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The role of neuroscience in drug policy: promises and prospects

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Abstract. *Crack cocaine use carries high costs for society, particularly in terms of increased crime. The tools of modern neuroscience may be able to reduce demand by addressing altered brain circuitry of individuals suffering from severe cocaine use disorder. Here, we review several rehabilitative strategies, including pharmacotherapies targeting neurotransmitter systems, immunotherapies that block cocaine from entering the central nervous system, brain stimulation to disrupt abnormal circuit function, and real-time feedback in neuroimaging to allow the strengthening of impulse control. These experimental treatments hold promise for treating severe cocaine use disorder, and such rehabilitative approaches could be employed as an alternative to widespread incarceration.*

Keywords: neurolaw, novel drug therapies, incarceration, rehabilitation, brain stimulation, neurofeedback, crack, cocaine

1. Introduction.

Drug addiction, also termed substance-use disorder, arises from a multifactorial set of risk factors including genetics, environment, exposure, and also dysfunctions in the brain. The strongest evidence that drug addiction has some root in the brain is that some animals will self-administer a variety of addictive drugs, especially stimulants like cocaine[1,2]. Moreover, changing

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brain circuitry (either pharmacologically[3–5], electrically[6], or optogenetically[7]) alters the degree to which animals will self-administer addictive drugs like cocaine. The field of neuroscience, therefore, plays a critical role in elucidating the mechanisms of drug addiction for addressing the issue.

Neuroscience has begun to reveal the circuitry involved in drug addiction, and many experimental methods are being developed to help individuals combat cocaine use disorders. Such rehabilitation methods, including pharmacological approaches, cocaine vaccinations, electrical and magnetic brain stimulation, and real-time feedback in functional magnetic resonance imaging (fMRI), offer potential to reduce craving and consumption of cocaine. If they deliver on their promise, these strategies could potentially serve as alternatives to existing approaches, particularly with regards to imprisonment which typically does not address addiction itself.

This article focuses on the subset of drug users who move beyond recreational use of cocaine to the level of severe cocaine use disorder, as defined by the DSM-5, which has several health-related consequences of cocaine addiction. For the purpose of this paper, however, we focus on crack cocaine due to its prevalence and established intersections with the criminal legal system. As researchers at a medical school, we note that our approach is more grounded in biology rather than sociology (e.g., critical addiction studies)[8].

We will first review the relationship between crack and crime. We then show how neuroscience research has developed the view that substance use disorder is, at least in part, a brain disease manifested by cravings and diminished impulse control. Finally, we review the promise and challenges of potential neuroscience-based treatments for addiction, from conventional pharmacotherapies to experimental uses of transcranial stimulation and neuroimaging. Each therapy has both scientific and social obstacles, but these approaches may help understand addiction fundamentally and how society can overcome it.

1.1. Crack & Crime.

From 1984 to 1994, there was a dramatic rise in violence in U.S. cities9. Researchers credit crack cocaine, pointing to an expansion of the U.S. crack market among poor inner-city youth beginning in 1985[10,11]. Crack contributed to violent crime as rival gangs competed to sell the lucrative drug[9,11]. Without crack cocaine, criminologists suggest that urban crime rates would have been as much as ten percent lower than the 1991 peak[12].

Several studies demonstrate that criminal activity positively correlates with offenders' drug consumption[13–16]. This relationship holds whether the individual was assisted or unassisted throughout the rehabilitation process, and whether the treatment was voluntary or involuntary[17]. The correlation is even stronger among adolescents[18–20]. These findings are consonant with interviews in which substance abusers cite the need for drug money as the most important reason they began offending[21,22]. To reduce aggregate crime, therefore, governments are well-served to address drug addiction itself.

When drug users move beyond recreational use to the level of a cocaine use disorder, they commit crimes at significantly higher rates than individuals who use cocaine less frequently[23]. Bennett et al., 2008 found that the odds of offending are over 6 times greater for crack users than non-crack users, and these odds are nearly twice as high as those using powder cocaine or even heroin – the other principal drugs most associated with criminal offending[24]. In particular, crack use correlates with an increased propensity to commit shoplifting, burglary, and robbery[24]. Crack-

dependent women often move beyond petty theft and turn to prostitution to finance their drug habit[25], and the rise of HIV and other sexually transmitted diseases from this linkage poses a serious public health concern[26]. Given the myriad of psychosocial influences, the causal relationship between crack and crime, however, cannot be inferred directly. Nonetheless, prolonged abstinence of cocaine has recently been shown to reduce impulsivity and restore response inhibition neural circuitry[27].

Even in the face of these grim statistics, drug treatment programs remain severely underfunded. The 2012 U.N. World Drug Report estimates that fewer than one in five people who could benefit from treatment receive it. In part, this is because different governments pursue widely different drug policies around the world. In countries such as Canada, Spain, Italy, Portugal, Luxembourg, the Netherlands, Germany, and the Czech Republic, drug policy includes an emphasis on rehabilitation. Most of these countries have adjusted their regulations so that carrying small amounts of illegal drugs no longer results in prosecution[28]. These countries, however, are the exceptions, in large part because international agreements have prioritized a criminalization approach to drug abuse since the 1961 UN Single Convention on Narcotic Drugs[29]. In the vast majority of the world, particularly Asia and most of the Americas, governments rely primarily on a zerotolerance approach to deter drug use, as reflected by lengthy minimum imprisonment sentences for possession. In the Philippines, for instance, the minimum sentence for possession of five grams of illegal drugs is twelve years in prison[28]. In some countries, such as Indonesia, drug trafficking carries an automatic death penalty[28].

Individuals suffering from severe substance use disorders are less likely to receive treatment when addiction leads to imprisonment. Prisons and jails are unlikely places to receive adequate drug addiction treatment, and this emphasizes the weaknesses of an incarceration-based approach[30]. Reports indicate that more than 50% of U.S. offenders need addiction treatment – with 85% of those inmates failing to receive any treatment during their sentence[31,32] – opening the door to a costly and vicious cycle of imprisonment and drug relapse[33]. While some prisoners likely lacked the intrinsic motivation to overcome their addiction, others were never given the opportunity to pursue a treatment option. For broader society, using prisons to force addicts into abstinence ignores the susceptibility and high rates of relapse that occur when inmates are released back into society[33]. Collectively, these considerations call for a more comprehensive approach to drug addiction.

In the United States, the government's focus on drug use can be traced back to June 17, 1971, when President Nixon declared the "War on Drugs" in a speech to U.S. Congress. For a short time afterward, the majority of U.S. funding for the effort to reduce drug use went to treatment that primarily relied on substitution strategies (e.g., methadone replacement therapy for opiates)[34]. This focus changed under President Reagan, who prioritized incarceration and initiated regional task forces of law enforcement officers to mobilize against drug traffickers[34]. As a result, the number of arrests for illicit drug use tripled, from fewer than 0.6 million drug-related arrests in 1980 to greater than 1.8 million in 2005[35].

Today, the focus on incarceration is beginning to change, with more governments heeding the call to treat addiction as an ailment rather than a crime. The United States has been increasing funding for preventative and intervention training for social services employees, as well as for substance use disorder treatment providers using behavioral therapy[36]. Incarceration is no longer seen as the sole option, as demonstrated by the gradual emergence of three approaches: (i) community-supervised treatment programs, (ii) specialized courts staffed by people with extensive experience with drug abuse, and (iii) civil commitments upholding treatment regimens. However, these approaches rely on behavioral regimens. A systematic review of 27 randomized

controlled trials found no single behavioral regimen (e.g., Cognitive Behavioral Therapy, Community Reinforcement Approach, Supportive-Expressive Psychodynamic Therapy) to significantly reduce psychostimulant use following the intervention[37]. A fundamental neural understanding of how addictive behavior manifests may help identify appropriate treatment regimens for individuals. For example, a recent functional electroencephalography (EEG) study was able to model and predict which individuals were more likely to complete treatment based on cortical brain activity measured while performing a cognitive inhibition task[38]. Overall, a general willingness to explore new approaches can open the door for neuroscience to play a critical role in the development of new waves of treatment for people suffering from drug use disorders.

2. Neural bases of addiction.

Neuroscience has the opportunity to explain drug demand by providing a greater understanding of the neurobiology of the individual who suffers from severe substance use disorder. Research has begun to lay bare the underlying mechanisms giving rise to addiction, from genetic and environmental influences, to molecular cascades and brain circuitry that may have gone awry. By identifying and understanding these root causes, treatment options are being researched to allow addicts to break free of the cycle of addiction, and thereby lower the likelihood of criminal recidivism.

Addiction arises from a complex interaction of genetic (with multiple genes accounting for 40-60% of vulnerability)[39], developmental (e.g., drug use in early childhood could increase addiction potential by as much as 4-fold)[40], and environmental factors (e.g., stress, parental support, and socioeconomic status)[41,42]. Collectively, these factors lead to the altered brain circuitry that predispose toward an addiction phenotype. The addiction cycle can be viewed in three stages: (1) craving, (2) binging, and (3) withdrawal. For each stage, relevant brain regions, their connections, and their neurotransmitter systems have been implicated in the cycle (**Figure 1**)[43].

The first stage, *craving*, integrates components of memory and affect that give rise to drug-seeking behavior. The hippocampus, orbitofrontal cortex, and anterior cingulate cortex all show increased activity during this anticipatory stage, with excitatory glutamatergic synaptic projections to the dopaminergic reward centers in the ventral striatum, including the nucleus accumbens (NAc). For non-addicts, cognitive inhibition can combat the desire for the drug, averting the transition from craving to drug seeking and abuse. However, addicts have abnormal valuations of futures[44,45] and weakened cognitive inhibition,[46–48] presumably from a loss of top-down control of the frontal cortex onto the ventral striatum[49,50]. This diminished control is thought to result from disruptions in the neural circuitry involving the dorsolateral prefrontal cortex (DLPFC) and the ventrolateral prefrontal cortex (VLPFC), which show diminished activity when cigarette smokers are asked to regulate cravings[51] or when stimulant addicts engage in a response inhibition task.[52] Intriguingly, manipulation of these frontal areas in animal studies,[53] particularly with direct optogenetic stimulation of rat prelimbic frontal cortex[7], reduces cocaine self-administration. When paired with research showing that the response inhibition circuitry regains function in abstinent cocaine users[27], the evidence suggests that addicts have deficient frontal inhibition[54].

The second stage, *binging*, invokes the reward system of the ventral striatum, including principally the NAc. One hypothesis on what makes individuals predisposed to addiction is lowered levels of brain dopamine D2 receptors in the brain. These dysfunctional brain areas may

encourage individuals to seek more dopamine. Cocaine can increase dopamine levels by blocking the dopamine transporter (DAT), which results in increased dopamine (DA) levels in the synaptic clefts[55,56]. Evidence shows that achieving a high may require the prevention of DA degradation, with a minimum threshold needed to experience the effects[57]. Positron emission tomography (PET) studies also demonstrate that a broad class of illicit drugs, including cocaine, cause an increase in DA in the NAc[42]. Studies have also been able to link animals with lowered levels of trait dopamine receptors with increased propensity for cocaine addiction[58]. Pharmacological approaches that target dopaminergic reward pathways seek to either substitute illicit drugs with compounds that increase basal levels of DA, or to inhibit endogenous DA metabolism mechanisms.

The third stage, *withdrawal*, invokes an emotional response driven by activation of the amygdala and its extensions[59]. The neurotransmitters involved in this widespread network include norepinephrine and corticotropin-releasing factor, and axons project to the hypothalamus[60] and brainstem to induce a visceral negative response. While consuming the drug will temporarily relieve the withdrawal and stress, the brain's stress response becomes abnormal; as such, treatment approaches often include therapeutics that can decrease brain stress systems[61,62].

3. Effects of cocaine addiction on the brain.

What about the long-term effects of cocaine on the brain? Biophysical experiments and models are actively being tested and developed to understand how chronic cocaine use alters the brain. Studies find both neurologically apparent deficits (e.g., seizures, strokes, and headaches[63]) and clinically silent brain disruptions (e.g., decreased frontal cortex metabolism[64] and accelerated brain aging[65]) occur as a result of chronic cocaine use. The cognitive effects of long-term cocaine use impact a broad range of function including attention, response inhibition, memory, and reward valuation[66]. The exact pathophysiological mechanisms that give rise to the neurologic sequelae of chronic cocaine use is not fully understood and is under active investigation. One such new theory claims that elevated dopamine levels in the brain may disrupt potassium channels creating disinhibition[67]. Ultimately, this could lead to a hyperexcitable state, especially when presented with relevant cues leading to heightened cravings in addicted in individuals, even if the cues are only briefly presented.

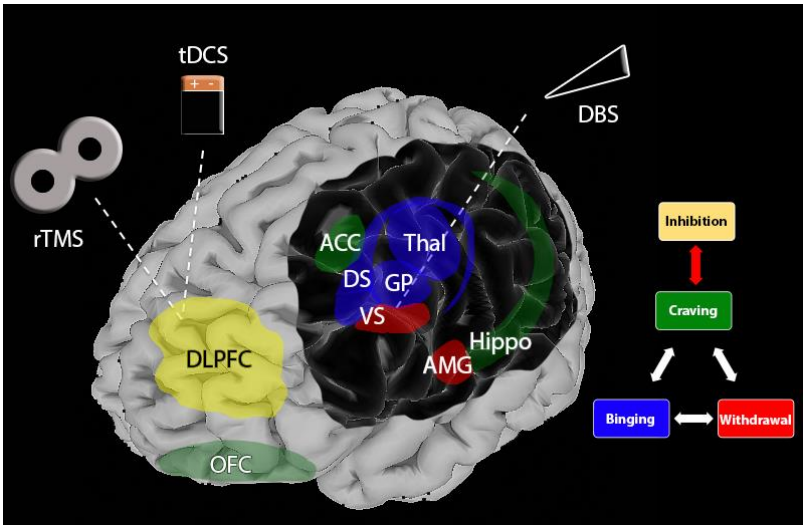

Figure 1. Neural circuitry underlying the three stages of addiction and targets of treatment approaches. The three stages of addiction include Craving (green), Binging (blue), and Withdrawal (red). Repetitive transcranial magnetic

stimulation (rTMS) and transcranial direct current stimulation (tDCS) target the DLPFC to increase inhibitory control and decision making via effects on the orbitofrontal cortex (OFC) and nucleus accumbens (NAc). The NAc is also one of the targets for deep brain stimulation (DBS) to decrease cravings for addictive substances. ACC, anterior cingulate cortex; OFC, orbitofrontal cortex; Hippo, Hippocampus; AMG, amygdala; VS, ventral striatum; DS, dorsal striatum; GP, globus pallidus; Thal, thalamus. Figure modified from Koob and Volkow 2010[43] and Wing et al., 2013[68].

4. Neuroscience-based treatments.

An increased understanding of the neural bases of the addiction cycle has opened the door to new rehabilitative approaches. Below, we outline four tailored treatment strategies for cocaine use disorder, from conventional to experimental.

4.1. Pharmacological strategies.

One approach is to combat the effects of drugs on the brain through pharmacotherapies. Drugs of abuse can induce specific modulation of neurotransmitters in different brain regions[69–71]. For example, because cocaine increases DA levels in the NAc (by blocking dopamine transport),[72] medications continue to be developed to restore dopamine homeostasis[73]. In general, therapies for cocaine addiction have targeted many aspects of dopaminergic regulation and its down stream effects. In one approach, cocaine can be substituted with dopaminergic agonists (e.g., disulfiram and modafinil) that reduce the craving for cocaine[74–76]. In another, the effects of cocaine can be blunted by γ- aminobutyric acid (GABA) agonists (e.g., tiagabine and topiramate) to suppress dopaminergic cell firing and reduce the positive reinforcement. In yet another approach, stress hormone responses induced as a result of NAc projections to catecholamine-releasing areas within the brainstem can be blunted via betaadrenergic blockers (e.g., propranolol)[77]. These varied pharmacotherapies have been developed to target the three stages of drug addiction.

One difficulty for pharmacological approaches is that the American Federal Drug Administration (FDA) requires treatments to overcome a challenging threshold before approving a therapy for cocaine use disorder: a medication must give rise to complete abstinence from cocaine use for 2 consecutive weeks at the end of the trial. This threshold suggests that medications that reduce cocaine use may have already been evaluated, though failed to advance for approval because they did not satisfy the rigorous abstinence definition[73]. Despite many therapies showing decrease in use or decrease in subjective cravings, the FDA has held firm on this requirement and has not granted approval to any addiction treatments for cocaine use disorder[78,79]. The FDA mandate for cocaine use disorder treatment differs from the standard for other neuropsychiatric diseases, like depression, which only requires substantial evidence of efficacy (generally speaking, significantly better than placebo) in order to gain approval[80]. Further, antidepressant outcome measures are especially vague with FDA providing little guidance as to the preferred assessment scale used to measure drug efficacy. A heightened threshold for FDA approval of medications for cocaine use disorder shuts the door on other potentially more accurate guides for the treatment of cocaine addiction, like cognitive and psychological screening.

Although pharmacological treatments are relatively cost effective – in the range of several thousand dollars[81] – they come with limitations. They take a blanket approach and target all receptors of a certain type, instead of specifically targeting only the impaired circuits. Therefore, it is possible – though unconfirmed – that these medications fail to address the underlying aberrant brain circuitry. Another well-known concern with several pharmaco-therapeutics is exposure to

adverse side effects. Moreover, some strategies simply substitute an illicit drug with another controlled substance (although research suggests that the abuse potential can be ameliorated through sustained release formulations)[82]. Further, medication compliance remains a significant issue, and dropout rates are often high for cocaine addiction studies.

These difficulties highlight the need for the development of novel approaches beyond pharmacological treatments. We next explore three promising strategies based on an understanding of mechanisms at the cellular and network levels, beginning with a treatment well into human subject trials.

4.2. Cocaine vaccine.

The cocaine vaccine seeks to circumvent the continued reinforcement of cocaine use disorder by preventing the drug from entering the brain. In the active immunization approach, the cocaine molecule is attached to immunogenic proteins to provoke a T-cell mediated humoral (antibody) response against cocaine. If the patient uses cocaine after the vaccination, antibodies bind the cocaine molecules to prevent them from crossing the blood-brain barrier (**Figure 2**). One example of this method, in which cocaine is attached to a cholera toxin B subunit, has shown some therapeutic benefit through phase IIb human clinical trials[83]. To induce higher titers of antibodies, cocaine molecules can be coupled to parts of the more immunogenic adenovirus[84,85], which leads to a dramatic reduction in the cocaine that reaches the brains of non-human primates[86].

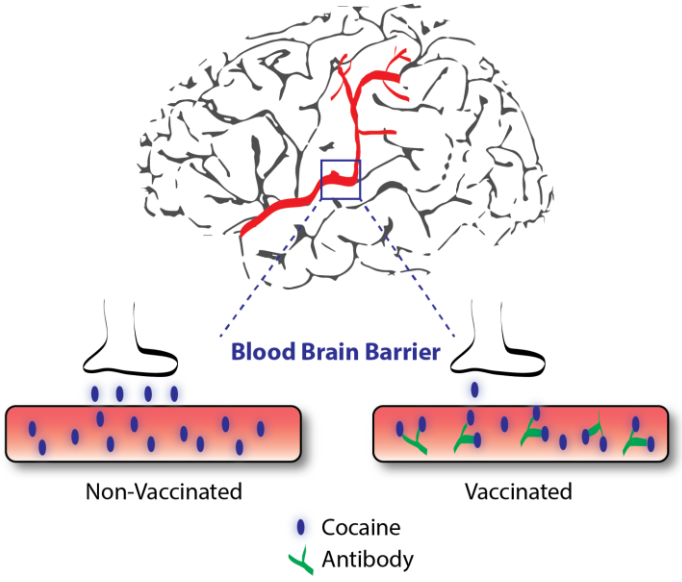

Figure 2. The cocaine vaccine harnesses the immune system to prevent absorption of the cocaine molecule. Figure adapted from Shen et al, 2012[87]

However, there are also concerns with the vaccine approach. In chronically addicted patients, the underlying brain circuitry and chemistry will be no different, and therefore this treatment will not address deficits in inhibitory control, reward processing, and many other factors, compromising its immediate usefulness: the remaining deficits may simply push the individual toward another drug to replace the cocaine high or they may attempt to use more

cocaine to overcome the blunted effects[88]. Finally, the approach is still in the experimental stages, with the recent phase III randomized double-blind placebo-controlled trials having failed to reduce cocaine use, even in patients with high IgG anti-cocaine titers[89].

Although promising, immunotherapies might not address underlying, compulsive drug-seeking behavior – and this again highlights the need for a diversity of approaches to address the multiple facets of drug addiction.

4.3. Direct and Transcranial Brain Stimulation.

For over a century, researchers have worked to directly manipulate and alter the physical brain to treat drug addiction (**Figure 3**). Invasive techniques, including lobotomies and the destruction of particular regions through ablative surgeries, have been used to in attempt to remove and rewire brain circuitry. Implicated brain regions include the anterior cingulate cortex (ACC) and the NAc[90]. Ablation of the ACC has been used to treat addiction to morphine, heroin, opiates, and alcohol with success rates ranging from 60-90%[90]. For the NAc, bilateral ablation trials were recently conducted in China for opiate[91] and alcohol[92] addictions. Both studies claimed to reduce relapse rates of drug addiction significantly with no or only minor temporary side effects.

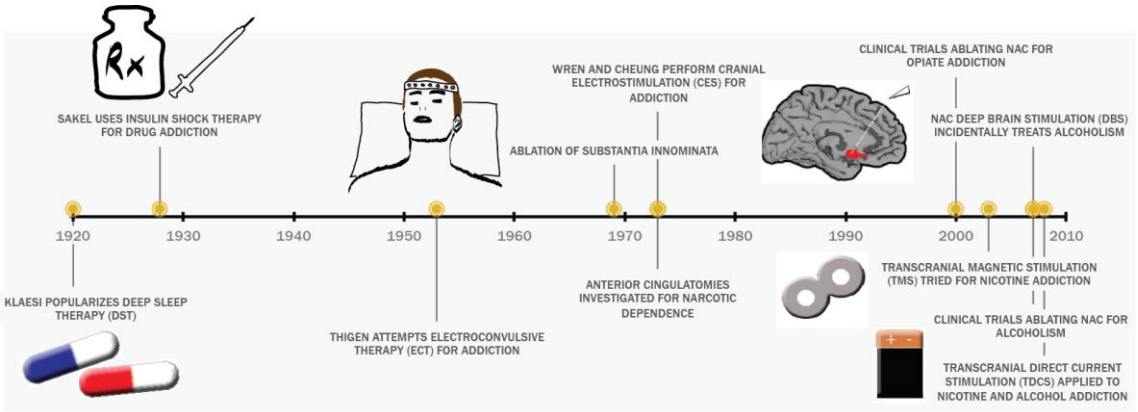

Figure 3. Historical progression of direct physiological manipulations for addiction therapy.

While some evidence supports the efficacy of ablative techniques in reducing drug addiction, these surgeries make permanent, irreversible changes to the brain. The search for a less destructive alternative has led to the use of deep brain stimulation (DBS), which uses high frequency electrical stimulation. DBS seems to have effects similar to the destruction of the tissue in the basal ganglia for movement disorders[93]. In one recent report, a patient suffering from agoraphobia and secondary depression was given DBS to bilateral NAc; while the DBS cured neither the anxiety nor the depression, it did reduce the patient's alcohol dependence[94]. The patient's alcohol consumption decreased from 10 drinks per day to 1-2 drinks per day. The authors then retrospectively examined all of their DBS studies involving the NAc as a target, and found that 3 out of 10 patients with nicotine dependence became abstinent after DBS[95]. Their fortuitous observations have prompted further investigation of DBS as a therapy for drug addiction,

including primary use of DBS for heroin[96–98] and alcohol[99]. These studies open the door for experiments seeking to treat cocaine use disorder via DBS.

While DBS is a promising therapy for drug addiction, it is in early stages of development. Researchers debate which brain regions to target, with some proponents suggesting subthalamic nucleus (STN) instead of NAc[100]. The disparity of approaches may stem from an incomplete understanding of how DBS works. While the technique is thought to induce local inhibition at the site of the electrode implant, pharmacological studies that inhibit local neuronal subtypes do not how similar effects, suggesting that the mechanism of action of DBS is not simply local neuronal inactivation[101]. Preclinical studies in rats exhibiting signs of cocaine addiction suggest that DBS to the NAc also stimulates fibers passing nearby, which may result in antidromic stimulation of other cortical brain regions[6].

At this early stage, DBS may be prohibitively expensive for drug rehabilitation. Moreover, several ethical issues like safety, insurance reimbursement uncertainty, and informed consent dilemmas may hinder DBS from ever becoming a broadly available treatment for substance use disorder[102,103].

Such considerations have fueled the search for a less invasive, more cost-effective alternatives to target the subcortical structures involved in reward. Techniques include repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). rTMS uses an alternating magnetic field to induce an electrical current that excites or inhibits neuronal activity based on the frequency of the oscillating magnetic field, with high frequency (>10 Hz) inducing excitation[104]. High frequency rTMS applied to the DLPFC has led to decreased subjective cravings for nicotine, alcohol, and cocaine in addicted patients (reviewed in refs)[104,105]. tDCS, which operates by delivering a constant low current between two electrodes on the scalp's surface, has also targeted the DLPFC and resulted in reduced alcohol[106] and nicotine[107] craving relative to sham stimulation[108]. Although these techniques demonstrate strong potential, studies involving rTMS and tDCS are in their infancies, clinical trials with more subjects are needed, and rigorous measures of reduced drug use need development. Further, the exact effects of how stimulation alters brain function connection and ultimate behavior is currently unknown. Nevertheless, non-invasive cortical stimulation may at some point provide a cost-effective therapy for cocaine use disorder.

4.4. Real time feedback using neuroimaging

Functional neuroimaging studies have identified a distributed network of brain regions involved in craving and its suppression (**Figure 4A, red**). The "craving" network increases activity in response to perceiving drug-related cues compared to neutral cues[109,110]; these same regions are implicated in normal reward processing, decision-making, and emotional responses. For example, the insula is implicated in emotional responses, and its activity correlates strongly with drug cravings[111,112], and damage to the insula appears to disrupt cravings for nicotine without changing the motivation for other behaviors[113].

The networks activated in the suppression of craving are involved in impulse control[114]. These regions include the DLPFC and VLPFC (**Figure 4A, blue**). While craving, individuals addicted to cocaine show lower activity than controls in these regions[115,116], and the level of activity correlates with self-control and performance on tasks that require inhibition of impulsive responses.

On the basis of this knowledge, our laboratory and others are exploring another experimental treatment for individuals suffering from severe crack use disorder: determining whether the activity in these brain areas can be manipulated through real-time neurofeedback using fMRI (known as rt-fMRI). While this idea dates back nearly two decades[117], the last two years have seen tremendous development of the technique[118]. In the real-time feedback approach, fast computation and efficient algorithms transform brain activity into a visual representation (e.g., a thermometer or a speedometer) which is viewed by the participant (**Figure 4B**). The aim is for individuals to downregulate neural activity that correlates with craving. To suppress their craving for cocaine, participants must activate the impulse control brain regions. The feedback they receive is in real-time and shows them the result of their effort. Ideally, the strategy will strengthen individuals' ability to inhibit their cocaine cravings.

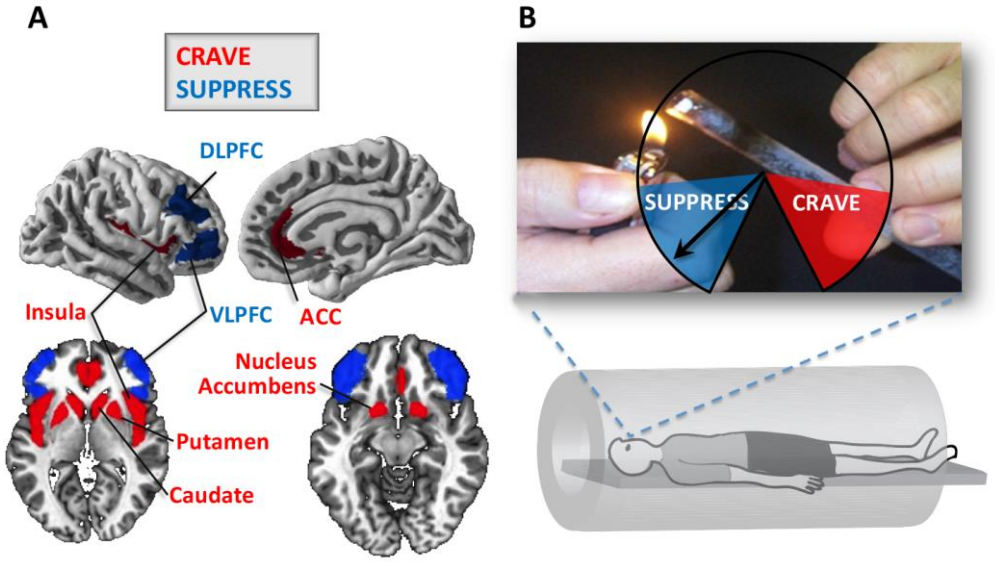

Figure 4. Real time neuroimaging as a technique to control craving developed in our lab. **A**. Regions involved in craving (red) include bilateral insula, putamen, caudate, nucleus accumbens, and anterior cingulate cortex (ACC). Regions involved in suppressing craving (blue) include dorsolateral prefrontal cortex (DLPFC) and ventrolateral prefrontal cortex (VLPFC). Not shown are areas that are implicated in both craving and suppression, such as medial orbital frontal cortex and bilateral amygdala. **B**. In ongoing studies in our laboratory, crack cocaine addicts are shown images of the drug and associated paraphernalia while in MRI. Participants are instructed to suppress their craving, and feedback representing the ratio of activities in the craving and suppression networks (panel A) is shown in the form of a meter on the screen. The end goal of this putative therapy is to strengthen cognitive control, fortifying participants with the capacity to overcome their craving when faced with enticing environmental drug cues.

While rt-fMRI feedback has been used with documented success for a variety of applications including managing pain[119], regulating emotion[120], and improving working memory[121] (see comprehensive reviews elsewhere) [122–128], few studies have assessed rtfMRI as a therapeutic tool for individuals suffering from severe substance use disorder. Preliminary data suggest that nicotine-dependent individuals can reduce context-induced cravings by voluntarily decreasing activation in ACC[129], which may substantially reduce the drive for the drug. In contrast, nicotine addicts were unable to increase activation in medial PFC[129] or indorsal medial PFC[130] when attempting to increase cognitive inhibition. These results may shed light on which brain regions are under direct cognitive control, as well as which cognitive strategies may combat drug addiction. Evidence also suggests participants can gain greater control of brain region activation after multiple neurofeedback sessions[119,131], pointing to a need for repeated therapeutic sessions.

One of the strengths of the rt-fMRI treatment is that it is individually tailored to each participant. That is, participants may discover unique strategies to succeed in increasing activity in suppression networks and decreasing activity in craving networks – for example, by exploring and assessing different cognitive strategies, such as thinking about cocaine's financial impact, emotional stress, or damage to relationships in their lives. Once participants have identified successful suppression strategies and refined their ability to suppress by engaging the corresponding networks through neurofeedback, the hope is that they can recreate those approaches after leaving therapy and returning to their day-to-day lives. Rt-fMRI feedback thus allows each participant to discover the optimal cognitive strategy to control his or her addiction.

Like all treatment strategies, rt-fMRI feedback has limitations. The early nature of the experimental treatment makes it difficult to accurately predict the number of sessions required by a person suffering from severe substance use disorder. The therapy also depends upon the addicted individual's willingness to manipulate his or her cravings, which means neurofeedback may only be promising for those actively seeking treatment. Another crucial component of neurofeedback is providing reliable control measures. This is an area of active debate[132], ranging from implementations of sham feedback, no feedback, and transfer runs. It is clear, however, that the feedback must be compared to an adequate control of some sort.

Many studies currently are developing the ideas and just trying to demonstrate if control over a brain region in the addicted population is at all achievable. But as progress is made, each study must be able to demonstrate the feedback from the brain area is actively being used and crucial to the therapy. These concerns highlight the need for a multiplicity of approaches to address different individuals' unique substance abuse problems.

5. Conclusions and Future Perspectives

We have shown how conventional pharmacotherapy-based approaches, as well as novel approaches like drug immunotherapies, brain stimulation, and real-time neurofeedback, all harness the field's current understanding of the neurobiology of addiction. The therapies show great promise, but each of these therapies follows a different approach with unique limitations: pharmacotherapies have systemic effects and are plagued by compliance issues; vaccinations fail to re-wire aberrant brain circuitry; stimulation therapies may be exceedingly costly (DBS) or impose only short-term effects (rTMS and tDCS); and rt-fMRI, also very costly, requires the individual to actively desire to learn how to suppress cravings.

We should note that some of these therapies remain in the experimental phases. Even if a therapy delivers on its potential and improve individual's lives, it may fail to scale effectively on a broader societal level. Nonetheless, each technique could serve as a new arrow for society's quiver of therapies for addicted individuals. On its own, each treatment may fall short of solving the problem of severe substance use disorders, but collectively, the multiplicity of approaches holds a promise for customizing treatment strategies for individuals, with potentially lower longterm rehabilitation expenses compared to the cost and collateral consequences of incarceration.

It is important to emphasize that viewing severe substance use disorder as an illness does not exculpate addicted individuals from responsibility for criminal actions. Instead, the goal of understanding the neurobiological basis of substance use disorders is to reduce severe drug addiction by introducing opportunities for customized rehabilitation and rational sentencing. Some countries, predominantly in the European Union, are experimenting with such approaches.

In 2001, Portugal moved away from incarceration as a solution and replaced jail time with a multilayered approach including a noncompulsory offer of therapy for those caught in possession of small amounts of drugs[133]. This reform includes people who simply use drugs as well as those who suffer from substance abuse disorders. The noncompulsory, therapy-based rehabilitation appears to have resulted in far fewer drug-related pathologies as well as drug usage rates that remain among the lowest in the EU. Perhaps most importantly, it may have contributed to a decrease in usage among the most malleable group: adolescents. From 2001 to 2006, a decrease in usage was reported among individuals 13-15 years (14.1% to 10.6%), and among 16-18 year olds (27.6% to 21.6%)[134]. Portugal's multilayered approach did not offer neurointervention therapies, yet its preliminary success with demand-reducing strategies suggests that offering therapy instead of incarceration is a step in the right direction.

The neuroscience-based interventions we explored in this article offer new inroads for other demand-reducing strategies. They reflect a deepened understanding of the interplay between addiction and the brain, which in turn has bolstered governments' willingness to explore demand-side strategies. In the United States, for instance, the National Institute on Drug Abuse has funded a five-site study of recently released, opioid-dependent parolees using pharmacotherapy-based strategies; this has so far achieved promising results[135].

We urge the United States to continue funding novel, neuroscience-based therapies for drug addiction. We also urge the U.S. criminal justice system to show a greater willingness to explore potential therapies. Rather than keep potential therapies confined to the lab, criminal justice departments should consider working more closely with neuroscientists at the cutting edge of addiction. For example, we could explore randomized controlled trials where repeat offenders or cocaine possession (without a history of violence) try a therapy in exchange for a deferred or reduced sentence. At the same time, it would speed research efforts if the justice system assisted scientists in finding suitable participants instead of leaving scientists to locate addicts on their own. We hope that increased governmental action will enable the testing of these therapies on a rand scale and thereby increase each therapy's odds of becoming established practice. Our vision is that advances in neuroscience will continue to illuminate the path ahead.

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