Brain Sabotages Sobriety, Right on Cue

Pavlov's Progeny Provide Pictures of Alcoholism

Brian Vastag

NEW HAVEN, CONN—Ivan Petrovich Pavlov never had it so good. He may have won the 1904 Nobel Prize in Physiology or Medicine—but only after collecting buckets of bodily fluids from his famously hungry dogs. A century later, his scientific progeny measure anticipation with brain scans, not drool pans.

The feisty physiologist would likely be pleased. Researchers peeking into the brain with sophisticated imaging are beginning to map the neurobiology of craving. While discovering why alcohol and other drug habits can be so hard to kick, they are also documenting the brain damage caused by alcoholism.

"Clearly, chronic alcohol use changes the brain," said Raymond Anton, MD, Medical University of South Carolina, Charleston, speaking at a recent meeting on neuroimaging of alcohol disorders held at Yale University School of Medicine in New Haven, Conn. Many of these changes sensitize individuals with addiction to specific cues—the sights, sounds, smells of their drink of choice. Even if they don't drool, the brain betrays them. It appears that deeply entrenched neural patterns light up the brain's memory, pleasure, and reward circuits moments before a sober alcoholic recognizes the familiar urge.

One key question is how, exactly, these preconscious moments undermine sobriety. "In recovery, can this response predict who will relapse?" asked Daniel Mathalon, MD, PhD, an imaging researcher at Yale. "That's a question we're now equipped to try to answer," he said.

TAKING THEIR CUES

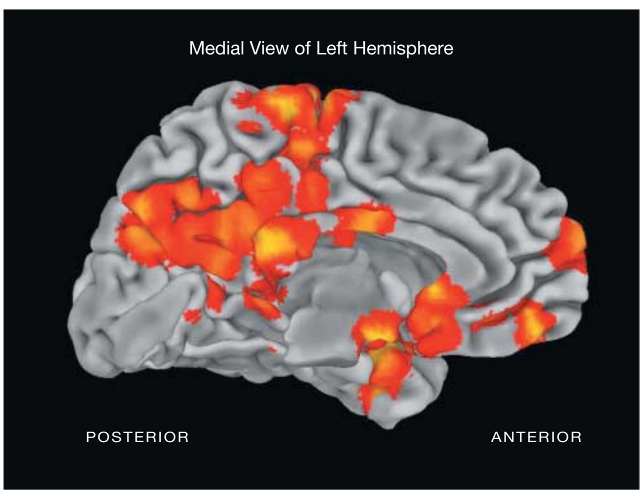
The most popular technology for this type of research—functional magnetic resonance imaging—clicks snapshots of the brain's activity as a patient lies inside a scanner. Wearing goggles or watching a video screen, the patient views a sequence of images designed to arouse craving. Or, to heighten the urge, an assistant plunks down a bottle of the patient's favorite beverage, letting him or her smell or sip it.

In some experiments, researchers give patients a trivial task to keep the conscious parts of their brains distracted. In others, patients are explicitly asked to rate their desire to drink. Computers collate all of the information, compiling pictures of which brain areas respond to which cues. Mathematically intense comparisons with control subjects can then isolate specific responses unique to alcoholics.

The most recently published cue-response study comes from a group at the Medical University of South Carolina, headed by Hugh Myrick, PhD (*Neuropsychopharmacology*. 2004;29:393-402). The group did not find any significant differences between 10 social drinkers and 10 alcoholics, perhaps a testament to the technical difficulty of neuroimaging research.

However, the team did identify several brain regions in the alcoholics that responded more intensely to images of alcohol vs images of other drinks. Three areas in particular stood out: the nucleus accumbens (a pleasure center), the insula (responsible for taste memory), and the cingulate (which gauges emotional response to stimuli).

These results partially match reports from cue-response studies in individuals addicted to cocaine and heroin, said Myrick. In addition, activity in the three brain regions corresponded to the alcoholics' self-rated



Susan F. Tapert, PhD, University of California, San Diego

When compared with control teens, teens with drinking disorders display enhanced brain activation (indicated by yellow and orange areas superimposed on this statistical brain map) in response to alcohol advertisements. Yellow indicates the largest between-group differences.

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desire to drink, strong evidence that these regions are involved in craving.

THE "HOWS" AND "WHYS"

While alcoholics may some day be helped by treatments that diminish craving by targeting salient brain regions, for now, the technology plays a more basic role. "I see these neuroimaging techniques helping us with the hows and the whys," said John Krystal, MD, director of the Center for the Translational Neuroscience of Alcoholism at Yale. "And someday . . . they may be helpful with the 'what,' which is the diagnostic issue."

In January, Krystal and the center hosted the first conference devoted to neuroimaging of alcoholism, and virtually everyone in the fledgling field attended—all 60 individuals. But quietly, this cadre—much overshadowed by their higher-profile, better-funded colleagues in the field of neuroimaging of "hard" drug addiction—is assembling a pixel-by-pixel map of changes to the brain during years or decades of heavy drinking.

It's not a pretty picture.

Their most consistent finding is that the brains of alcoholics are smaller, by about 5%, than brains of nonalcoholics. Especially vulnerable is the prefrontal cortex, known as the seat of "executive" brain functions such as reasoning. Some of this damage appears reversible, as scans have shown brain expansion after just a few weeks of sobriety. But when a relapse strikes, the gray and white matter shrivels up again, as if hiding from the boozy assault.

In addition, it appears that alcoholism rewires how the brain performs routine tasks. Stanford University School of Medicine behavioral scientist Edith Sullivan, PhD, recently completed a series of experiments testing the cognitive skills of alcoholics. In a presentation at the Yale meeting, she reported that alcoholics tend to perform at the same level as nonalcoholics, but their brains work much harder to get there.

During a verbal memory task, in which the subject was asked to identify a lower case letter that had moments before appeared in upper case, "Alcoholics recruited more widely spread brain areas [than controls] to achieve the same performance," said Sullivan. Similarly, the brains of alcoholics labor to remember the arrangement of colored dots. Whereas control subjects solved the task by activating the "where" circuitry of their brain (originating at the back of the prefrontal cortex), alcoholics used the much more processing-intense "what" circuitry (originating at the front of the prefrontal cortex). It is as if each time they saw a blue dot, they had to remember not only where it appeared, but what exactly it was.

Sullivan's conclusion: "Although alcoholics have impaired executive function, under certain circumstances they can overcome it. But," she added, "only at the expense of brain processing power." To use a computer analogy, when confronted with multiple tasks, the brains of alcoholics grind away like a 1980s-era PC, while normal brains glide through the challenge with the alacrity of a 3-gigahertz processor.

These findings match clinical reality: alcoholics in professional jobs, such as lawyers, tend to score in the normal range on single-task cognitive tests. But these same drinkers often complain that they have lost their edge in court, the classroom, or wherever they encounter the need for complex thinking.

TEENAGE RISK

A second stream of research is buttressing the "reward deficit" theory of addiction, which posits that individuals turn to drugs because everyday accomplishments provide precious few thrills. These same studies are helping to explain why adolescence is so treacherous, a period when most alcoholics start their drinking careers.

The latest report from the field (to be published in an upcoming issue of *J Neurosci*), from Daniel Hommer, MD, director of the laboratory of clinical studies at the National Institute of Alcohol Abuse and Alcoholism in Bethesda, Md, used money to gauge the motivational maturity of teenagers and young adults. While being scanned, subjects were asked to complete simple button-pushing tasks. Some tasks won the subject $0.20, others $5. Not surprisingly, activity in the brain's reward-focused nucleus accumbens—rats will press a bar indefinitely to receive a jolt of electricity there—increased as the winnings grew.

However, teenagers displayed much less activation in the region than did young adults. "My guess is that this is developmental," said Hommer. "Adolescents have less [brain] involvement in motivation—it's not fully developed." As parents of teenagers usually know, "there's something less than optimal about their motivational systems."

In addition, Hommer reports that teenagers with a positive family history of alcoholism show even less activation in the nucleus accumbens. This blunted response may be a risk factor, said Hommer—evidence supporting the reward-deficit theory. One of the reasons drugs and alcohol can take over some individuals' motivation systems so readily may be that their motivation system does not respond to normal social rewards, he said.

"But the drugs and alcohol go right to the brain [and] say, 'This feels really good. I don't feel this good very much,'" said Hommer. One possibility is that genetic factors come into play in such individuals; another is that the blunted response results from "living in a home where the reward system is erratic," he explained.

Another brick in the road to alcoholism may be teenagers' response to advertisements for beer and liquor. In a study from the University of California, San Diego, Susan Tapert, PhD, and colleagues, found that the nucleus accumbens and other areas of the brains of teens who abused alcohol lit up—a lot—when exposed to advertisements (*Arch Gen Psychiatry*. 2003;60:727-735).

"When I first saw the extent of the differences [in activation of these brain regions] between normal kids and kids abusing alcohol, I fell off my chair," said Tapert, who reran her analysis of the 30 teenagers several times to rule out computer glitches and other errors. "I

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mean, these adolescent abusers aren't homeless or in treatment, they're from upper-middle class families; they're getting by in high school. Physically, they're fine."

But, when viewing advertisements for their drink of choice, these teens appear to get a jolt of pleasure. It resembles euphoric recall, said Tapert, who wants the alcohol industry to take note of her study. "I would love for them to tone down their ads, not make drinking look so enjoyable."

And in a finding that builds on Hommer's, Tapert has tentative imaging data suggesting that teens with a family history of alcoholism—regardless of whether they drink themselves—respond more favorably to advertisements than teens without such a family history.

To confirm this, Tapert is launching a first-of-its-kind prospective study with 60 young teens who are at risk for developing drinking disorders, but who do not yet drink. "Unfortunately, some of them will begin abusing alcohol," said Tapert. When they do, the scans may reveal preexisting differences in their brains compared with the brains of their sober peers.

Citing the latest statistics on teen drinking—about one third of high school seniors get drunk once a month, and 6% to 9% of high school students qualify for a drinking disorder—Tapert expressed surprise that no one has yet performed a similar study. "This is a huge problem." □

Prevent Genetically Modified Organisms From Escaping Into Nature, Report Urges

Tracy Hampton, PhD

BIOCONFINEMENT IS THE MESSAGE of a new report by the National Academies' National Research Council (NRC) that encourages developers to design and incorporate effective ways to prevent transgenic animals and plants from breeding or competing with their wild counterparts. More research is needed to understand how well bioconfinement strategies such as induced sterility or a growth deficiency work under a wide variety of conditions, said the expert committee that wrote the document.

"Deciding whether and how to confine a genetically engineered organism cannot be an afterthought," stated committee chair T. Kent Kirk, PhD, of the University of Wisconsin in Madison.

The report was requested by the US Department of Agriculture, which is considering how to regulate genetically engineered organisms and ensure their confinement. The committee encouraged researchers to develop new methods of bioconfinement; because no current method is 100% effective, the committee also warned that several methods should be combined to ensure safety when necessary.

The heterogeneity of genetically modified organisms necessitates a case-by-base evaluation, the group noted. Certain organisms—such as those carrying benign traits—might not need to be confined.

Because ecological studies have shown that some genetically engineered organisms are viable in the wild, officials say it is important to devise techniques to monitor any escapees and to mitigate their effects. The NCR report also cautioned that developers need to consider the consequences that ineffective bioconfinement methods could have outside the United States.

The report's release comes at a time when a number of successfully modified organisms—particularly fish, plants, insects, and microbes—are currently undergoing regulatory evaluation. Concerns include the possibility that transgenic plants made resistant to herbicides and diseases could pass their genes to weeds and make them more invasive, that plants and animals engineered to produce pharmaceutical drugs could be harmful to humans or other animals if consumed, and that transgenic fish could mate with wild fish or outcompete them for food.

Scientists have documented examples of unforeseen consequences following the introduction of transgenic organisms into the environment. For example, corn engineered with a bacterial gene produces toxins that defend against a number of insect pests, but untargeted insects such as monarch butterflies also have been negatively affected.

Engineered microbes and insects pose some of the greatest challenges. Microbes have rapid adaptability, and the large number of insects in any population could make a confinement failure particularly problematic. A recent report by the Pew Initiative on Food and Biotechnology states that genetically modified insects have great potential for improving public health and enhancing agricultural production, but the government's lack of regulatory clarity must be addressed before these organisms are released (http://pewagbiotech.org/research/bugs/).

Researchers stress that despite the risks, genetically modified organisms hold great promise for a number of applications. For example, genetically modified animals in medical research can act as models of human disease and help in the development of new therapies. And transgenic agricultural crops, such as rice enriched with β-carotene, may someday conquer vitamin deficiencies.

The NRC report is available online at http://books.nap.edu/openbook/0309090857/html/. □

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