Breaking Bad Habits

December 31, 2013

This month marks the 50th anniversary of the landmark US Surgeon General's report linking cigarette smoke to lung cancer. Yet despite the endless antismoking campaigns, medical research documenting tobacco's caustic health effects, and litigation against cigarette makers that has surged since that time, the rewarding and euphoric effects of nicotine keep more than 1 billion smokers worldwide craving their next puff.

Tobacco is one of the deadliest culprits, accounting for nearly 6 million fatalities annually. But it is only one of many addictive drugs, ranging from cocaine to prescription pain-killers to the crystal methamphetamine that drives the plot in the acclaimed TV series *Breaking Bad*, that contribute to billions of dollars in lost productivity, increased health-care costs, and crime throughout the world.

Just as with other psychological disorders, drug dependence is a complex phenomenon. In addition to the social factors involved — peer pressure, for instance — drug abuse also brings about a variety of biological changes in the brain, some of which researchers are only now beginning to understand. This

nuanced interplay between brain, behavior, and environment in drug addiction requires an equally nuanced approach to treatment. The last several decades of drug abuse research have seen progress toward this necessary integration. And what was once a competition for intellectual and scientific primacy between psychological science and neuroscience is now a burgeoning opportunity for collaboration.

Drugs and the Dual System of Choice

As multiple scientific perspectives are brought to bear on the study of self-control and drug-seeking, convergent findings have allowed researchers to contextualize their own work. At a recent scientific meeting organized by the Science of Behavior Change initiative of the National Institutes of Health, Warren Bickel described how neuroimaging experiments have played a significant role in generating hypotheses for psychological phenomena.

Bickel, of Virginia Polytechnic Institute and State University, studies drug abuse and decision-making about the future. In his early experiments, chronic cocaine users tended to favor immediate rather than larger, delayed rewards — a firmly ensconced tendency Bickel couldn't alter. But a related functional magnetic resonance imaging (fMRI) study published in 2004 revealed that certain brain regions are differentially active when making an immediate- versus a delayed-option choice.

"All of a sudden, it became clear to me," Bickel said. "It's a two-part system. We have an impulsive system and an executive decisions system. If you're healthy, you should be able to use the whole range of the system depending upon the circumstance."

But as subsequent studies revealed, cocaine users don't show the same regulatory balance between these two brain systems. By and large, they exhibit a greater activation in limbic and paralimbic brain regions than in prefrontal regions — patterns correlated with impulsive behavior and a preference for immediate rewards.

This integration of brain and behavior research has paved the way for a new understanding of effective interventions for drug dependence: striking a balance between reducing impulsivity *and* boosting executive function.

APS Fellow David Zald of Vanderbilt University analogized this dual-process model as one of decision-making "races." Essentially, when someone is deciding between two options — either the immediate or the delayed reward — each choice doesn't necessarily have an equal chance, a phenomenon most pronounced among drug-dependent individuals.

According to Zald, this is one reason drug-taking behavior becomes so habitual: Choosing the immediate reward (the drug) consistently wins out over the delayed reward (saving money or maintaining a job, for instance). To combat this entrenched bias, training executive function in the absence of an immediate drug reward may be an effective intervention — essentially, giving the long-term decisions a "head start" over impulsivity in the decision-making race. In doing so, Zald would expect to see more balanced activation between the limbic system and prefrontal cortex — resulting in healthier choices overall.

Predictions From the Brain

Researchers are also using neuroimaging to gain insight into future behavior, revealing which individuals are most susceptible to drug relapse and which would benefit most from targeted interventions.

Rajita Sinha, a researcher at Yale School of Medicine, described how relative levels of brain activation can signify the severity and onset of relapse into drug abuse. Using resting-state fMRI, Sinha and her colleagues discovered that greater sustained activation in the medial prefrontal cortex (mPFC) predicted a longer delay between drug-use cessation and relapse — essentially, individuals with greater activation stayed clean longer. Individuals with less activation in this brain area were quicker to relapse.

These data, Sinha argued, illustrate a potential application of basic fMRI research in clinical populations: Individuals who have less activation in the mPFC may benefit from more targeted and intense interventions, or perhaps more support immediately after they cease using drugs.

Still, many researchers agree that these tests are too expensive for the clinic and wield inadequate diagnostic power. "I think the jury's still out on what kinds of neurobiological predictors are going to show the best sensitivity and specificity," Sinha cautioned. "We get our glucose levels checked, we get our insulin levels checked. Are there ways of thinking about neurobiological markers and metrics as predictors of behavior?"

According to Diana Martinez of Columbia University Medical Center, answers to that question are on the horizon. She and her group of researchers have been using positron emission tomography (PET) to investigate predictors of the success or failure of drug-dependence therapy. In particular, Martinez discovered that concentrations of a certain dopamine receptor (the D_2 receptor) and overall levels of dopamine release in the ventral striatum brain region were effective in predicting success in behavioral therapy treatment for cocaine addiction. In essence, subjects who had more dopamine release and more D_2 receptors were more likely to complete treatment and remain cocaine-free 6 months later than were those with lower levels of dopamine.

For Martinez, the next questions were obvious: "Can this neurobiology be fixed in any way? Can we increase D_2 receptors or increase dopamine release?"

Studies using animal models suggest these goals may be achievable. Martinez is currently experimenting with gene therapy in mice to boost the number of dopamine D_2 receptors in the brain. In these studies, a strand of engineered DNA is packaged within a harmless viral vector and transported inside the nuclei of mouse cells. Once inside, the new bit of DNA takes advantage of the cell's existing machinery to manufacture and distribute the specific dopamine receptor protein. A recent experiment using this method revealed that mice with more D_2 receptors self-administered less cocaine than mice without the gene therapy treatment. Preliminary findings like these, according to Martinez, suggest that the notion of gene therapy for drug addiction in humans may not be as far-fetched as scientists once believed.

In addition to increasing receptor levels, it may be possible to affect other neurotransmitter systems that modulate dopamine release — thereby protecting against relapse. One particular protein, the kappa opioid receptor, has been shown to decrease dopamine release and is expressed in high concentrations in the

post-mortem brains of cocaine users. By using therapeutic drugs that block this opioid receptor, Martinez predicts that dopamine release would increase and behavioral therapy for cocaine dependence would be more effective overall.

When taken together, these techniques act synergistically — from the level of genes and neurotransmitters to systems neuroscience and whole-brain analyses, integration in addiction science is progressing from basic research to clinical application.

Mindfulness as Medicine

Instead of using neuroscience data to predict treatment outcomes, some investigators have asked a different question: Can a patient's brain activity be used as personalized treatment?

In an attempt to reduce craving in cigarette smokers, Kathleen Brady and Mark George of the Medical University of South Carolina have been using neurofeedback, a real-time display of a brain region's activity. One particular region, the anterior cingulate cortex (ACC), becomes reliably activated for nicotine-dependent individuals in response to smoking cues — that is, greater activation is indicative of greater craving when looking at pictures of cigarettes. Because of this, Brady and George were interested in seeing if patients in an fMRI machine could tone down their craving by seeing real-time illustrations of their own brain activity.

After just three visits to the lab and with no medicine or explicit therapy, subjects who used the neurofeedback had both a reduction in craving and less activity in the ACC when looking at pictures of cigarettes. Encouraged by these preliminary results, Brady and George hope to replicate the findings with more participants, since this pilot study was conducted with only nine smokers.

Even if this method is confirmed as a viable therapy, however, neurofeedback using fMRI is not a feasible tactic to implement in the general population. Fortunately for millions of cigarette smokers, there are less expensive behavioral techniques that might produce similar results — an overall reduction in craving.

According to APS Fellow Yi-Yuan Tang of Texas Tech University, Rongxiang Tang of the University of Texas at Austin, and APS William James Fellow Michael Posner of the University of Oregon, mindfulness meditation might be one such technique. After just two weeks of mindfulness training — only 5 hours in aggregate — smokers puffed about 60% less and reported less craving than when they started the study, even if they had no intention to quit beforehand. In addition, participants who practiced mindfulness meditation also showed increased baseline brain activity in the ACC and prefrontal cortex — signals associated with greater self-control.

Just as with other studies in the field, unanswered questions remain. It's still unclear, for instance, whether participants would need to continue the training to keep cravings at bay over the long term. Still, the data are promising, if only for their originality. Mindfulness meditation does not explicitly require participants to resist craving or to quit smoking; instead, it focuses on improving self-control capacity writ large.

Cautionary Steps Forward

Despite the powerful interplay between psychological science and neuroscience for understanding drug addiction, research in this area is still riddled with roadblocks and confounds. Among these, as every researcher is quick to point out, is the struggle to obtain the necessary funding to run large-scale, randomized, controlled trials. These trials — which often require millions of dollars and many researchers — are difficult to execute and sometimes provide inconclusive data.

Martinez, whose PET experiment totaled 48 participants but took years to finish, explained that while she is interested in running another, larger experiment, it may be unlikely.

"It's a lot of money. PET scans are incredibly expensive, and they require a lot of effort," Martinez explained. "We know that dopamine levels are a *biomarker* for addiction, but do they *predict* anything? I've been doing these studies for over 10 years, and this is a question that vexes me often. I've exposed myself and many other people to a lot of radioactivity. The question is, how relevant are these results?"

One potential solution, many researchers argue, is to find measures that are equally effective at predicting drug addiction treatment outcomes but are simpler and more cost-effective to use. Electroencephalography (EEG) — a considerably less expensive brain scan — might be one possible avenue for future research, as long as researchers can be confident that it wields the same predictive power as PET or fMRI.

But even if assembling the necessary funds weren't an issue, brain imaging technology is still in its infancy as a diagnostic tool.

"We don't know if the observed patterns are specific enough to be useful as biomarkers," said Tor Wager of the University of Colorado at Boulder. "We don't know how precise these brain patterns are to particular psychological phenomena. Therefore, we don't know what the diagnostic value of our brain images actually is. We can't apply them to individual patients or participants. We're correlating brain and behavior, but not very strongly."

Wager did not issue his compelling indictment without recommendations for improvement. Moving forward, he said, we need more precise definitions of psychological disorders, their antecedents, and the neuroplastic changes that accompany them. Disorders of the brain, including drug addictions, are immensely complicated. And while brain-imaging technology is chipping away at the divide between the psyche and biology, our tools for understanding the neural substrates of behavior are only as good as our understanding of behavior itself.

"Ideally," Wager said, "we'd like to see patterns of brain activity that predict a behavioral outcome, not the other way around."

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