhouse-Five*, he wrote about coma: “How nice—to feel nothing and still get full credit for being alive.”

Clinically speaking, coma is a state of unawareness from which one cannot be aroused. “A comatose patient does not arouse, or open the eyes, to any stimulus and does not have any awareness of self or environment,” says Brian Edlow, a clinical fellow in neurology at Harvard Medical School who treats coma patients in the Neurosciences Intensive Care Unit at Massachusetts General Hospital. “A neurological examination of such a patient demonstrates only reflexive, not purposeful movements.”

The inability to maintain consciousness and to respond actively to sensory stimuli is the crux of the definition of coma. For a human to be or to remain conscious, two regions of the brain, the cerebral cortex and the ascending reticular activating system, or ARAS, must function appropriately. The cerebral cortex controls central functions such as complex thinking, reasoning, sensory perception, information processing, and producing and understanding language. The ARAS is a more foundational structure, part of what is often referred to as the brain’s primitive region,

Some patients fully recover from a coma—although, unlike in the movies, they don’t suddenly become alert and full of energy. Others partially recover and often experience ongoing paralysis.

located in the brainstem. It helps regulate arousal, alertness, and attention, and works with the cerebral cortex to maintain consciousness.

Comas, which can be reversible but are sometimes long-lasting, are caused by trauma to the brain. More than half of comas are attributed to head trauma, in which swelling or bleeding damages the ARAS, or to conditions such as stroke or hypoxia, each of which deprives the brain of blood flow or oxygen.

Being in a coma is not the same as being in a vegetative or a minimally conscious state, although the terms are often used interchangeably. Edlow describes the three as “profoundly different states

of consciousness.” Although a patient in a coma cannot be aroused, a patient in a persistent vegetative state will open his eyes, but will not demonstrate any evidence of awareness. By comparison, a minimally conscious person will not only open his eyes but will also display a clear, albeit inconsistent, awareness of self and environment. These distinctions, says Edlow, are critically important for patient diagnosis and for understanding the pathophysiology of altered consciousness. The most commonly used bedside test to determine a patient’s level of consciousness is the Glasgow Coma Scale (GCS), which is used to help gauge the severity of acute traumatic brain injuries. Because the GCS does not reliably distinguish between the vegetative and minimally conscious states, many clinicians are turning to the Coma Recovery Scale developed by Joseph Giacino, an HMS assistant professor of physical medicine and rehabilitation and director of rehabilitation neuropsychology at Spaulding Rehabilitation Hospital. This scale was specifically developed to differentiate between these states of consciousness.

Some patients fully recover from a coma—although, unlike in the movies, they don’t suddenly become alert and full of energy. Others partially recover and often experience ongoing paralysis, seizures, and neurocognitive impairment. Patients who don’t recover, may transition to a vegetative state or even to brain death, when all brain activity ceases.

The key to consciousness

Currently, says Edlow, it is difficult to predict whether a comatose patient will recover consciousness and functional independence. The use of imaging, such as functional MRI, to determine how much brain activity persists in a patient experiencing a coma is still being refined. Recent imaging studies, however, are beginning to tell clinicians and neuroscientists more about brain activity during the early stage of recovery from coma. Scientists at Mass General and elsewhere have shown that regions of a patient’s brain may activate in response to a stimulus—spoken words transmitted into the patient’s ears via headphones, for example—even if the patient does not exhibit a behavioral response to the stimulus. The findings were observed in patients who

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had recently emerged from a coma and entered either a vegetative or minimally conscious state.

In a 2012 study in the *Proceedings of the National Academy of Sciences*, an international team of scientists discovered that coma patients have radically reorganized brain networks. Using fMRI scans, the scientists compared the brain scans of 17 comatose patients with the brain scans of healthy participants. They looked for changes in blood flow, an indicator of brain activity, in more than 400 brain regions. In the healthy patients, nearly 40 high-traffic hubs that process much of the brain's electrical firing showed activity. Those same hubs are without activity in the brains of the comatose patients. The comatose patients also showed fewer hubs of activity in the precuneus region of the brain, an area that plays a role in self-consciousness and episodic memory. Because these hubs direct so much of the brain's activity, the researchers say their findings may hold clues to consciousness.

Such studies, says Edlow, have not been validated by larger ones, but their findings do offer promise for increasing our understanding of brain function during coma. "Our hope is that with rigorous testing of comatose patients using fMRI and other advanced imaging techniques, we will ultimately be able to determine whether the patient has the potential to recover consciousness."

Mapping recovery

At Mass General, Edlow is part of a research team investigating the use of high angular resolution diffusion imaging (HARDI) as a tool for mapping the structural connectivity of brain networks critical to consciousness. The scientists are following traumatic coma patients by charting the patients' brain networks during the acute stage of injury, with the hope of determining whether the HARDI network maps are useful predictors of consciousness recovery six months after injury.

If this tool proves effective as an indicator of recovery potential, Edlow says clinicians could use the maps to better inform families about recovery possibilities. "Ultimately," he adds, "once we identify these pathways, we can develop new therapies to promote the healing of neurons within them, or we can try to replicate the functions of these pathways with medications or other interventions." ♥

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