I. INTRODUCTION

Drug addiction is an ancient problem for society, leading to crime, diminished productivity, mental illness, disease transmission, and a burgeoning prison population. According to the Bureau of Justice Statistics, nearly seven out of ten jail inmates met the criteria for substance abuse or dependence in the year before their admission.\(^1\) One study found that 35.6% of convicted jail inmates were under the influence at the time of arrest.\(^1\)
their criminal offense. The cost to society of drug abuse has been estimated at $180.9 billion, of which $107.8 billion is derived from drug-related crime.\textsuperscript{3} The linkage between drug abuse and crime has been thoroughly established elsewhere. Promising new developments relating to emerging knowledge and technologies may provide a bridge between the failed policies of the past and novel solutions in the future. Drug addiction is rooted in the biology of the brain, and society’s best hope for breaking addiction lies in new ideas for rehabilitation, not in repeated incarceration.

The past two decades have witnessed remarkable progress in understanding the neural basis of drug addiction.\textsuperscript{4} Chronic drug use leads to enduring physical changes in the structure of the brain, and these are thought to undermine what we understand as voluntary control.\textsuperscript{5} Drug addiction manifests itself as an irrepressible drive to take a drug despite its undesirable consequences.\textsuperscript{6} For decades it was thought that drug addiction resulted from physical dependence on the drug; because withdrawal symptoms could be serious, even life-threatening, drug addiction was thought to be the same as physical dependence. By contrast, a new way of thinking suggests that drug addiction is more than dependence; it is the result of a reconfiguration of the circuitry of the reward and

\begin{itemize}
  \item \textsuperscript{2} \textit{Bureau of Justice Statistics, U.S. Dep't of Justice, Special Report: Drug Use, Testing, and Treatment in Jails} 1 (2000), \textit{available at} http://www.ojp.usdoj.gov/bjs/pub/pdf/duttj.pdf (showing that, in 1998, 35.6% of convicted jail inmates, or 138,000 individuals, were under the influence at the time of offense).
  \item \textsuperscript{3} \textit{National Institute on Drug Abuse, Nat'l Insts. of Health, Principles of Drug Abuse Treatment for Criminal Justice Populations: A Research Based Guide} 26 (2006), \textit{available at} http://www.drugabuse.gov/PDF/PODAT_CJ/PODAT_CJ.pdf (“In 2002, it was estimated that the cost to society of drug abuse was $180.9 billion . . . a substantial portion of which—$107.8 billion—is associated with drug-related crime, including criminal justice system costs and costs borne by victims of crime.”).
  \item \textsuperscript{4} \textit{E.g., Alan I. Leshner, Addiction Is a Brain Disease, and It Matters}, 278 SCI. 45, 45 (1997) (“Dramatic advances over the past two decades in both the neurosciences and the behavioral sciences have revolutionized our understanding of drug abuse and addiction.”).
  \item \textsuperscript{5} \textit{Nora D. Volkow & Ting-Kai Li, Drug Addiction: The Neurobiology of Behaviour Gone Awry}, 5 \textit{Nature Revs. Neurosci.} 963, 963 (2004) (“[R]ecent studies have shown that repeated drug use leads to long-lasting changes in the brain that undermine voluntary control.”).
  \item \textsuperscript{6} \textit{Id.}
\end{itemize}
decision-making systems, leading to increased cravings and diminished impulse control. In other words, addiction may be reasonably viewed as a neurological problem that allows for medical remedies, just as pneumonia may be viewed as an affliction of the lungs that allows for the same. As we progress in our understanding of the underlying circuitry of addiction, how that circuitry leads to drives, and how drugs hijack and reregulate that circuitry, we have the opportunity to leverage that understanding into more effective drug policy that rests on treatment rather than punishment.

Part II briefly reviews the extent of the drug addiction problem in the United States and describes where American drug policy has fallen short in its attempts to move from punishment toward rehabilitation. Part III reviews the modern neuroscientific understanding of reward and addiction, building the argument that treating addiction requires an understanding of the neural mechanisms involved in reward systems, craving, and impulse control. Given the growing biological understanding of addiction, we argue that science must play a critical role in reforming drug policy. Part IV explores cutting-edge ideas that offer new hope for treating addiction directly rather than resorting to repeated rounds of incarceration. Here, we describe two innovative strategies—cocaine vaccines and real-time feedback in neuroimaging—which offer fresh approaches to rehabilitation and new opportunities for dialogue regarding the problem of drug addiction.

II. WHAT TO DO ABOUT DRUG ADDICTS?

A. HISTORICAL TENSIONS BETWEEN PUNISHMENT AND REHABILITATION

For centuries, societies have grappled with complex ethical questions about how to deal with drug addicts. In Robinson v. California, Justice Douglas wrote that an approach of moral condemnation “continues as respects drug addicts . . . . [T]hose living in a world of black and white put the addict in the category of those who could, if they would, forsake their evil ways.” Rather than looking at drug addiction as a

scientific and medical phenomenon, many continue to cast the issue in moral terms. It is perhaps not surprising that the criminal justice system has generally used retributive justice to deal with addicts, much like it once did for the mentally ill. 8 The retributive stance generally extols “just deserts” and diminishes rehabilitative attempts, even those guided firmly by physiological understandings of the underlying pathologies. Nevertheless, rehabilitative efforts have made meaningful appearances throughout the twentieth century.

In the twentieth century, American drug policy vacillated between punishment and rehabilitation. For example, in the mid-twentieth century, attempts to treat and rehabilitate addicts, rather than simply incarcerate them, dominated social policy. 9 These developments were facilitated by advances in psychology and psychiatry. 10 At that time, even the Supreme Court seemed to embrace rehabilitation rather than retribution.

In 1962, the Supreme Court found unconstitutional a California statute that made addiction a crime. 11 The statute stated that “[n]o person shall . . . be addicted to the use of narcotics . . . .” 12 Rather than criminalizing conduct, the California statute mandated a minimum ninety day jail sentence based on a person’s status as an addict. 13 In striking down the statute, the Court reasoned that addiction is a physiological condition requiring treatment rather than

8. Id. at 668 (citing ALBERT DEUTSCH, THE MENTALLY ILL IN AMERICA: A HISTORY OF THEIR CARE AND TREATMENT FROM COLONIAL TIMES 13 (Holley Press 2008) (1937)).
10. Id. (“Sociologists, psychologists, and psychiatrists found fertile fields behind bars in which to test experimental behavior-modification programs.”).
11. Robinson, 370 U.S. at 667 (“[A] state law which imprisons a person thus afflicted as a criminal, even though he has never touched any narcotic drug within the State or been guilty of any irregular behavior there, inflicts a cruel and unusual punishment in violation of the Fourteenth Amendment.”).
12. Id. at 660 n.1.
13. Id. (“Any person convicted of violating any provision of this section . . . shall be sentenced to serve a term of not less than 90 days nor more than one year in the county jail.”).
punishment.\textsuperscript{14}

By the late 1960s, however, the failure of science to find biological solutions for addiction led to increased skepticism about rehabilitation in the Supreme Court. In 1968, the Court rejected Leroy Powell’s argument that alcoholism excused him from being drunk in public.\textsuperscript{15} Powell argued that his public intoxication was not volitional and, therefore, punishing him for it was cruel and unusual.\textsuperscript{16} The psychiatrist who testified in the case acknowledged that there was no medical consensus over a definition of alcoholism or whether alcoholism was a disease; however, he asserted that the defendant, as a “chronic alcoholic” was “not able to control his behavior.”\textsuperscript{17} But the Court found his argument a stretch because it went “much too far on the basis of too little knowledge.”\textsuperscript{18} At that time, there existed a lack of effective treatment options and consensus regarding treatment efficacy.\textsuperscript{19} Moreover, treatment facilities and trained providers were scarce.\textsuperscript{20} Finally, without adequate treatment and facilities, a civilly committed addict could be held indefinitely without being criminally confined due to the fact that he had virtually no chance of being successfully rehabilitated.\textsuperscript{21} Finding no viable treatment alternatives, the Court concluded that criminal process was still necessary.\textsuperscript{22}

\begin{footnotesize}
\begin{enumerate}
\item 14. \textit{Id.} at 667.
\item 16. \textit{Id.} at 517.
\item 17. \textit{Id.} at 517–18.
\item 18. \textit{Id.} at 521.
\item 19. \textit{Id.} at 527. The Court noted:

There is as yet no known generally effective method for treating the vast number of alcoholics in our society. Some individual alcoholics have responded to particular forms of therapy with remissions of their symptomatic dependence upon the drug. But just as there is no agreement among doctors and social workers with respect to the causes of alcoholism, there is no consensus as to why particular treatments have been effective in particular cases and there is no generally agreed-upon approach to the problem of treatment on a large scale.

\textit{Id.}
\item 20. \textit{Id.} at 528–29.
\item 21. \textit{Id.} at 529.
\item 22. \textit{Id.} at 530. Explaining its reasoning further, the Court went on to state:

Faced with this unpleasant reality, we are unable to assert that the use of the criminal process as a means of dealing with the public aspects of problem drinking can never be defended as rational . . . . If, in addition to the absence of a coherent approach to the problem of
The 1970s heralded the “era of harsh prison sentences.”\footnote{Stephen A. Saltzburg & James R. Thompson, 2007 A.B.A. SEC. CRIM. L. REP. 2, available at http://meetings.abanet.org/webupload/commupload/CR209800/newsletterpubs/Report1.PDF.121306.pdf.} Between 1972 and 2000, the incarcerated population grew to more than two million.\footnote{E.g., Steven D. Levitt, Understanding Why Crime Fell in the 1990s: Four Factors that Explain the Decline and Six that Do Not, J. ECON. PERSP., Winter 2004, at 163, 177.} According to recent studies, the “sharp rise in incarceration for drug-related offenses” directly fueled this increase.\footnote{Id.} This trend was further driven by societal problems in the 1980s, the crack cocaine epidemic began,\footnote{E.g., Saltzburg & Thompson, supra note 23, at 2.} and with it came the “War on Drugs.”\footnote{E.g., Saltzburg & Thompson, supra note 23, at 2.} The role of crack was implicated by researchers in the rise of violence and crime,\footnote{E.g., Levitt, supra note 24, at 179–80.} leading to calls for longer prison sentences and cleaning up of the streets.

By the 1990s, the trend began to shift back toward rehabilitation. In 1990, President George H.W. Bush and Congress officially designated the 1990s as the “Decade of the Brain.”\footnote{E.g., Edward G. Jones & Lorne M. Mendell, Assessing the Decade of the Brain, 284 SCI. 739, 739 (1999).} In parallel with the acceptance and developments of neuroscience, the shift from a retributive criminal policy toward a more rehabilitative stance has continued. Recent government\footnote{See SUBSTANCE DEPENDENCE, supra note 1, at 8. The report indicates that, in 2002, 47% of addict inmates participated in treatment or other programs while under correctional supervision. Trends indicate that these numbers are growing.} and American Bar Association\footnote{See Saltzburg & Thompson, supra note 23, at 4–8. The recommendations urge governments to move away from pure incarceration methods of punishment toward community supervision, deferred adjudication, mental health treatment, and substance abuse treatment when the offender is not a threat to the community, has not committed a predatory or other serious crime, and lacks prior criminal history. The report explicitly acknowledges lingering doubts about rehabilitation but attempts to assuage these doubts} data bear out treatment, we consider the almost complete absence of facilities and manpower for the implementation of a rehabilitation program, it is difficult to say in the present context that the criminal process is utterly lacking in social value.

\footnote{24. Id. at 179.} 
\footnote{25. E.g., Saltzburg & Thompson, supra note 23, at 2.} 
\footnote{26. E.g., Levitt, supra note 24, at 179–80.} 
\footnote{27. E.g., Saltzburg & Thompson, supra note 23, at 2.} 
\footnote{28. E.g., Edward G. Jones & Lorne M. Mendell, Assessing the Decade of the Brain, 284 SCI. 739, 739 (1999).}
this trend, with examples coming from jurisdictions across the United States. The American Bar Association’s 2007 recommendations demonstrate this shift. Currently, programs across the nation are shifting from retribution to rehabilitation.32 Promising changes such as the increased use of drug courts,33 civil commitments, community-supervised treatment programs, and other rehabilitative strategies are beginning to supplant the old focus on incarceration. Neuroscience is critical to this new wave of treatment and rehabilitation.

Now, at the dawn of the twenty-first century, the decades-long demand for punishment is straining the criminal justice system. Recidivism rates are high. In fact, “more than two-thirds of those being released from prison [are] rearrested within three years of release, and 42% of parolees [are] returning to prison or jail within 24 months of their release . . . .”34 This prison exodus means that 650,000 prisoners are temporarily returning to their communities every year. Do addicts benefit from their incarceration? If not, can we do more to enhance treatment outcomes and potentially reduce the future societal costs? Rather than cataloging addiction’s cost to society, new neuroscientific developments illuminate knowledge and technologies that provide a bridge between the

with evidence about the inefficacy of long prison sentences. Further, the report emphasizes that cost-effective strategies will depend upon a balancing of interests between protecting the public through incarceration and preventing recidivism through rehabilitation.

32. Beginning in 1993 in Arkansas, community-based substance abuse treatment, drug courts, and other measures have been combined under a system that allows for dismissal of charges and expungement of records. This program has seen significant drops in recidivism rates. In Connecticut, every court now has access to substance abuse evaluations and outpatient treatment programs, and the state has inpatient treatment programs for substance abusers. These strategies have also shown reduced recidivism rates. In Kings County, New York, repeat drug offenders facing prison time have access to treatment programming. The Multnomah County, Oregon STOP program provides certain drug offenders with the option to complete a treatment program to avoid prosecution. In Kansas, a new program for non-violent drug offenders provides a long-term treatment program. Particularly promising is the program’s recognition that relapse is not necessarily a failure to recover. Id. at 9–13.


34. Saltzburg & Thompson, supra note 23, at 3.
doctrinal literature about criminal punishment and new treatment solutions for the future.

B. SCIENTIFIC EXPLANATIONS OF BEHAVIOR

Many people share a concern about incorporating scientific explanations for behavioral problems into the law, and this may stem in part from historical misuse. As Zedi and Goodenough state:

Incorporating biology into legal doctrine is . . . problematic. To the extent that biological approaches had been included in the great arguments of the twentieth century between fascism, communism, capitalism, socialism, dictatorship and liberal democracy, they often wore a distorted and appropriately discredited aspect that had more to do with political expediency than with any accurate application of the admittedly limited science of the times.35

Considering recent history, apprehension to the use of science in making social policy is justified. “But that biology should have been thus misused in the past is not a good reason for not taking account of its findings in the future, always of course with appropriate safeguards.”36

A second concern, also shared by many, is that a neuroscientific understanding may exculpate criminals, allowing them to “blame their brains” for their behavior. Most people believe that there is some sense in which criminals should be held responsible for their actions, irrespective of the states of their brains, and therefore the idea of exculpation is unpalatably. We suggest that this belief does not need to be a concern. Societies will continue to remove dangerous people from the streets. Explanation does not equal exculpation; instead it can equal rational sentencing and customized rehabilitation. Rehabilitative treatments remove the threat addicts pose to innocent people and save society the associated costs that would be incurred were the addicts incarcerated. In this respect, a consequentialist or utilitarian approach may be more effective and less expensive than retribution and punishment. The ultimate issue, then, from a scientific perspective, is not how the criminal justice system can exact revenge for an evil act, but, instead, whether the underlying problem can be fixed through utilization of what is known of

36. Id.
the neuroscience of addiction so that neither the addict nor the next victim has to suffer.

We suggest that the most fruitful path is to forego the arguments of responsibility in favor of concentrating neuroscientific efforts on rehabilitation. The onus is on neuroscience to prove that it has something to offer. If it can, then the legal system can act accordingly to leverage those assets. In this article we review the neuroscientific understanding of addiction and propose new treatments for breaking addiction and the consequent cycles of incarceration. In this paper we illustrate how neuroscience can back up its claims of addiction as a biological problem and bring actionable solutions to the table.

III. NEUROSCIENCE AND ADDICTION

A. BIOLOGICAL UNDERPINNINGS

The human brain consists of hundreds of billions of cells called neurons, and over a trillion cells called glia. The number of connections between these cells amounts to between 60–240 trillion. The complex pattern of connectivity in the brain—its 'circuitry'—is dynamic: connections between cells are constantly blossoming, dying, and reconfiguring. The pattern of connectivity in the brain determines behaviors, thoughts, and capacities, and damage to the circuitry impairs these functions.

Although addiction may involve volitional choices early on, it is best understood in the chronic state as a brain disease. As Volkow and Li put it: "[D]rug addiction is a disease of the brain, and the associated abnormal behaviour is the result of dysfunction of brain tissue, just as cardiac insufficiency is a disease of the heart and abnormal blood circulation is the result of dysfunction of myocardial tissue." The proposal that addiction is biologically rooted is not new; however, modern

40. Volkow & Li, supra note 5, at 963.
techniques have progressed our understanding of the neural basis of addiction from general ideas to specific mechanisms. In 1968, the Supreme Court pointed out that incarceration was still necessary as long as a real understanding of addiction and useful methods of rehabilitation were lacking. Almost half a century later, we are close to meeting that challenge.

The brain contains circuitry that properly guides animals in cognitive functions such as decision-making, motivation, learning, and emotion. These circuits, largely involving the neurotransmitter dopamine (and hence referred to as dopaminergic) seem to be almost identical across the family tree of animal species, which typically suggests deep evolutionary importance. These systems evolved to guide animals’ decisions in their pursuit of food, drink, and mates.

Drugs of abuse hijack these reward and decision-making systems. One of the first steps in addiction is reinforcement from drug-induced increases in dopaminergic activity. In other words, the drug is interpreted as a highly positive stimulus, and the brain’s dynamic circuitry is reconfigured to make the brain seek more of it. The same mechanisms that normally lead to proper foraging (e.g., if you find a good food source, you seek more of it), are now commandeered by the drug. In this framework, addiction is understood as a normal process gone awry.

42. See generally Read Montague, Why Choose This Book?: How We Make Decisions 335 (2006).
43. A neurotransmitter is a small chemical that is secreted from one cell and detected by another. It is the main mode of communication between cells in the brain. Although several different neurotransmitter types in the human brain are implicated in addiction, dopamine is one of the main players.
45. Id.
46. In other words, the drug causes increased levels of dopamine, and this causes the brain to reinforce the last behavior (i.e., the taking of the drug). Reinforcement is the same concept used with Pavlov’s dogs: by delivering food after the bell, the bell becomes a predictor of reward.
48. Redish, supra note 477, at 1944; Volkow et al., supra note 477, at 557;
As a consequence of the reinforcement, the brain becomes physically dependent on the chemicals provided by the drug taking. The number of neurotransmitter receptors for the drug will often increase, which, in the homeostatic environment of the brain, causes ripples of change throughout the system—these changes include gene expression, protein products, and neural networks. This re-wiring of the brain often leads to dangerous consequences: when an addict stops taking a drug, there can be severe negative withdrawal effects. Anyone who has witnessed an alcoholic suffer through the delirium tremens (which, in the worst cases, can be fatal) can grasp that withdrawal symptoms are a factor in sustaining addiction. For many decades, scholars theorized that drug addiction results from an avoidance of these negative withdrawal effects—i.e., once a person is physically dependent on a substance, withdrawal difficulties serve as the basis of addiction. But certain clinical facts do not fit this physical-dependence model of drug addiction. For example, addicts will often detoxify entirely, moving past the initial period of physical withdrawal symptoms, and then years later they will re-commence their compulsive drug-taking. Thus, the question remained why addicted brains continue to stay addicted. The answer seems to be two-fold: increased craving and diminished impulse control.

The first issue—craving—involves the maintenance of drug addiction from conditioned sensory cues. That is, stimuli associated with the drug (such as the location of drug-taking, paraphernalia associated with the drug, and so on) begin to drive cravings, and hence drug-seeking behavior. Under the positive incentive theory, addicts continue to use drugs due to

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**see David M. Egelman et al., A Computational Role for Dopamine Delivery in Human Decision-Making, 10 J. COGNITIVE NEUROSCI. 623, 629 (1998) (implicating the dopaminergic system in human decision-making).**

49. A neurotransmitter receptor is a specialized protein molecule situated on the surface of cells. Chemical signals of the right shape (neurotransmitters) attach to the receptor, initiating a cellular response.

50. A system is homeostatic if it adjusts its internal environment so as to maintain stability. When new chemicals (e.g., drugs) are introduced into the brain, adjustments take place at many levels and at many time scales. Eric J. Nestler, *Molecular Basis of Long-Term Plasticity Underlying Addiction*, 2 NATURE REV. NEUROSCI. 119, 122, 125–26 (2001).

their cravings for the drug effects. This helps account for factors which a physical dependence theory alone does not. For example, former addicts tend to relapse more often if they find themselves in a familiar environment that was previously associated with drug use—this suggests that it is the learned, anticipated pleasure that drives these actions. In fact, one can make predictions about the likelihood of relapse based on responses (both physiological and subjective craving) triggered by drug-related cues. Because of the role of conditioned drug-related cues, craving reduction is now considered a major target for interventions, both psychological and pharmaceutical. As discussed in Part III below, new technologies may directly target the neural networks underlying these subjective cravings.

The second contributor to addictive behavior is the inability to control impulses. Normally, in the service of

52. Id. at S92–S93; see also Samuel M. McClure et al., A Computational Substrate for Incentive Salience, 26 TRENDS IN NEUROSCI. 423, 423–24 (2003) (proposing that dopamine is crucial to the initiation of reward-seeking behavior).

53. NAT'L INST. ON DRUG ABUSE, supra note 3, at 19.

54. See Delwyn Catley et al., Absentminded Lapses During Smoking Cessation, 14 PSYCHOL. ADDICTIVE BEHAVIORS 73, 75–76 (2000) (demonstrating that relapses can occur, independent of craving, when the subject is in a situation consistent with previous use patterns); see also Joel D. Killen et al., Prospective Study of Factors Influencing the Development of Craving Associated with Smoking Cessation, 105 PSYCHOPHARMACOLOGY 191, 195 (1991) (showing subjective craving to be a strong predictor of relapse); Joel D. Killen & Stephen P. Fortmann, Craving is Associated with Smoking Relapse: Findings from Three Prospective Studies, 5 EXPERIMENTAL & CLINICAL PSYCHOPHARMACOLOGY 137, 140–41 (1997) (exploring subjective craving as a predictor of relapse).


56. Steven E. Hyman, The Neurobiology of Addiction: Implications for Voluntary Control of Behavior, 7 AM. J. BIOETHICS 8, 9–10 (2007); see Antoine Bechara et al., Different Contributions of the Human Amygdala and Ventromedial Prefrontal Cortex to Decision-Making, 19 J. NEUROSCI. 5473, 5479–81 (1999) (implicating the amygdala in making advantageous decisions);
longer-term goals, behavioral guidance signals will inhibit urges. But in addicts, diminished inhibition allows the unmasking of compulsive drug-seeking and drug-taking. Simple cognitive tasks that measure an individual’s capacity for cognitive control, such as quickly inhibiting a motor response, serve as strong predictors of treatment compliance and relapse. In methamphetamine addicts, brain activity while performing such simple tasks correlates with relapse up to a year after cessation. Again, Part III leverages this understanding to illustrate ways of targeting this deficit in a specific manner.

B. WHY THE SCIENCE SHOULD SHAPE THE POLICY

The United States has a history of combating the drug problem with increased law enforcement rather than...
customized intervention and rehabilitation. For years, experts have weighed in on this topic and come to similar conclusions about current drug policy. One author has stated: “[D]rug treatment programs remain notoriously underfunded, turning away tens of thousands of addicts seeking help even as increasing billions of dollars are spent to arrest, prosecute, and imprison illegal drug sellers and users.”60 Another author approached the issue in this way: “The investment of more than 70% of the federal [U.S.] drug control money into supply reduction seems misplaced . . . . Curtailing the supply of demanded drugs has been compared to squeezing a balloon: constrict it in one place and it expands somewhere else.”61

In light of the current science, it would appear there is a better strategy for combating the drug trade: instead of concentrating on controlling the supply, concentrate on controlling the demand. Below we will consider biologically-based strategies for addressing demand—those strategies that are currently in use, and some that are on the horizon. The new frameworks remove the emphasis on punishment in favor of reducing craving while strengthening impulse control.

III. NEUROSCIENTIFIC STRATEGIES FOR REHABILITATION

Cutting-edge ideas on the horizon offer new hope for directly treating drug addiction rather than focusing on punishment. We briefly outline the evidence-based strategies currently in use. We then turn to two innovative strategies—cocaine vaccines and real-time feedback in neuroimaging—which offer fresh approaches and new opportunities for dialogue in the problem of drug addiction. Such neurally-based treatments can equip policy-makers with tools to treat additions with maximal efficacy and minimum cost.

A. PHARMACEUTICAL STRATEGIES

Essentially there are two classes of pharmaceutical intervention: those that obstruct the effects of the drug and its reinforcing effects, and those that try to counterbalance

changes to the brain brought on by the drug use. In the first class, biological mechanisms include direct binding of the medication to the receptors for the drug, or medications that trigger negative sensations. The second class includes medications that work to decrease the positive incentive of the drug or increase the incentive of natural reinforcers.

For cocaine, several medications have been found to reduce use. Some examples include disulfiram (a medication with dopaminergic effects), GABA medications (tiagabine and topiramate), a beta-adrenergic blocker (propranolol), and a stimulant (modafinil).

For alcoholism, medications like naltrexone are used to antagonize the normal relationship of alcohol with its receptors, thus interfering with reinforcement. Other strategies, such as disulfiram, are used to trigger aversive responses.

Heroin (and more generally, opiate) addiction is also being treated with naltrexone (again as an antagonist for the drug receptors), as well as with substitution strategies. Other medications (e.g. methadone and buprenorphine) bind to the opiate receptors with different kinetics, and thus reduce craving and incentive by blocking the effects of the high. In other words, these medications are intended to reduce craving without inducing intoxication or later withdrawal symptoms.

In general, these measures reflect a conception of the brain based mainly in neurotransmitter systems. Recently, neuroscience has begun to develop a greater understanding of the mechanisms at cellular and circuitry levels as well. This

62. Volkow & Li, supra note 5, at 967.
64. Antagonism is a concept in pharmacology in which one substance (the antagonist) binds to the receptors that would normally be bound by a different substance (in this case, the molecules of the drug), thereby blocking the drug's effects. See Noeline C. Latt et al., Naltrexone in Alcohol Dependence: A Randomised Controlled Trial of Effectiveness in a Standard Clinical Setting, 176 MED. J. AUSTL. 530, 530–34 (2002).
has opened the door to new strategies, two of which are discussed below.

B. REAL-TIME FEEDBACK USING NEUROIMAGING

With new understandings come new opportunities for more precise intervention. This is illustrated here with a new approach to two targets: reducing craving and strengthening impulse control.

As discussed above, subjective cravings triggered by drug-related cues are considered main actors in clinical and neuroscientific accounts of drug addiction. Therefore, craving reduction—already a prime target of cognitive-behavioral, psychotherapeutic, and pharmaceutical approaches—is one of the prime objectives for new technologies. Dozens of functional neuroimaging studies, mostly in nicotine and cocaine-dependent individuals, have highlighted a distributed network of brain regions that show increased activity in response to drug-related cues. Not coincidentally, the areas involved are also implicated in normal reward processing, decision making, and emotional responses. One area that deserves special attention is an area of the cortex known as the insula, which is involved in emotional responses. Activation of the insula is strongly correlated with drug craving across different classes of


drugs.69 Interestingly, damage to the insula disrupts subjective urges to smoke, without changing the motivation of other behaviors (such as eating).7071 These data point to the distributed neural network involved in craving (and the insula in particular) as prime targets for craving-reduction.

As mentioned above, there is another half to drug addiction besides craving: deficits in impulse control.72 Neuroimaging has revealed a related network of areas involved in cognitive control, involving areas known as the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and dorsolateral prefrontal cortex (DLPFC). For example, cocaine addicts show abnormal OFC and ACC activity,73 as well as diminished DLPFC activity,74 hand-in-hand with diminished self-control and poor performance on tasks that require inhibition of impulsive responses. In chronic smokers, the brain’s reward systems appear to function properly, but they are not engaged in the normal way for the proper cognitive control signaling.75 These data suggest direct therapeutic interventions should be used to enhance cognitive control in drug addicts.

How can we hope to directly affect specific brain

70. Nasir H. Naqvi et al., Damage to the Insula Disrupts Addiction to Cigarette Smoking, 315 SCIENCE 531–34 (2007); Gray & Critchley, supra note 67, at 183–86.
71. Hyman, supra note 56, at 9–10; see also Antoine Bechara, Decision Making, Impulse Control and Loss of Willpower to Resist Drugs: A Neurocognitive Perspective, 8 NATURE NEUROSCI. 1458, 1458 (2005); Kalivas et al., supra note 56, at 647; Goldstein & Volkow, supra note 47, at 1649.
72. Nora Volkow & Joanna Fowler, Addiction, a Disease of Compulsion and Drive: Involvement of the Orbitofrontal Cortex, 10 CEREBRAL CORTEX 318, 320 (2000).
networks? A new technology on the horizon—real-time neurofeedback—suggests one possibility. Neuroimaging known as functional magnetic resonance imaging (fMRI) allows the viewing of neural activity. In a new development owing to the introduction of fast computation and efficient algorithms, raw data from the imaging can be reconstructed on-the-fly (in close to ‘real-time’) and visually displayed in the scanner. In this way, neural activity can be shown directly to an individual and that person can attempt to modify it. This technique is known as real-time fMRI, or rt-fMRI, or simply as neurofeedback.76

The approach is similar to the biofeedback strategies of previous decades, except that it allows a view inside the skull, giving a level of precision never before possible. This technology has the potential to enable a dramatically new level of sophisticated exploration of brain function that goes beyond simple measurements of correlations between stimuli and their associated fMRI activations. It puts the individual in the driver’s seat of his own neural circuitry.77 To date, this technology has been used to address pain and depression. Neuroscience is leveraging this technology for a novel approach to addiction. Specifically, rt-fMRI is being used to decrease neural activations associated with craving and increase neural activations associated with cognitive control. This strategy may allow the overcoming of habitual responses to drug-cues in addicts. We have begun this experimental endeavor here at Baylor College of Medicine with nicotine addicts.78 It may be almost a year before the efficacy of this approach can be accurately gauged, but this integration of neural substrates of addiction and real-time neuroimaging is highly promising. This technology, together with other new developments, may


77. In other words, users can view a graphical representation of the amount of activity in particular areas of their brain (say, as a bar that moves up or down), and they can work to control it.

78. This work is spearheaded by our colleagues Drs. Steven LaConte, Pearl Chiu, Brooks King-Casas, and P. Read Montague.
reinvigorate the discussion of possibilities for customized rehabilitation.

C. THE COCAINE VACCINE

Another complementary approach circumvents the continued reinforcement generated by the drug high. This possibility is a drug vaccine, an intervention that renders the individual unable to become high since the immune system will “fight” the drug before it reaches the brain.79

A drug vaccination is accomplished in the traditional biological manner of all inoculations: a foreign substance is injected into the blood stream, and the immune system then raises antibodies against the invader. In this case, the cocaine molecule, which is attached to a large protein molecule, is injected. The new antibodies come to recognize not only the cocaine-protein complex, but also the naked cocaine molecule. Now that the body has hosted an immune response, new injections of cocaine into the bloodstream will be surrounded by the body’s natural antibodies. In this way, the vaccination prevents—or at minimum slows down—the crossing of the cocaine molecules across the blood-brain barrier.80 The high is thus eliminated or at least attenuated.81 Currently, the cocaine vaccine is in clinical trials and shows early promise.

Dr. Tom Kosten, one of the lead developers of the vaccine, sees the vaccine as most useful for addicts who desire to stop using cocaine, but continue to be stymied by relapses. The strategy is simple (if yet unproven): if an individual vaccinates and then relapses, she will not find the expected high, and her craving will eventually recalibrate. In other words, she will lose interest.

If the vaccine works well, it could shift treatment from counseling and rehabilitation programs to a mandatory vaccination. There are, of course, some potential problems with the notion of a drug vaccine. One is that addicts inoculated

80. The blood-brain barrier is a collection of cells that protect the brain from certain chemicals in the blood while passing others through.
against cocaine may well turn to another drug for satisfaction, and this highlights the importance of addressing the craving and impulse control issues surrounding drug taking. As Robert Julien notes: “Just as focus cannot be solely on the drug of dependence and its rewarding and withdrawal effects . . . neither can it be only on pharmacotherapy for treatment . . . . [A]ddicts will have to be able to handle later exposure to craving-eliciting cues in the environment.”

Vaccines in combination with neurofeedback may well prove to be a fruitful combination.

IV. CONCLUSION

Drug addiction reflects abnormal operation of normal neural circuitry. More than physical dependence, addiction represents changes in the brain that lead to increased craving and diminished capacity for the control of impulses. Given the growing biological understanding of addiction, it is critical for scientists to play an active role in drug policy. As neuroscientific understanding develops, we will, to a much greater degree, be able to target specific behavioral, pharmaceutical, and neurological treatments for specific addictions. It is important to emphasize that biological explanation will not somehow become equivalent to exculpation. Instead, the goal of explanation is to introduce rational sentencing and the opportunity for customized rehabilitation. This approach is likely to show more utility and less cost than incarceration. The neuroscientific community should continue to develop rehabilitative strategies so that the legal community can take advantage of those strategies for a rational, customized approach to drug addiction.

82. ROBERT M. JULIEN, A PRIMER OF DRUG ACTION 661 (10th ed. 2004).