Why Neuroscience Matters for a Rational Drug Policy, 11.1 MINN. J.L. SCI. & TECH. __ (forthcoming 2010)

WHY NEUROSCIENCE MATTERS FOR RATIONAL DRUG POLICY

David M. Eagleman, Ph.D., Mark A. Correro, J.D.,

and Jyotpal Singh*

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 prisoners meet the criteria for substance abuse or dependence.[1] In one study, 35.6% of convicted inmates were under the influence at the time of their criminal offense.[2] The cost to society of drug abuse is estimated at $180.9 billion, of which $107.8 billion is derived from drug-related crime.[3] The linkage between drug abuse and crime has been thoroughly established elsewhere. The interesting new development relates to emerging knowledge and technologies that may possibly provide a gateway between the failed policies of the past and novel solutions for the future. Drug addiction is rooted in the biology of the brain, and our 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.[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.[5] Drug

---

* David M. Eagleman is a neuroscientist at Baylor College of Medicine (BCM) (eagleman@bcm.edu). He is the founder and director of BCM's *Initiative on Neuroscience and Law* (www.neulaw.org). Mark A. Correro is a practicing attorney specializing in pharmaceutical litigation under the Federal False Claims Act. He is currently working with the Law Offices of Mark Kleiman (mcorrero@quitam.org). Jyotpal Singh is a law student at University of Houston Law Center and a Research Fellow in the *Initiative on Neuroscience and Law*.

[1] BUREAU OF JUSTICE STATISTICS, SPECIAL REPORT: SUBSTANCE DEPENDENCE, ABUSE, AND TREATMENT OF JAIL INMATES (2002) *available at* http://www.ojp.usdoj.gov/bjs/abstract/sdatji02.htm (last visited March 3, 2009) ("In 2002, 68% of jail inmates reported symptoms in the year before their admission to jail that met substance dependence abuse criteria.").

[2] BUREAU OF JUSTICE STATISTICS, SPECIAL REPORT: DRUG USE, TESTING, AND TREATMENT IN JAILS (2000), *available at* http://www.ojp.usdoj.gov/bjs/abstract/duttj.htm (last visited March 3, 2009) (showing that 35.6% of convicted inmates, or 138,000 individuals, were under the influence at the time of the offense).

[3] NAT'L INST. ON DRUG ABUSE, PRINCIPLES OF DRUG ABUSE TREATMENT FOR CRIMINAL JUSTICE POPULATIONS: A RESEARCH BASED GUIDE, *available at* http://www.drugabuse.gov/podat_cj/ (last visited March 3, 2009).

[4] Alan I. Leshner, *Addiction is a Brain Disease, and it Matters*, 278 SCIENCE 45–47 (1997); Wolfram Schultz, et al., *A Neural Substrate of Prediction and Reward*, 275 *SCIENCE* 1593–99 (1997); A. Thomas McLellan, et al., *Drug Dependence, A Chronic Medical Illness: Implications for Treatment, Insurance, and Outcomes Evaluation*, 284 J. AM. MED. ASS'N 1689–95 (2000); Carlton K. Erickson, THE SCIENCE OF ADDICTION: FROM NEUROBIOLOGY TO TREATMENT 290 (W.W. Norton & Co. 2007).

[5] Nora Volkow and Ting-Kai Li, *Drug Addiction: The Neurobiology of Behaviour Gone Awry*, 5 NATURE REVIEWS NEUROSCIENCE 963–70 (2004).

addiction manifests as an irrepressible drive to take the drug despite the undesirable consequences. For many decades it was thought that drug addiction resulted from physical dependence on the drug: because withdrawal symptoms could be serious, and sometimes life-threatening, drug addiction was thought to be the same as physical dependence. But a new understanding shows that drug addiction is more than dependence, and results from a reconfiguration of the circuitry of the reward and decision-making systems, leading to increased cravings and diminished impulse control. In other words, addiction can be reasonably viewed as a neurological problem that allows for medical solutions, just as pneumonia can be viewed as a lung problem. As we progress in understanding the underlying mechanisms of addiction, how that circuitry leads to drives, and how drugs both hijack and rewrite that circuitry, we have the opportunity to leverage that understanding into more effective drug policy that rests on treatment rather than punishment.

Part I 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 II 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 III explores cutting-edge ideas on the horizon that offer new hope for directly treating addiction rather than engaging in repeated rounds of incarceration. Here, we describe two innovative strategies—cocaine vaccines and real time feedback in neuroimaging—both of which offer fresh approaches to rehabilitation and new opportunities for dialogue in the problem of drug addiction.

I. WHAT TO DO ABOUT DRUG ADDICTS?

A. HISTORICAL TENSIONS BETWEEN PUNISHMENT AND REHABILITATION

Societies have grappled for centuries with complex ethical questions about what to do 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." [6] Rather than looking at drug addiction as a scientific and medical phenomenon, many still 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 traditionally did the mentally ill.[7] The retributive stance generally extols "just deserts" and diminishes rehabilitative attempts, even when rehabilitation is guided firmly by physiological understandings of the underlying pathologies. Nonetheless, rehabilitative efforts have made meaningful appearances throughout the twentieth century.

[6] Robinson v. California, 370 U.S. 660 (1962).

[7] *Id.* (citing ALBERT DEUTSCH, THE MENTALLY ILL IN AMERICA: A HISTORY OF THEIR CARE AND TREATMENT FROM COLONIAL TIMES 13 (1937)).

In the twentieth century, American drug policy vacillated between punishment and rehabilitation. For example, in the mid-twentieth century, attempts to rehabilitate and treat addicts, rather than merely incarcerate them, dominated social policy.[8] These developments were facilitated by advances in psychology and psychiatry.[9] At this time, even the Supreme Court seemed to embrace rehabilitation rather than punishment.

In 1962, the Supreme Court found unconstitutional a California statute that made addiction a crime.[10] The statute stated that "[n]o person shall . . . be addicted to the use of narcotics . . . ."[11] Rather than criminalizing conduct, the California statute conferred a mandatory prison sentence based on a person's status as an addict.[12] The Court reasoned that addiction is a physiological condition requiring treatment rather than punishment.[13]

Beginning in 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 Supreme Court rejected Leroy Powell's claim that alcoholism excused him from being drunk in public.[14] Leroy argued that his public intoxication was not volitional and, therefore, punishing him for it was cruel and unusual.[15] The psychiatrist who testified in the case acknowledged that there was no medical consensus for 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 own behavior."[16] But the Court found his argument a stretch because it was "bas[ed] [on] too little knowledge."[17] At that time, there was a lack of effective treatment options and consensus regarding treatment efficacy.[18] Moreover, there was a paucity of treatment facilities and trained providers.[19] Finally, without adequate treatment and facilities, a civilly committed

---

[8] Symposium, *Prison Reform and Rehabilitation: Forward: A Consumer's Report*, 14 ST. LOUIS. U. PUB. L. REV. 1, 4 ("Following World War II reformers made their greatest gains since the late 1800s . . . 'Rehabilitation' based on the "medical model," achieved penal prominence and credibility. Criminals could be "cured" of the "disease" of criminality, so the theory went, and returned "rehabilitated" to society.").

[9] *Id.* ("Sociologists, psychologists and psychiatrists found fertile fields behind bars in which to test experimental behavior-modification programs.").

[10] Robinson v. California, 370 U.S. 660, 660 (1962).

[11] *Id*. at 660 n.1 (1962) "[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." *Id*. at 667.

[12] *Id.* at 666.

[13] *Id.*

[14] Powell v. Texas, 392 U.S. 514, 516 (1968).

[15] *Id.*

[16] *Id.* at 517–18.

[17] *Id.* at 521.

[18] *Id.* at 527 ("There is 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.").

[19] *Id.* at 528–29.

addict could be indefinitely incarcerated without being imprisoned due to the fact that he had virtually no chance of being effectively rehabilitated.[20] Finding no viable treatment alternatives, the Court concluded that criminal process was still necessary.[21]

The 1970s heralded the "era of harsh prison sentences."[22] From 1972 to 2000, the prison population quadrupled to more than two million."[23] According to recent studies, the "sharp rise in incarceration for drug-related offenses" was the direct cause of this increase.[24] This trend was further fueled by the problems in the 1980s. The crack epidemic began in the mid-1980s,[25] and with that came the "War on Drugs."[26] The role of crack was implicated by researchers in the rise of violent crimes. The violence and crime led to increased calls for longer sentences and cleaning up of the streets.

Beginning in the 1990s, the trend began to shift back to rehabilitation. President George Bush signed House Joint Resolution 174, which designated the 1990s as the "Decade of the Brain."[27] In parallel with the acceptance and developments of neuroscience, the shift away from a retributive criminal policy towards a more rehabilitative policy also has made progress. The government's data indicates that this shift is occurring.[28] The American Bar Association's 2007 recommendations demonstrate this shift.[29] Currently, programs across the nation are shifting

---

[20] *Id.* at 529.

[21] *Id.* at 530 ("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 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.").

[22] 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/ReportI.PDF.121306.pdf (last visited March 3, 2009).

[23] Steven D. Levitt, *Understanding Why Crime Fell in the 1990s: Four Factors that Explain the Decline and Six that Do Not*, 18 J. OF ECON. PERSP. 163, 177 (Winter 2004).

[24] *Id.*

[25] *Id.* at 179.

[26] ABA Report, s*upra* note 33, at 2.

[27] *See* Edward G. Jones and Lorne M. Mendell, *Assessing the Decade of the Brain*, 284 SCIENCE 739 (1999).

[28] According to the Bureau of Justice, in 2002, 47% of addict inmates participated in treatment or other programs while under correctional supervision. Trends indicate that these numbers are growing. Bureau of Justice Statistics, Special Report: Substance Dependence, Abuse, and Treatment of Jail Inmates, 2002, *available at* http://www.ojp.usdoj.gov/bjs/abstract/sdatji02.htm (last visited March 3, 2009)

[29] *See* ABA Report, *supra* note 33. Their recommendations basically urge governments to move away from pure incarceration methods of punishment towards community supervision, deferred adjudication, mental health treatment, and, most relevant here, substance abuse treatment when the offender is not a threat to the community, has not committed a predatory or other large-scale crime, and lacks prior criminal history. Their recommendation explicitly acknowledges the doubts from the 1970s about rehabilitation; however, the recommendations rebut this argument with evidence about the inefficacy of longer prison sentences. Further, they emphasize that cost-effective strategies will depend upon a balancing of interests between protecting the public through incarceration and preventing recidivism through rehabilitation.

from retribution to rehabilitation.[30] Positive changes such as the increased use of drug courts, 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. In fact, "more than two-thirds of those . . . released from prison [are] rearrested within three years of release, and 42% of parolees returning to prison or jail within 24 months of their release . . . ." This prison exodus means that 650,000 prisoners are flocking back to their communities every year. Are addicts improved by their penitentiary experience? If not, then 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 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, and this may stem in part from historical misuse.

> 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.[31]

Considering recent history, apprehension to the use of science in making social policy is not unjustified. "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."[32]

A second concern, also shared by many, is that a neuroscientific understanding may exculpate criminals if they can "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 sits unpalatably on the public tongue. We suggest that this does not need to be a concern. Societies will continue to remove

[30] Beginning in 1993 in Arkansas, community-based substance abuse treatment, drug courts and other measures have been combined under a system that provides for avoidance of conviction records upon completion of a community-based program. This program has seen significant drops in recidivism rate. In Connecticut, every court now has access to substance abuse evaluations and outpatient treatment programs for offenders, and the state has expanded inpatient treatment programs for substance abusers. These strategies have also shown reduced recidivism rates. In New York, repeat drug offenders have access to the DTAP program. The Multonmah County STOP program provides certain drug offenders with the ability to complete a treatment program to avoid prosecution. In Kansas, a new program for non-violent drug offenders provides a long-term treatment program.

[31] Semir Zeki & Oliver R. Goodenough, *Law and the Brain: Introduction*, 359 PHIL. TRANS. R. SOC. LOND. B. 1661–65 (2004).

[32] *Id.* at 1661.

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 incarceration costs. 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 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, and 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 and we illustrate how neuroscience can back up its claims of addiction as a biological problem and bring actionable solutions to the table.

II. NEUROSCIENCE AND ADDICTION

A. BIOLOGICAL UNDERPINNINGS

The human brain consists of hundreds of billions of cells called neurons and over a trillion glial cells. The number of connections between these cells numbers between 60–240 trillion.[33] The complex patterns of connection in the brain—its 'circuitry'—is dynamic: connections between cells are constantly blossoming, dying, and reconfiguring.[34] The pattern of connectivity in the brain determines behaviors, thoughts, and capacities. Damage to the circuitry impairs these functions.[35]

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: "drug 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."[36] The proposal that addiction is biologically rooted is not new; however, modern techniques have progressed our understanding of the neural basis of addiction from general ideas to specific mechanisms. In 1968, the Supreme Court pointed out incarceration was still necessary as long as a real understanding of addiction and useful methods of rehabilitation were lacking.[37] Almost half a century later, we are close to meeting that challenge.

---

[33] Gordon M. Shepherd, THE SYNAPTIC ORGANIZATION OF THE BRAIN (Oxford Univ. Press 2004); Christof Koch, BIOPHYSICS OF COMPUTATION: INFORMATION PROCESSING IN SINGLE NEURONS (Oxford Univ. Press, 1999).

[34] David M. Eagleman, PLASTICITY: HOW THE BRAIN RECONFIGURES ITSELF ON THE FLY (Oxford Univ. Press, 2009).

[35] David M. Eagleman, DETHRONEMENT: THE SECRET HEGEMONY OF THE UNCONSCIOUS BRAIN (Pantheon Books, 2009).

[36] Nora Volkow and Ting-Kai Li, *Drug Addiction: The Neurobiology of Behaviour Gone Awry*, 5 NATURE REVIEWS NEUROSCIENCE 963–70 (2004).

[37] Powell v. Texas, 392 U.S. 514, 516 (1968)

The brain contains circuitry that properly guides animals in cognitive functions such as decision-making, motivation, learning, and emotion.[38] These circuits, largely involving the neurotransmitter[39] dopamine (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 help animals steer 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.[40] 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.[41] The same mechanisms that normally lead to proper foraging (e.g., if you find a good food source, seek more of it), are now commandeered by the drug. In this framework, addiction is understood as a normal process gone awry.[42]

As a consequence of the reinforcement, the brain becomes physically dependent on the chemicals provided by the drug taking. The number of neurotransmitter receptors[43] 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.[44] 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 intuit that withdrawal symptoms are a factor in sustaining addiction. For many decades it was 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

---

[38] Read Montague, WHY CHOOSE THIS BOOK?: HOW WE MAKE DECISIONS 335 (Dutton Adult 2006).

[39] 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.

[40] 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.

[41] A. David Redish, *Addiction as a Computational Process Gone Awry*, 306 SCIENCE 1944–47 (2004); Nora Volkow, et al., *Dopamine in Drug Abuse and Addiction: Results from Imaging Studies and Treatment Implications*, 9 MOLECULAR PSYCHIATRY 557–69 (2004); Rita Z. Goldstein and Nora Volkow, *Drug Addiction and Its Underlying Neurobiological Basis: Neuroimaging Evidence for the Involvement of the Frontal Cortex*, 159 AM. J. PSYCHIATRY 1642–52 (2002).

[42] David M. Egelman, et al., *A Computational Role for Dopamine Delivery in Human Decision-Making*, 10 J. COGNITIVE NEUROSCIENCE 623–30 (1998); A. David Redish, *Addiction as a Computational Process Gone Awry*, 306 SCIENCE 1944–47 (2004); Nora Volkow, et al., *Dopamine in Drug Abuse and Addiction: Results from Imaging Studies and Treatment Implications*, 9 MOLECULAR PSYCHIATRY 557–69 (2004).

[43] 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.

[44] A system is homeostatic if it adjusts its internal environment 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 Nestler, *Molecular Basis of Long-term Plasticity Underlying Addiction*, 2 NATURE REVIEWS 119–28 (2001).

physical withdrawal symptoms, and then years later they will re-commence their compulsive drug-taking. Thus, the question remains why addicted brains continue to stay addicted. The answer seems to be two-fold: increased craving and diminshed 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 their cravings for the drug effects.[45] This helps account for factors that 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 predict the likelihood of relapse based on responses (both physiological and subjective craving) triggered by drug-related cues.[46] Because of the role of conditioned drug-related cues, craving reduction is now considered a major target for psychological and pharmaceutical interventions.[47] 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.[48] Normally, in the service of longer-term goals, behavioral guidance signals will inhibit urges. But in addicts, diminished inhibition allows the unmasking of compulsive drug-seeking and drug-taking.[49] Simple cognitive tasks that measure an individual's capacity for cognitive control, such as quickly inhibiting a pre-planned motor response, serve as strong predictors of treatment

---

[45] Terry E. Robinson & Kent C. Berridge, *The Psychology and Neurobiology of Addiction: An Incentive-Sensitization View*, 95 ADDICTION S91–S117 (2000); Samuel M. McClure, et al., *A Computational Substrate for Incentive Salience*, 26 TRENDS IN NEUROSCIENCES 423–28 (2003).

[46] D. Catley, et al., *Absentminded Lapses During Smoking Cessation,*14 PSYCHOL. ADDICT BEHAVIOR 73–76 (2000); Joel D. Killen, et al., *Prospective Study of Factors Influencing the Development of Craving Associated with Smoking Cessation*, 105 PSYCHOPHARMACOLOGY 191–196 (1991); Joel D. Killen & Stephen P. Fortmann, *Craving is Associated with Smoking Relapse: Findings from Three Prospective Studies*, 5 EXPERIMENTAL & CLINICAL PSYCHOPHARMACOLOGY 137–142 (1997).

[47] Arthur L. Brody, et al., *Attenuation of Cue-induced Cigarette Craving and Anterior Cingulate Cortex Activation in Bupropion-treated Smokers: A Preliminary Study*, 130 PSYCHIATRY RESEARCH: NEUROIMAGING 269–281 (2004); Paul M. Cinciripini, et al., *Combined Effects of Venlafaxine, Nicotine Replacement, and Brief Counseling on Smoking Cessation*, 13 EXPERIMENTAL & CLINICAL PSYCHOPHARMACOLOGY 282–92 (2005); C.C. DiClemente, et al., *Readiness and Stages of Change in Addiction Treatment*, 15 AM. J. ADDICTION 103–119 (2004).

[48] Steven E. Hyman, *The Neurobiology of Addiction: Implications for Voluntary Control of Behavior*, 7 AM. J. BIOETHICS 8–11 (2007); Antoine Bechara, et al., *Different Contributions of the Human Amygdala and Ventromedial Prefrontal Cortex to Decision-Making*, 19 J. NEUROSCIENCE 5473–81 (1999); P. Kalivas, et al., *Unmanageable Motivation in Addiction: A Pathology in Prefrontal-Accumbens Glutamate Transmission*, 45 NEURON 647–50 (2005); Rita Z. Goldstein and Nora Volkow, *Drug Addiction and Its Underlying Neurobiological Basis: Neuroimaging Evidence for the Involvement of the Frontal Cortex*, 159 AM. J. PSYCHIATRY 1642–52 (2002).

[49] Dan I. Lubman, et al., *Addiction, A Condition of Compulsive Behavior? Neuroimaging and Neuropsychological Evidence of Inhibitory Dysregulation*, 99 ADDICTION 1491–1502 (2004); Rita Z. Goldstein, et al., *Severity of Neuropsychological Impairment in Cocaine and Alcohol Addiction: Association with Metabolism in the Prefrontal Cortex*, 42 NEUROPSYCHOLOGIA 1447–58 (2004).

compliance and relapse.[50] In methamphetamine addicts, such simple tasks correlate with relapse up to a year after cessation.[51] 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 U.S. 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:

> Drug treatment programs remain notoriously underfunded, turning away tens of thousands of addicts seeking help even as billions of dollars are spent to arrest, prosecute and imprison.[52]

> 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.[53]

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 from punishment in favor of reducing craving and 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—both of 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

[50] In essence, such an experiment would involve pressing a button when cued to do so. In some trials, the participant is suddenly asked to *not* press the button. People with high impulsivity are unable to stop themselves. As an example of using these impulse control tasks as outcome predictors, see W. Miles Cox, et al., *Alcohol Attentional Bias as a Predictor of Alcohol Abusers' Treatment Outcome*, 68 DRUG AND ALCOHOL DEPENDENCE 237–43 (2002); Andrew J. Waters, et al., *Attentional Bias Predicts Outcome in Smoking Cessation,* 22 HEALTH PSYCHOL. 378–87 (2003); Chris C. Streeter, et al., *Performance on the Stroop Predicts Treatment Compliance in Cocaine-Dependent Individuals,* 33 NEUROPSYCHOPHARMACOLOGY 827–36 (2008).

[51] Martin P. Paulus, *Neural Activation Patterns of Methamphetamine-Dependent Subjects During Decision Making Predict Relapse*, 62 ARCHIVES GEN. PSYCHIATRY 761–68 (2005).

[52] E.A. Nadelmann, *Drug Prohibition in the United States: Costs, Consequences, and Alternatives,* 245 SCIENCE 939–47 (1989).

[53] M.E. Jarvik, *The Drug Dilemma: Manipulating the Demand,* 250 SCIENCE 387–92 (1990).

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.[54] 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).[55]

For alcoholism, medications like naltrexone are used to antagonize[56] the normal relationship of alcohol with its receptors, thus interfering with reinforcement. Other strategies, such disulfiram, and 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.[57] 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 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.

[54] Nora Volkow and Ting-Kai Li, *Drug Addiction: The Neurobiology of Behaviour Gone Awry*, 5 NATURE REVIEWS NEUROSCIENCE 963–70 (2004).

[55] Mehmet Sofuoglu and Thomas R. Kosten, *Emerging Pharmacological Strategies in the Fight Against Cocaine Addiction*, 11 EXPERT OPINION ON EMERGING DRUGS 91–98 (2006).

[56] 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.

[57] Noeline C. Latt, et al., *Naltrexone in Alcohol Dependence: A Randomised Controlled Trial of Effectiveness in a Standard Clinical Setting*, 176 MED. J. AUSTL. 530–34 (2002); Sandra D. Comer, et al., *Injectable, Sustained-Release Naltrexone for the Treatment of Opioid Dependence: A Randomized, Placebo-controlled Trial*, 63 ARCHIVES GEN. PSYCHIATRY 210–18 (2006).

As discussed above, subjective cravings triggered by drug-related cues are considered main actors in clinical and neuroscientific accounts of drug addiction.[58] 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 to drug-related cues.[59] 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.[60] Intriguingly, damage in the insula disrupts subjective urges to smoke, without changing the motivation of other behaviors (such as eating). In rodent models as well, inactivation of the insula inhibits drug-seeking.[61] These data point to the distributed neural network involved in craving (and to the insula, in particular) as prime targets for craving-reduction.

There is another half to drug addiction besides craving: deficits in impulse control.[62] Neuroimaging has revealed a related network of areas involved in cognitive control, involving

---

[58] Arthur L. Brody, et al., *Neural Substrates of Resisting Craving During Cigarette Cue Exposure*, 62 BIOLOGICAL PSYCHIATRY 642–51 (2007); Marcus A. Gray & Hugo D. Critchley, *Interoceptive Basis to Craving*, 54 NEURON 183–86 (2007); Rajita Sinha, et al., *Neural Activity Associated with Stress-induced Cocaine Craving: A Functional Magnetic Resonance Imaging Study*, 183 PSYCHOPHARMACOLOGY 171–80 (2005); Clinton D. Kilts, et al., *The Neural Correlates of Cue-Induced Craving in Cocaine-Dependent Women*, 161 AM. J. PSYCHIATRY 233–41 (2004); Susan F. Tapert, et al., *Neural Response to Alcohol Stimuli in Adolescents with Alcohol Use Disorder*, 60 ARCHIVES GEN. PSYCHIATRY 727–35 (2003).

[59] The distributed network involved in cue-triggered craving includes the orbitofrontal cortex, dorsolateral prefrontal cortex, anterior cingulate cortex, striatum, and insular cortex. Arthur L. Brody et al., *Brain Metabolic Changes During Cigarette Craving*, 59 ARCHIVES GEN. PSYCHIATRY 1162–72 (2002); Brian L. Carter & Stephen T. Tiffany, *Meta-analysis of Cue-reactivity in Addiction Research*, 94 ADDICTION 327 (1999); F. Joseph McClernon, et al., *Abstinence-Induced Changes in Self-Report Craving Correlate with Event-Related fMRI Responses to Smoking Cues*, 30 NEUROPSYCHOPHARMACOLOGY 1940 (2005); Stephen J. Wilson, et al., *Prefrontal Responses to Drug Cues: A Neurocognitive Analysis*, 7 NATURE NEUROSCIENCE 211 (2004); Thomas R. Kosten, et al., *Cue-Induced Brain Activity Changes and Relapse in Cocaine-Dependent Patients*, 31 NEUROPSYCHOPHARMACOLOGY 644 (2006); Pearl Chiu, et al., *Self-responses along Cingulate Cortex Reveal Quantitative Neural Phenotype for High-Functioning Autism*, 57 NEURON 463 (2008); TR Franklin, *Limbic Activation to Cigarette Smoking Cues Independent of Nicotine Withdrawal: A Perfusion fMRI Study*, 32 NEUROPSYCHOPHARMACOLOGY 2301 (2007).

[60] Arthur L. Brody et al., *Brain Metabolic Changes During Cigarette Craving*, 59 ARCHIVES GEN. PSYCHIATRY 1162–72 (2002); Gene-Jack Wang, et al., *Regional Brain Metabolic Activation During Craving Elicited by Recall of Previous Drug Experiences*, 64 LIFE SCIENCES 775–84 (1999); L. Sell, et al., *Neural Responses Associated with Cue Evoked Emotional States and Heroin in Opiate Addicts*, 60 DRUG & ALCOHOL DEPENDENCE 207–16 (2000); Katherine R. Bonson, et al., *Neural Systems and Cue-induced Cocaine Craving*, 26 NEUROPSYCHOPHARMACOLOGY 376–86 (2002).

[61] Nasir H. Naqvi, et al., *Damage to the Insula Disrupts Addiction to Cigarette Smoking*, 315 SCIENCE 531–34 (2007); Marcus A. Gray & Hugo D. Critchley, *Interoceptive Basis to Craving*, 54 NEURON 183–86 (2007).

[62] Steven E. Hyman, *The Neurobiology of Addiction: Implications for Voluntary Control of Behavior*, 7 AM. J. BIOETHICS 8–11 (2007); Antoine Bechara, *Decision Making, Impulse Control and Loss of Willpower to Resist Drugs: A Neurocognitive Perspective*, 8 NATURE NEUROSCIENCE 1458–63 (2005); P. Kalivas, et al., *Unmanageable Motivation in Addiction: A Pathology in Prefrontal-Accumbens Glutamate Transmission*, 45 NEURON 647–50 (2005); Rita Z. Goldstein and Nora Volkow, *Drug Addiction and Its Underlying Neurobiological Basis: Neuroimaging Evidence for the Involvement of the Frontal Cortex*, 159 AM. J. PSYCHIATRY 1642–52 (2002).

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,[63] as well as diminished DLPFC activity,[64] 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.[65] These data suggest direct therapeutic interventions to enhance cognitive control in drug addicts.

How can we hope to directly affect specific brain networks? A new technology on the horizon—real-time neurofeedback—suggests one possibility. Neuroimaging known as functional magnetic resonance imaging (fMRI) allows viewing neural activity in near "real-time." 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.[66]

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 their own neural circuitry.[67] 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

---

[63] Nora Volkow & Joanna Fowler, *Addiction, a Disease of Compulsion and Drive: Involvement of the Orbitofrontal Cortex*, 10 CEREBRAL CORTEX 318–25 (2000).

[64] Robert Hester & Hugh Garavan, *Executive Dysfunction in Cocaine Addiction: Evidence for Discordant Frontal, Cingulate, and Cerebellar Activity*, 24 J. NEUROSCIENCE 11017–22 (2004); Rita Z. Goldstein, et al., *The Effect of Practice on a Sustained Attention Task in Cocaine Abusers*, 35 NEUROIMAGE 194–206 (2007).

[65] Pearl H. Chiu, et al., *Smokers' Brains Compute, but Ignore, a Fictive Error Signal in a Sequential Investment Task*, 11 NATURE NEUROSCIENCE 514–20 (2008).

[66] Stephen M. Laconte, et al., *Real-time fMRI Using Brain-state Classification*, 28 HUMAN BRAIN MAPPING 1033–44 (2007); Christopher R. deCharms, *Reading and Controlling Human Brain Activation Using Real-time Functional Magnetic Resonance Imaging*, 11 TRENDS IN COGNITIVE SCIENCE 473–81 (2007); Nikolaus Weiskopf, et al., *Physiological Self-regulation of Regional Brain Activity Using Real-time Functional Magnetic Resonance Imaging (fMRI): Methodology and Exemplary Data*, 19 NEUROIMAGE 577–86 (2003); Christopher R. deCharms, et al., *Learned Regulation of Spatially Localized Brain Activation Using Real-time fMRI*, 21 NEUROIMAGE 436–43 (2004); Phan K. Luan, et al., *Real-time fMRI of Cortico-limbic Brain Activity During Emotional Processing*, 15 NEUROREPORT 527–32 (2004); Christopher R. deCharms, et al., *Control Over Brain Activation and Pain Learned by Using Real-time Functional MRI*, 102 PROCEEDINGS NAT'L ACAD. SCI. U.S. 18626–31 (2005).

[67] 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.

nicotine addicts.[68] It may be almost a year before the efficacy of this approach can be accurately gaged, but this integration of neural substrates of addiction and real-time neuroimaging is highly promising. This technology, together with other new developments, may 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.[69]

A drug vaccination is accomplished in the traditional biological manner of all innoculations: 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, 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 bound up 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.[70] In this way, the high is eliminated or at least attenuated.[71] 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, they will not find the expected high, and their craving will eventually recalibrate. In other words, they 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 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: "[o]ther forms of therapy would also be necessary as it is more than just the physiological addiction that causes people to use again (relapse). Craving is a very complex issue that won't necessarily be solved with a pharmacological intervention."[72] Vaccines in combination with neurofeedback may well prove to be a fruitful combination.

---

[68] This work is spearheaded by our colleagues Drs. Steven LaConte, Pearl Chiu, Brooks King-Casas and P. Read Montague.

[69] Frank M. Orson, et al., *The Future of Vaccines in the Management of Addictive Disorders*, 9 CURR PSYCHIATRY REPS. 381–87 (2007).

[70] The blood-brain barrier is a collection of cells that protect the brain from certain chemicals in the blood while passing others through.

[71] Bridget A. Martell, et al., *Vaccine Pharmacotherapy for the Treatment of Cocaine Dependence*, 58 BIOLOGICAL PSYCHIATRY 158–64 (2005).

[72] Robert M. Julien, A PRIMER OF DRUG ACTION, 10th Ed. (Worth Publishers 2004).

V. CONCLUSIONS

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 because, 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 explanations will not 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.