

ON THE BRAIN

THE HARVARD MAHONEY NEUROSCIENCE INSTITUTE LETTER



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Humor, Laughter, and Those Aha Moments

A DUCK WALKS into a bar. ...It's a joke! Hearing just the first few words, your brain springs into action. The path of neuronal activity is a complex one that enlists various brain regions: the frontal lobe, to process the information; the supplementary motor area, to tap learned experience to direct motor activities such as the movements associated with laughter; and the nucleus accumbens, to assess the pleasure of the story and the reward that the "aha!" brings. When the punch line hits home, your heart rate rises, you jiggle with mirth, and your brain releases "feel good" neurotransmitters: dopamine, serotonin, and an array of endorphins.

Jokes work because they defy expectations. The surprise aspect of these tales kicks in the frontal lobe's search for pattern recognition. The punch-line moment shifts one's orientation away from information processing toward an emotional response arising deep within the nucleus accumbens. This response is then tagged for an overall relevance check. If the prefrontal cortex, which is part of the frontal lobe, deems the information attention worthy, it dedicates more processing power to it, along with conscious awareness. If the information remains relevant through the punch line, the brain shifts its response to its pleasure-and-reward center, which in turn triggers a guffaw.

"It's important to make a distinction between humor and laughter," says Carl Marci, MD, an assistant professor of psychiatry at Harvard Medical School and the director of social neuroscience in the Psychotherapy Research Program at Massachusetts General Hospital. "Humor is an evoked response to storytelling and shifting expectations. Laughter is a social signal among humans. It's like a punctuation mark."

To Titter Is Human

Humans experience the humor of a joke in three phases. First, the listener encounters some type of

incongruity: a punch line that seems out of place compared with the joke's set-up. Then, following a cognitive construct called surprise and coherence, the listener tries to resolve this incongruity. Finally, the listener's brain determines the joke's sense—or lack thereof—and decides whether or not the joke is funny.

"The body sends a signal to the brain that says, 'Hey, that's clever, that's worth it,' and we laugh," says Marci.

So incongruity and dashed expectations form the foundation of what's funny. But, as any comic will tell you, timing is everything. Most successful jokes are funny because the incongruity occurs within the few beats that exist between the set-up and the punch line. The following joke provides an example:

Gymnast: Can you teach me to do the splits?

Gymnastics instructor: How flexible are you?

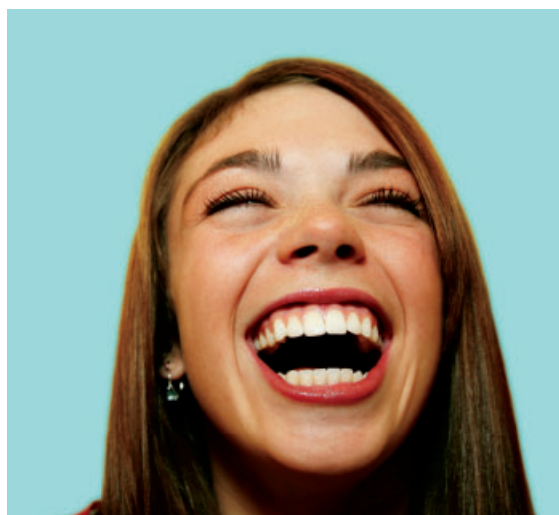
Gymnast: Well, I can't come in on Thursdays.

We suss out the humor of this joke using the concept behind what scientists call the incongruity-resolution theory. The set-up gets us thinking in one direction, then the punch line comes along

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and jars us into realizing there is a completely different way to interpret the situation. By resolving the incongruity—in this case, the double meaning of “flexible”—we are suddenly surprised. Our proverbial funny bone gets tickled, and we snicker.

Studies have shown that the prefrontal cortex plays a vital role in the flexible thinking required to “get” a joke. This region of the frontal lobe, located forward of the brain’s motor regions, processes sensory information gathered by our eyes, ears, and other senses, then combines this information in a manner that helps us form useful, behavior-guiding judgments. The region also oversees the processing needed for planning complex cognitive behaviors, showing personality characteristics, and moderating social behavior. And it is the prefrontal cortex that helps us make sense of a joke’s punch line by sending signals along connections to both the supplementary motor area and the nucleus accumbens, producing a strong sense of surprise and eliciting laughter. In short, our prefrontal cortex is on the case as soon as we hear the first mention of that gymnast and that trainer.

Why We Laugh

“Laughter was a safe, early social signal to form human bonds,” says Marci. “Before we could speak, laughter told early humans that ‘Everything’s okay, you can come over to my side.’”



Laughter is thought to have predated human speech, perhaps by millions of years, and may have helped our early ancestors clarify intentions during social interactions. But as language began to evolve, laughter may also have provided an emotional context for conversations—a signal of acceptance.

Scientists have described laughter’s evolution as one that preserved shared expressions of relief marking the passing of danger. Certain contemporary researchers think that jokes link with this: We laugh out of relief when we recognize the surprise element of the joke.

Humans, however, are not the only species to laugh; when tickled, some primates, including apes, gorillas, orangutans, and chimpanzees, will giggle, hoot, and scrunch their faces in a laugh-like manner. Yet scientists have no evidence that these other primates have a sense of humor. In fact, many researchers doubt they do. Unlike the brains of humans, the brains of primates are not thought to have evolved in a manner that would allow them to process the incongruities introduced in a joke.

A Powerful Contagion

Although the neural mechanisms of depression, anger, and fear have been tracked by scientists for years, only recently have investigators begun to look at how the brain processes humor.



The brains of depression sufferers, for example, show decreased activity in the regions that are engaged during the processing of something humorous. Researchers are studying whether this decrease in activity somehow impairs the brain's ability to process humor. If indeed researchers find processing abnormalities in parts of the brain that handle humor, then some speculate it might be possible to boost activity in these key regions to lessen the symptoms of depression.

"The core deficit in depression is an imbalance between the frontal lobe and reward centers of the brain," says Marci. "If those areas are important for laughter, then someone who is depressed will laugh less."

Marci has in fact investigated humor's role in mood disorders. In 2004, he published a study in the *Journal of Nervous and Mental Disease* on the effects of laughter during psychotherapy. Among the study's participants, Marci found that for patients being treated for depression, anxiety, and other mood disorders, laughter was less about humor and more about communicating emotions. On average, these patients laughed about fifteen times in each fifty-minute psychotherapy session. To determine whether laughter had an effect on the patients, Marci measured the skin conductance, basically a measure of sweat, of both patients and psychiatrists. Skin conductance increases with the nervous system activity that controls blood

pressure and heart rate, which together signal an aroused state. When clinicians did not laugh with patients, conductance measures still indicated both parties were aroused. But when patients and psychiatrists laughed together, the arousal measures for each group doubled.

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The contagion of laughter, Marci says, suggests patients felt that the emotions they expressed were being validated. It also supports the notion that empathy is a shared experience. That laughter is catching is a reason television sitcoms use laugh tracks: taped laughter invites audience participation.

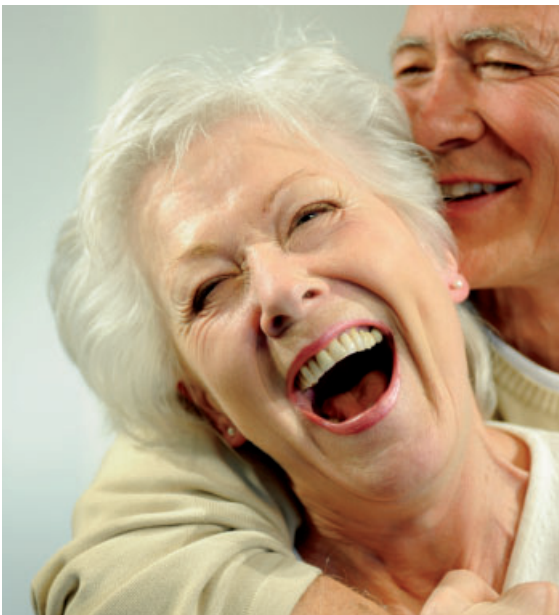
The findings, Marci adds, also suggest that mirror neurons, which are linked to empathic behavior, are often involved in laughter. Mirror neurons are a subset of neurons that fire both when we perform an action and when we observe that same action performed by others.

Once Daily, with Gusto

Laughter may also confer health benefits. For the past forty years, studies have shown that good, hearty laughter can relieve tension and stress; boost the immune system, by reducing stress hormones and increasing activity among immune cells and antibodies; and help reduce the risk of heart attack and stroke, by improving blood flow and blood vessel function.

Laughter and humor can be a tonic for the brain, as well. Triggering the brain's emotional and reward centers spurs the release of dopamine, helping the brain to process emotional responses and enhancing our experience of pleasure; of serotonin, to buoy our mood; and of endorphins, to regulate our pain and stress and to induce euphoria.

The next time you hear a joke, whether you get it or not, let yourself go and enjoy a good, hearty laugh. It's good for you! ♥



Creating Immunity to Addiction

IMAGINE THE DAY when a person addicted to cocaine can walk into a clinic, get a series of shots—and never crave cocaine again. While this relief is not yet on pharmacy shelves, a vaccine that helps significantly block cocaine’s addictive action may not be that far away.

According to Kevin Hill, MD, such a therapeutic approach would alleviate one major frustration for clinicians in addiction psychiatry. “Although we’ve been excited to think that pharmacogenomics, brain imaging, and other potential avenues to therapy could help us make progress against addiction,” he says, “so far, we haven’t been able to make the strides we’ve hoped for.”

Hill, an instructor in psychiatry at Harvard Medical School and the psychiatrist-in-charge at McLean Hospital’s Alcohol and Drug Abuse Treatment Program, has been closely following research on a vaccine called TA-CD—Therapy for Addiction-Cocaine Dependence. As with vaccines for pneumonia, the flu, and measles, TA-CD stimulates an immune response, prompting the body to produce antibodies that bind to cocaine molecules as they enter the bloodstream. Usually, the immune system automatically jumps into action on encountering foreign substances, such as bacteria or viruses. Cocaine, however, can enter undetected. As is often the case with street drugs and even drugs with therapeutic value, cocaine molecules are too tiny for the immune system to detect. In addition, cocaine’s size allows it to slip easily into the brain.

The TA-CD vaccine cuts out cocaine’s tiny-size advantage. When coupled with an antibody, cocaine becomes too large to cross the blood-brain barrier and create the euphoric high that helps foster addiction.

To be effective, the vaccine must be delivered in five shots over a three-month period, with follow-up boosters every two months. This regimen and the efficacy of the vaccine have been established by a husband-and-wife research team at Baylor College of Medicine. Thomas Kosten, a psychiatrist, and Therese Kosten, a neuroscientist, vaccinated fifty-eight volunteers suffering from cocaine addiction and found that 38 percent produced enough antibodies to blunt the stimulant’s effects. More than half of the participants reduced their cocaine use by up to 50 percent.

“The Kostens found that the vaccine worked really well for people who developed a sufficient number of antibodies,” says Hill.

A Hunger for Pleasure

Although the number of cocaine users in the United States has declined slightly since 2000, cocaine remains popular. An estimated 5.3 million Americans over age 12 abused cocaine in 2008. And in 2009, more than 1 million used crack, the street name for cocaine that has been processed as rock crystal. When heated, crack forms smoke that can be inhaled.

Cocaine stimulates the brain’s production of dopamine, a neurotransmitter associated with pleasure. Normally, a neuron releases dopamine in response to a pleasurable sensory signal, then recycles the chemical back into the cell to end this response. Cocaine prevents dopamine reuptake, which causes the neurotransmitter to build up in the synaptic regions between neurons. It is this excessive build-up of dopamine that creates euphoria.

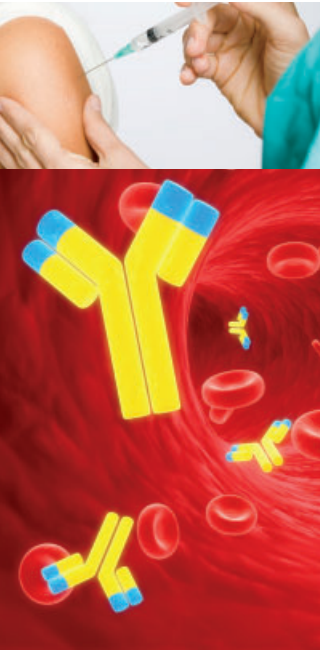
“With increased use of cocaine,” says Hill, “and concurrent rise in the amount of dopamine in the synapses, the brain’s physiology can change over time and essentially create a hunger for the drug.”

That hunger is addiction. Addiction alters the brain’s reward system, which includes the ventral tegmental area, the nucleus accumbens, and the prefrontal cortex. With prolonged use of the drug, neurons produce less dopamine. Between doses, euphoria is replaced by fatigue, depression, anxiety, and agitation. To reclaim their high, users require larger amounts of the drug. As their intake increases, addicts experience mood disturbances, irritability, restlessness, and even paranoid psychosis, which comes with auditory hallucinations and an inability to remain grounded in reality.

Hurdles Remain

Excitement within the research and clinical communities about the Kosten study is tempered by the understanding that some vaccinated subjects did not make enough antibodies to blunt cocaine’s effects. Researchers are still seeking the scientific mechanism behind the vaccine as well as the formula needed to trigger effective levels of antibodies.

How addicts take cocaine can pose an obstacle to the vaccine’s effectiveness. People who smoke crack cocaine, for example, might not develop the necessary antibodies because they heat the drug before inhaling it. Hill says the high temperature of the cocaine molecules stimulates an inflammatory reaction that prevents antibodies from binding to



Deciphering the Teenage Brain

the cocaine. Thus the cocaine molecules remain small enough to enter the brain.

Users also might foil the vaccine's effects by taking so much of the drug that the body cannot mount a sufficient immune response.

"Patients are very clever," says Hill, "and often are ambivalent about treatment—and their desire to maintain abstinence."

A Treatment Tool

The TA-CD vaccine is not a preventive measure, but rather a therapeutic option only. Hill says the vaccine is geared toward hard-core rather than recreational users. The success of the treatment depends largely upon the user having a strong desire to stop taking cocaine.

Says Hill, "The National Institute on Drug Abuse is excited about this vaccine, researchers are excited about it, and clinicians are excited about it. But I'm skeptical about any drug therapy being a panacea. The brain is a complicated organ."

Hill instead believes any effective treatment for cocaine abuse must combine medications with behavioral therapies. Currently, no medications are approved by the U.S. Food and Drug Administration for treating cocaine addiction. Several, however, are being studied, including acetylcysteine, used to treat acetaminophen overdose; baclofen, employed against certain types of alcohol dependence; and vigabatrin, an epilepsy treatment that may help relieve cocaine and amphetamine dependence. A cocaine substitute, vanorexine, is being investigated as a mitigator of cocaine's withdrawal symptoms and as a block to its euphoric effects, just as methadone is for heroin.

Because addiction is a behavior, cognitive behavioral therapy and motivational therapy can help with the social, emotional, and psychological problems associated with continued drug use. Cognitive behavioral therapy aims to address dysfunctional emotional and behavioral problems by encouraging goal setting. Motivational therapy, by comparison, encourages patients to develop a negative view of their drug abuse and a desire to change their behavior.

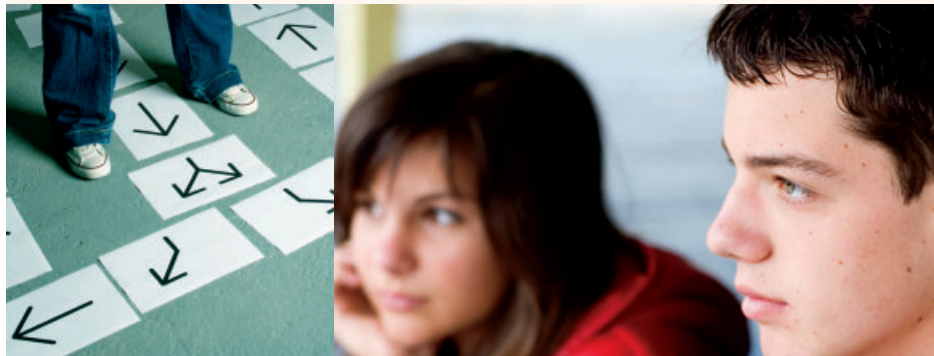
As scientists continue work on a cocaine vaccine, Hill remains cautiously optimistic.

"Treating addiction requires a variety of behavioral and pharmacological approaches," says Hill. "It's probably the same with a cocaine vaccine. To be successful, it should be part of a comprehensive treatment program." ♥

AS MANY PARENTS can attest, the teenage years are a time of trial and triumph, a time for learning and adapting, and, for many teens, a time for risk-taking. This latter characteristic can be especially disturbing to parents and teachers. No matter their intelligence or level of engagement with peers and parents, teenagers simply make perplexing, disturbing, and sometimes dangerous decisions. Why are they such caldrons of contradiction?

"Teens are in a discovery mode," says Frances Jensen, MD, an HMS professor of neurology. "They're experiencing new things, and their brains are developing accordingly. There's simply a lot going on in their brains."

This is the fifth in a series on how internal and external forces affect the brain.



Jensen, who directs epilepsy research at Children's Hospital Boston, found herself taking a professional interest in the developmental arc of the teenage brain as she watched her two sons reach adolescence and "morph into other beings." That domestic prod led her to share her knowledge and research findings in public forums with parents and teachers as well as teens.

Throughout the past decade, a growing number of scientists have been using powerful technologies like functional magnetic resonance imaging (fMRI) to investigate how young brains change. This research has shown that for teenagers, brain cells rapidly form new connections with other neurons, allowing information to move quickly and learning to accumulate. This high degree of connectivity does not exist for all regions of the teenage brain, which may help explain teens' impulsive behavior and poor decision-making. Studies have, in fact, shown that the adolescent brain is only about 80 percent developed, findings that Jensen says make

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it clear that teenagers are not just “young adults with fewer miles.”

Not Fully Online

From childhood through adolescence, the brain’s billions of neurons and synapses form and re-form connections, giving it the plasticity needed for learning. Throughout the development continuum, says Jensen, the brain is like a sponge, soaking up experiences. That is why children and teenagers can master such skills as foreign languages and musical instruments more easily than adults can.

The teenage brain matures from back to front. The posterior regions, especially those above the spinal column, are largely responsible for motor control. Their earlier maturation helps account for the quick acquisition of locomotion and other movement skills by young people. Maturation of many sensory regions also occurs early, enabling a growing person to learn from the surrounding world. The maturing of the forward regions of the brain, particularly the frontal lobe, doesn’t occur until late adolescence or early adulthood; some researchers say the region’s maturation may not be complete until age 30.

The frontal lobe is the seat of executive function, a term for the cognitive processes that allow us to plan, make decisions and judgments, formulate insight, and assess risk. The delayed maturation of connections to the frontal lobe, Jensen says, contributes to teenagers’ risk-taking. “Their frontal lobes,” she says, “are simply not yet fully online.”

The percentage of neurons in the adolescent brain that are myelinated is also lower than that in the adult brain. Myelin is the insulating coating that helps neurons pass signals along rapidly. As the brain matures, the number of myelinated neurons grows, forming a dense mass—the brain’s white matter. To underscore the developmental track that myelination takes, Jensen points to fMRI studies that show myelinated cells beginning to appear in the brains of people in their early twenties.

Statistics also bear out the link between teenagers and such health- and life-imperiling behavior as dangerous driving, unsafe sex, poor dietary habits, and experimentation with alcohol and drugs. One area in which teens’ recklessness and inexperience collide is motor vehicle crashes: Per mile driven, 16- to 19-year-olds are four times more likely to crash than older drivers. According to the U.S. Centers for Disease Control and Prevention, motor vehicle crashes are the leading cause of death among U.S. teenagers.

The Double-Edged Sword of Learning

The ease of learning that most teens enjoy, however, can carry a steep cost: addiction. “The brain builds itself as it responds to experiences,” Jensen says. “With teens who experiment with drugs, this can result in addiction. It’s the same pattern as learning—we want more, more, more.”

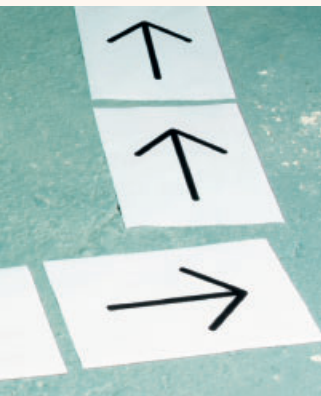
At play in this scenario is the brain’s limbic system—its pleasure-and-reward hub. This region matures earlier than the frontal lobe, which may explain in part why teenagers who experiment with drugs and alcohol often relish the attendant “highs” but fail to appreciate fully their associated risks. Two studies from 2004 support this supposition. Researchers at Emory University found that reward circuits involving pleasure and addiction in teen brains are hyperactive compared with adults, suggesting that teens may have a greater biological sensitivity to reward than adults do. Similarly, investigators with the National Institute on Alcohol Abuse and Alcoholism found that the teen brain’s nucleus accumbens, part of the limbic system thought to play a central role in the reward circuit, responds to reward at a level similar to that found for adults, whereas teen-brain frontal lobes respond at a level similar to that of younger children.

No Free Pass

The challenge for parents, educators, clinicians and others who deal with teenagers is to determine whether their exasperating behavior is just the stuff of growing up or whether their moodiness and lack of judgment are indicative of a larger, perhaps pathological, problem. Many mental disorders begin to manifest during adolescence, including schizophrenia, anxiety, depression, eating disorders, and drug and alcohol abuse.

“The key,” says Jensen, “is to be aware of what’s going on with your kids. Teens today are exposed to more stress than ever before, including drugs, alcohol, and violence. We all have to be mindful.”

What is interesting, says Jensen, is that most adolescents are eager for information about how their brains change during their teen years. She adds, “Because of the amount of research being conducted and the findings that are available, these teens are the first generation to really know what’s going on in their brains. We need to tell them what the warning signs are for abnormal, risky behavior. This is a time of self-discovery, and these kids are ripe for this type of information.” ♥



Manual of Mental Disorders Being Revised

A REVISION TO THE “bible” for professionals who make psychiatric diagnoses in the United States—the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders (DSM)—will be delivered in 2013. The revised diagnostic manual, which will be known as DSM-V, will supersede one that’s been in use nearly twenty years.

The manual provides diagnostic guidance on conditions driven by psychosocial stressors such as relocation, divorce, and unemployment as well as guidance on nearly 300 clinical disorders that range from schizophrenia, depression, and autism to obsessive-compulsive disorder, narcissistic personality disorder, and mental retardation.

The book’s revision has been a monumental undertaking, involving more than 600 experts in mental health throughout the world. Within any of thirteen work groups, they were tasked to assess existing material, propose changes, and review and analyze revisions. Among those involved in two of the work groups are Harvard Medical School faculty members Deborah Blacker, MD, ScD, a geriatric psychiatrist and epidemiologist, and Anne Becker, MD, PhD, a medical anthropologist, psychiatrist, and epidemiologist. Blacker, an HMS associate professor of psychiatry, directs the Gerontology Research Unit at Massachusetts General Hospital; Becker, an HMS associate

professor of psychiatry and of social medicine, heads up that hospital’s Eating Disorders Clinical and Research Program.

‘Minor’ Cognitive Impairments

Blacker serves on the Neurocognitive Disorders work group. So far, she says, two significant changes are being proposed for her group’s section of the revised manual. One is a name change: The category now called Delirium, Dementia, Amnesic, and other Cognitive Disorders will now be named Neurocognitive Disorders. Compared with people whose neurological disorders result from developmental deficits, individuals suffering from neurocognitive disorders experience a decline in cognitive function from a known baseline. By renaming the category, work group members hope to clarify the distinctions between disorders that can develop quite early in life and those that are often age- or injury-related.

“People with head injuries, AIDS, and other conditions, including many young people, are often troubled by diagnoses from a category with a dementia label,” says Blacker. “They see dementia as an ‘old people’s’ disease. Professionals, on the other hand, don’t like dropping dementia. The Neurocognitive Disorders work group is trying to develop a compromise and to satisfy the needs of both groups.”

While retaining delirium and “major neurocognitive disorder” or dementia, the group’s also suggesting the category be expanded to include minor neurocognitive disorders such as mild cognitive impairment, which does not interfere significantly with daily function. In the decades since the last DSM revision, Blacker points out, clinicians have acquired a better understanding of the breadth of disorders that should be classified as neurocognitive.

Says Blacker, “People in the field now recognize that this category of patient includes those who don’t meet the threshold of a dementia diagnosis but are having real difficulties with memory or other aspects of thinking.”

Binge Eating Stands Alone

Becker’s contributions to the revision center on eating disorders. A name change is in order: an expansion to Eating and Feeding Disorders. The change allows for a grouping of sets of diagnostic criteria related to disordered eating across the lifespan.

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For additional copies or changes to the *On the Brain* mailing list, please contact Ann Marie Menting at 617-432-7764 or by email at ann_menting@hms.harvard.edu

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Becker, however, thinks her group's most substantial change will be recognizing binge eating as a bona fide disorder. The disorder is characterized by recurrent overeating; it is not necessarily associated with the purging behaviors of patients with bulimia nervosa. The previous DSM didn't list binge eating disorder within the manual's main body; it appeared only in an appendix that listed sets of diagnostic criteria needing further research.

"There's been a trove of papers on binge eating disorder published since the last DSM revision," says Becker, "so we now have adequate data to recognize it as a stand-alone diagnosis. Placing the disorder in the Eating and Feeding Disorders chapter will also give it the greater visibility it needs among clinicians and may help spur research on therapeutic interventions."

Blacker and Becker say the revisions their groups seek face two years of review and refinement. Only then will the changes become part of the chapter and verse that guides their profession. ♥

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