

ON THE BRAIN

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A Question of Free Will?

QUESTIONS ABOUT free will—the capacity to choose a course of action from among various alternatives—have plagued philosophers since the beginning of time. These questions also confront those who study, treat and suffer from drug addiction.

“Drug addiction has been used as a yardstick for reward-based behavior,” according to Harvard University Provost Steven E. Hyman, M.D., who discussed the issue of free will and addiction in Harvard’s first Provostial Lecture in May. “With addiction, there is a narrowing of life focus in that drug-seeking behavior crowds out all other motivations and goals.”

Dr. Hyman is a professor of neurobiology at Harvard Medical School and was the first director of Harvard’s Mind, Brain and Behavior Initiative. He also served as director of the National Institute of Mental Health.

While free will is more of a philosophical construct than a neurobiological one, Dr. Hyman says the concept can be discussed in terms of addiction without addressing metaphysical concerns. The relationship between the two stems from the fact that certain brain processes and neurochemical mechanisms govern our ability to exert voluntary control over our actions—the essence of free will.

A ‘go’ signal for the brain

Addictive drugs affect the brain’s prefrontal cortex (PFC), which powers our ability to think, plan, solve problems and make decisions, as well as the limbic system, which contains the brain’s reward circuit.

Addictive drugs interfere with the way nerve cells send, receive and process information by mimicking the chemical structure of neurotransmitters, the brain’s chemical messengers. An important end result caused by all addictive drugs

is a highly excessive release of the neurotransmitter dopamine in synapses, the structures across which nerve cells communicate

Dopamine plays a role in marking experiences as positive and highly significant. Released whenever we experience a new or unexpectedly strong reward, dopamine instructs nerve cells to form memories that will guide future behavior toward repeating the actions that led to such positive or “rewarding” experiences. Naturally rewarding experiences, such as a good meal or a cold drink on a hot day, are given different values by the brain and are stored in the prefrontal cortex. As their novelty wears off or we have other rewarding experiences, our brain assigns them different values, and we are able to make relatively free choices among them. Addictive drugs take over the normal mechanisms by which we make choices. Every time a person takes an addictive drug, a big slug of dopamine is released in the brain, both in the parts of the brain that govern emotions and in the prefrontal cortex, which guides our choices.

“Normally, the job of dopamine is to signal important life enhancing, positive survival goals,” says Dr. Hyman. “Addictive drugs short-circuit the natural mechanism that releases dopamine in the brain. They basically hijack the normal survival system involved in decision making by altering the function of the prefrontal cortex and other brain regions. Thus, drug-seeking behavior becomes the addict’s most important behavioral priority.”

Drugs have an advantage over natural rewards such as food because addictive drugs act directly in the brain to release dopamine. For example, when we go to a restaurant and have a tasty new dish our reward system helps to consolidate the memory and tells us, “That was good. Let’s do it again, and let’s remember how we did it.”

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A Systems Approach to Autism

AS FAR BACK AS 1943, when psychiatrist Leon Kanner published his paper “Autistic Disturbances of Affective Contact” in *Nervous Child*, the signs for a systems-based approach to autism were evident, suggests Martha Herbert, M.D., Ph.D., a pediatric neurologist at Massachusetts General Hospital. Of the 11 children Kanner studied, most had signs of gastrointestinal problems such as diarrhea and malabsorption or immune abnormalities such as recurrent infections.

Kanner’s findings didn’t mean much to the psychiatry, psychology and neurology communities when they were published, but now several scientists, including Dr. Herbert, an assistant professor of neurology at Harvard Medical School, are advocating the idea that autism is less a brain-based disorder and more of a systemic condition. In a 2005 paper in *Clinical Neuropsychiatry*, she wrote: “...autism is not confined to the brain, given abnormalities in peripheral biomarkers and in other organ systems, prominently gastrointestinal and immune, that are common fellow travelers with autism behaviors.”

Changing the thinking about autism

Autism is defined as a neurodevelopmental disorder that manifests before age 3 and is marked by impaired social interaction, communication and restricted and repetitive behavior. The number of children diagnosed with autism has risen dramatically since 1980. Federal health authorities say about one in every 150 children now have autism spectrum disorder (ASD). The Massachusetts Department of Education recently reported an increase in autism diagnoses from 4,000 to 7,521 in the past five years.

Autism affects each individual differently—from mild delays in language to greater challenges with social interaction. Some of the more common characteristics of autism include: resistance to change, difficulty expressing needs, repeating words or phrases, preference for being alone, tantrums, difficulty socializing with others, little or no eye contact, sustained odd play, spinning objects, obsessive attachments to objects, and uneven gross and fine motor skills.

For years, scientists and clinicians have considered autism to be a strongly genetic, brain-based disorder; however, that thinking is now changing, with many believing that the behavioral

symptoms of autism are linked to less obvious biological dysfunction.

Quoted in an April 2007 *Discover* magazine article, Dr. Herbert said: “What I believe is happening is that genes and environment interact, either in a fetus or young child, changing cellular function all over the body, which then affects tissue and metabolism in many vulnerable organs. And it’s the interaction of this collection of troubles that leads to altered sensory processing and impaired coordination in the brain. A brain with these kinds of problems produces the abnormal behaviors that we call autism.”

Systemic dysregulation

The most prominent aspect of a whole-body approach, says Dr. Herbert, appears to be the high level of gastrointestinal and immune disorders in autistic children, including food and airborne allergies, ear infections, eczema and chronic diarrhea. Dr. Herbert says she’s “not willing to stop” at just the gut and immune system, since doctors who see many autistic children note subgroups with problems such as seizures, low muscle tone, sleep disorders and sensory disturbances, as well as osteoporosis, renal problems and hormonal issues.

While scientists for years have considered the brain the primary target of autism, this new approach to autism is attempting to determine if the brain is affected at the same time as or even “downstream” of other bodily changes.

“The brain may produce [autistic] behaviors,” Dr. Herbert says, “but there’s also dysregulation at other levels that makes the brain act differently. We may find some overlap [between the brain and body biology].”

Gene-environment interaction

This newer model of autism considers autistic behaviors as one of many effects of genetics and the environment on the whole body, not just the brain. While there is a certain component of heritability to autism, no single gene explains the prevalence of the disorder. Rather, says Dr. Herbert, certain high-risk genes “put you perilously close to the disorder and just a little puff of stimulus from the environment can push you over the edge.”



Other risk genes may need more of a “second hit” from the environment before autism develops.

In fact, she argues, the rising number of autism diagnoses points to an environmental role in the disorder, since genetic changes don’t occur as quickly as the numbers have risen. Further, she says, genes and environmental exposure are not confined to a single body system.

“A genetic change may express itself in many bodily systems and an environmental exposure may target a biochemical vulnerability that is widely distributed in the body... Some bodily systems more directly interface with the environment, such as the gastrointestinal system, which is the first port of entry of many environmental exposures, and the immune system, which deals with responses to

outside intrusions into the body. From the perspective of gene–environment interactions, it should come as no surprise that we are seeing gastrointestinal and immune problems in many autistic individuals,” she writes in the 2006 *Autism Advocate*.

Interactions of the body and brain

The whole–body model opens new avenues for early identification of medical features, as well as for potential treatments to halt or even reverse the effects of autism. By identifying what is causing the harm—either genetically or environmentally—scientists can work on preventive measures.

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The next time we go to the restaurant, however, even if the dish is just as good as the last time, dopamine is not released in our brain; it has already done its job of consolidating the memory of where and how to get this tasty dish. Addictive drugs, on the other hand, directly release dopamine every time they are taken, signaling regions of the brain that set behavioral goals. Whatever the subjective experience, says Dr. Hyman, the brain gets a “go” signal, telling the individual to take the drug again and again and again. Even if a smoker takes a drag and has a painful cough, even if a drinker feels nauseated or depressed, dopamine gets released, and tells the brain, “That was good. Let’s do it again.”

Rewiring the reward circuit

Over time, regions of the addicted person’s brain that have mechanisms to encode memories become rewired as a result of this bombardment by dopamine. Brain cells don’t deteriorate, per se, but rather undergo a set of changes that, under normal circumstances, would help one to remember positive goals and experiences. Drugs, Dr. Hyman says, provide a “grossly excessive” dopamine signal, which alters the brain’s plasticity, or ability to change, eliciting automatic drug craving and drug seeking in response to reminders of drug use. This rewiring of the brain’s circuitry and the resulting loss of control over normal goal–setting and goal–seeking behavior, makes relapse common, even after someone has gone through painful withdrawal symptoms to become drug–free.

The action of dopamine in the addict’s brain would seem like a natural target for drugs that can help treat and cure addiction. If you block dopamine release, however, you block the individual’s normal ability to experience pleasure and learn new information. This, says Dr. Hyman, is “not a suitable approach” to treating addiction.

“We need better pharmacological treatments that don’t block pleasure, but rather weaken the pathological neural connections made under the influence of drugs so that the addicted person can make new and healthy behavioral choices,” he adds.

Behavioral therapies have had some success in treating addiction because they help addicts modify their attitudes and behaviors related to drug abuse and assist them in dealing with triggers that may cause drug craving. Family, friends and other caregivers, says Dr. Hyman, need to act as a “prosthesis” for the brain functions that are compromised by drug abuse. Because the addict’s brain has been rewired to prefer drugs, these advocates must be implacable about getting the addict into and staying in treatment.

Despite the fact that drug addicts’ brains are compromised, diminishing their capacity to control their behavior, Dr. Hyman says it doesn’t help to treat them as if they cannot be responsible for themselves. Because they are addicted, we should not be surprised when they slip. In the end, despite needing help, they have to be the owners of their lives.

Obesity's Right Brain Hypothesis

BY NOW, most of us know: Americans are getting heavier and heavier, and the rates of obesity among both adults and children are rising to epidemic—and dangerous—levels. Thirty years ago, 15 percent of Americans were obese; by 2004, that number had risen to nearly 33 percent, with an alarming increase in the child and adolescent populations. Today, nearly 65 percent of Americans are either overweight or obese.

The rise in obesity has also raised the risk for developing hypertension, Type 2 diabetes, coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea and other respiratory problems, as well as certain cancers. These conditions carry an economic burden costing the U.S. billions of dollars each year.

While many people regard obesity as an eating disorder, research over the past decade has pointed to the brain's role in regulating food intake and the mechanisms by which obesity occurs. Studies have found that, in addition to other health problems, obesity can cause a loss of brain tissue and cognitive decline. Now, Harvard Medical School researchers at Beth Israel Deaconess Medical Center have developed what they call a "right brain hypothesis" for obesity. That is, say HMS neurology professor Alvaro Pascual-Leone, M.D., Ph.D., and postdoctoral fellow Miguel Alonso, M.D., M.Sc., both of BIDMC's Berenson-Allen Center for Noninvasive Brain Stimulation, the right hemisphere of the brain's prefrontal cortex (PFC) plays a critical role in the cognitive control of food intake. The PFC is a region of the brain that controls many complex behaviors that separate humans from other species.

"Cognitive control of food intake is a general term that defines our capacity to process information, apply knowledge, and make decisions," says Dr. Pascual-Leone. "We decide what to eat using our ability to predict the future consequences of our actions. We also take into account factors that can be merely constructs of our mind. Good examples of this are religious diet codes or our beliefs of the impact of diet on health and body shape. This is a uniquely human way to regulate food intake that is not found in animals. It is mostly inhibitory, and its dysfunction could represent a pathway that contributes to overweight and obesity."

Further, say the researchers, it is in thinking about the human dimensions of food intake regulation that they point to the right PFC as a critical brain structure.

Neural circuits of obesity

Simply put, obesity is a condition characterized by the excessive accumulation and storage of body fat. This means that obese people take in more calories than they burn. The coordination of food intake and physical activity is necessary for regulating body weight.

Appetite is a function of the brain, primarily the hypothalamus, an area of the brain that regulates our basic bodily functions. A collection of neurons in the hypothalamus, called the arcuate nucleus, is the brain's appetite center, coordinating the need to eat in relation to our energy availability (i.e., how well our body is fed). This is accomplished by crosstalk between the hypothalamus and signals arising from the gastrointestinal system and adipose, or fat-storing, tissue.

Dr. Pascual-Leone says that two particular neural circuits connected to the arcuate nucleus promote or suppress appetite, respectively. "These circuits help regulate the body's nutritional state, which is why we remain more or less the same weight over the long-term. They help to provide balance to our weight," he says.

In addition, our limbic system, which includes the brain's "pleasure center," contains patterns of food preferences acquired over our lifespan, based on a set of "hard-wired responses to the primary aspects of food, such as tastes or smells," says Dr. Alonso. Sensory organs send signals to the brain about food that can release dopamine, a neurotransmitter that plays an important role in motivation and reward.

Most of this process, he says, comes from learning of associations. For example, if we inspect something brown, gooey and sweet-smelling, we assume that it is chocolate. More than the food, he says, it is the expectation that causes the secretion of neurotransmitters.

"We associate certain foods with certain tastes and smells," says Dr. Alonso, "so eating really starts before the food even gets in our mouths."

Critical area for food intake

In a paper in the July 25 issue of the *Journal of the American Medical Association*, Drs. Pascual-Leone and Alonso say that the “current state of knowledge may not include critical aspects” of the cause of obesity, and that means the role of the prefrontal cortex in appetite control. The researchers write that studies of obese patients with brain diseases point to the PFC as a “critical area” involved in the control of food intake.

Indeed, studies from the mid-1990s found that damage to the right frontal lobe can cause so-called “gourmand” syndrome, which is characterized by a preoccupation with eating and a preference for fine food. Another study found decreased blood flow to the right PFC in Kleine-Levin syndrome, a symptom of which includes excessive food intake. A third study showed that increased activity in the PFC could lead to anorexia-like symptoms.

“The hypothesis,” says Dr. Pascual-Leone, “is not that there is damage to the right PFC. Rather, there’s a certain amount of activity in the right PFC that is needed to exert appetite control. In obese people, this activity is decreased. The right PFC is not necessarily damaged, but it is working too little.”

The BIDMC researchers also say that the right PFC is a critical area for what they call “moral cognition,” the process by which we ascribe values of “good” or “bad” to different foods, influencing our perceptions and decisions about what to eat. Neural circuits in the prefrontal cortex, especially the right hemisphere, also mediate self-recognition and self body image. Dysregulation of the right PFC, then, could “result in a failure to appropriately weigh the adverse consequences of indulging in a bad diet,” which could lead to behaviors that contribute to obesity, they write in *JAMA*. Some data suggest that obesity is associated with low levels of body awareness and right hemisphere dysfunction.

“Society sets us up with a double-edged sword,” says Dr. Alonso. “We offer more food than we can eat, but we also have ideas about body image that are unattainable for many of us. Some of us will never look like Adonis; it’s difficult to achieve this ideal with such easy access to food. This creates a dangerous double-whammy to the mechanism that controls appetite regulation. Nowadays, more than ever, avoiding obesity and keeping weight off may depend on our ability to consciously decide and monitor what we eat.”

Targeting PFC activity to control appetite

There are currently drugs on the market that indirectly target the PFC through effects on neurotransmitter systems, such as dopamine and serotonin. These drugs, however, do not specifically affect PFC activity. “The challenge,” says Dr. Pascual-Leone, “is to understand these drugs and modify them to take action in a specific part of the brain. Higher specificity is needed for them to be effective. We don’t know yet how to do this.”

While many people regard obesity as an eating disorder, research over the past decade has pointed to the brain’s role in regulating food intake and the mechanisms by which obesity occurs. Studies have found that, in addition to other health problems, obesity can cause a loss of brain tissue and cognitive decline.



There are also safety concerns with these drugs. Because obese people are at higher risk for other medical conditions, says Dr. Pascual-Leone, “they may not be able to handle the side effects” of obesity drugs. In their *JAMA* paper, the researchers say that their neuromodulation-based approaches may also enhance activity in the right PFC to “decrease appetite and reestablish inhibitory mechanisms controlling eating.”

The researchers say that, while their hypothesis sheds new light on the brain’s structural role in controlling appetite, the behavioral aspects of eating must not be discounted. “There has been little focus on the human dimension of eating,” says Dr. Pascual-Leone, “and until there is, we probably won’t overcome obesity.”

While work continues on ways to reestablish the inhibitory mechanisms in the brain that control eating, Drs. Pascual-Leone and Alonso say particular attention needs to be paid to the behavioral aspects of obesity for diets and other interventions to be successful.

“Obesity is not just an accumulation of fat,” says Dr. Alonso. “We need to look at what leads to obesity, and that is behavior. We need to turn obesity into a behavioral issue, because a key factor [for obesity] is in the brain where all behaviors start.”

Alcohol Shrinks the Brain, but What are the Effects?

A RECENT STUDY found that the brains of heavy drinkers shrink more than the brains of people who don't drink—and more than is associated with normal aging. The study also showed that there is no beneficial effect on brain volume from even light or moderate drinking, a finding in stark contrast to earlier studies showing that small amounts of alcohol can have a protective effect on brain cells.

What the research does not show—and what still confounds scientists—is how this loss of volume affects how the brain functions.

Conducted by Carol Ann Paul, a researcher at Wellesley College, the study examined MRI scans acquired from 1999 to 2002 of more than 1,800 participants from the Framingham Offspring Study and was designed to determine whether the cardiovascular benefits associated with light-to-moderate alcohol consumption could also be seen in the brain. The study found that people who had more than 14 drinks per week—considered heavy

drinkers—had an average 1.6 percent reduction in brain volume compared with people who never drank. Further, the study found that brain volume decreased 0.25 percent for every increase in drinking category (non-drinkers, former drinkers, low drinkers, moderate drinkers and high drinkers). Even light drinking had no beneficial effect, contradicting studies showing the cardiovascular benefits of a daily drink.

On the whole, says Bruce H. Price, M.D., chief of neurology at McLean Hospital and professor of neurology at Harvard Medical School, the Wellesley College study adds to the “immensely controversial and not at all definitive” nature of the study of alcohol's effects on the brain.

The findings of this study of brain volume, presented at a recent meeting of the American Academy of Neurology but not yet published, contradict earlier findings that small amounts of alcohol—one to one-and-a-half glasses of red wine daily—can protect brain cells. The point at which



the effects of drinking on brain size outweigh the previously shown cardiovascular benefits of light drinking remains unknown.

Slowing down brain activity

What is well known is that alcohol is a depressant that slows down brain activity. After one or two drinks, most people begin to feel relaxed. While producing a sense of pleasure, alcohol can also distort judgment and lower one's inhibition. As more alcohol is consumed, it reaches the cerebellum, the brain's center for movement and balance, affecting coordination and perception. When alcohol reaches the midbrain, reflexes become diminished and confusion and stupor set in, often followed by loss of consciousness. Once the alcohol reaches deep within the brain's inner core, the medulla (which controls the body's automatic functions), heart rate decreases, breathing becomes shallow, and body temperature drops. At this point, alcohol intoxication can become life-threatening.

Many of the impairments that result from drinking—difficulty walking, blurred vision, slurred speech, and impaired memory—usually resolve once the drinking stops and the alcohol has left the system. Over the long term, however, heavy alcohol consumption can cause extensive damage to the brain and body, resulting in simple memory problems to more permanent, debilitating conditions that require lifelong care such as liver disease, heart failure, and impaired immunity.

Advanced imaging technologies, including MRI, diffusion tensor imaging (DTI), positron emission tomography (PET), and electrophysiological brain mapping, now allow researchers to study, in more detail, the effects of alcohol on how our brains function.

MRI and DTI are being used to study how long-term heavy drinking leads to deficiencies in the white matter fibers that carry information between brain cells. MRI studies are also helping researchers determine how alcohol affects memory and attention. PET scans allow scientists to examine the living brain to determine the effect alcohol has on neurotransmitters (parts of the brain's communications system), brain cell metabolism, and blood flow in the brain. Other studies, using electroencephalography, help to show real-time electrical activity in the brain.

Effect on function is unknown

While the Wellesley study shows a relationship between total brain volume and alcohol consumption, Dr. Price says the findings need to be more fully parsed out. Because the study did not also show effects on cognition, we don't know what effect the shrinkage has on brain function, nor what, if any, correlation exists with other well-known effects of heavy drinking.

Nor, adds Dr. Price, do we know what role diet, mood, recurrent depression or chronic stress may have played in the volume loss. Scientists do know that a gene associated with increased risk for developing Alzheimer's disease, called APOE4, along with alcohol and a poor diet, can cause brain shrinkage greater than normal aging would suggest. In addition, he says, scientists know that chronic alcoholics lose subcortical white matter, resulting in decreases in total brain volume.

The question, however, remains: what does all this mean in terms of brain function? Scientists are still seeking the answer.

Favoring a protective effect for the brain

The plus side, however, is that the brain volume of alcoholics expands if they abstain from drinking for more than a year or so. Dr. Price likens this to a muscle that grows if it is exercised after periods of disuse. "But," he adds, "we don't know about the cognitive correlates. There's no solid evidence that brain function improves with volume increases. We'd like to think that's the case, but there's no proof."

The caveat about the Wellesley study, adds Dr. Price, "is that the devil is in the details. The study is probably more of a minority view in that it shows no beneficial effect on brain volume even in small doses." But neither does it definitively prove that decreases in brain volume adversely affect brain function.

While Dr. Price says the "favored view" among scientists will continue to be that a drink of wine or two a day does, indeed, protect the brain, he cautions that the negative effects of heavy drinking must factor into one's decision about just how much alcohol to consume.



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A Systems Approach to Autism

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Knowing how particular causes or triggers contribute to autism, researchers may be able to develop blood or urine tests, as well as biomedical therapies. Additionally, understanding interaction between the brain and body in autism may lead to interventions that treat the body and also have an impact on brain function and behavior.

Studies of how autism develops have been conducted tracking high-risk younger infant siblings of children diagnosed with autism, but until now these studies have only measured behavior and have not studied body and medical issues.

"My hunch," says Dr. Herbert, "is that when we do whole-body studies of how autism develops, the biological responses will change before behaviors. It's important to identify autism early, and we'll do a better job [with early identification] when we understand what's going on not just behaviorally but also in the whole body. Remember that when we call autism a systems disorder, we aren't down-playing the brain part. We're just saying that the brain is in the body, and that there are multiple dimensions at work here, not just the brain."

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