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Understanding that Addiction Is a Brain Disorder Offers Help and Hope

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Abstract

We refute the controversial statement that addiction is not a brain disorder. Extensive peer-reviewed studies support the underlying neurobiological and neurogenetic basis of addiction's "disease model". In the 70s and 80s, a few clinical scientists suggested that it is possible to use behavioral training to teach controlled drinking. However, this controversial model failed drastically and increased labeling and stigmatization. Additionally, it was unhelpful in the search for treatment. Instead, we assert that addiction is a neuropsychiatric disorder characterized by a recurring desire to continue taking substances despite harmful physical and mental consequences. Work from our laboratory in 1995 supported the Reward Deficiency Syndrome (RDS) concept based on a common neurogenetic mechanism (hypodopaminergia) that underlies all substance and non-substance addictions. Non-substance addictions include behaviors like pathological gambling, internet addiction, and mobile phone addiction. Certain impulsive and compulsive behaviors or the acute intake of psychoactive substances result in heightened dopaminergic activity, while the opposite, hypodopaminergia, occurs following chronic abuse. Patients with Substance Use Disorder (SUD) can have a genetic predisposition compounded by stress or other epigenetic insults that can impact recovery.

Relapse will occur post-short-term recovery if dopaminergic dysfunction remains untreated. Addiction, a brain disorder, requires treatment with DNA-directed pro-dopamine regulation and rehabilitation.

Keywords

Reward Deficiency Syndrome, Abstinence, Controlled Drinking, Neurogenetic Brain Disorder

1. Introduction

As neuroscientists working in the field of substance and non-substance addictions for at least six decades, we are concerned about the view of Mark Lewis as espoused in his book "The Biology of Desire: Why Addiction is Not a Disease" (2015) [1].

Here we refute the controversial statement that addiction is not a brain disorder. We agree with Zou *et al.* that substance addiction is a neuropsychiatric disorder characterized by a recurring desire to continue taking the drug despite physical and mental harmful consequences [2].

Undoubtedly, there are many people, as suggested by Lewis,1 who do not have a problem with substance seeking. Indeed, Gumbley, following a review of the literature, found that changes associated with the recovery-oriented approach include viewing Substance Use Disorders (SUD)s as a chronic problem that requires long-term support focusing on the management of recovery rather than acute management [3].

This disease model of addiction as chronic has resulted from an exhaustive neurobiological and neurogenetic literature involving thousands of peer-reviewed studies and treatment modalities. This invited editorial refutes the controversial statement that addiction is not a brain disorder.

2. The Reward Deficiency Syndrome Is a Model of Addiction

Reward Deficiency Syndrome is a neurogenetic and epigenetic model of addiction—that proposes hypodopaminergia (reduced dopaminergic function) is a common phenomenological and etiological mechanism of action for different addictive and related behaviors [4]. The nomenclature of addictions has changed in line with thinking about addictions to include non-substance behaviors that can also be classified as addictions [5]. Initially classified as process addictions, non-substance behavioral addictions, such as pathological gambling, internet addiction, and mobile phone addiction, involve (hypodopaminergia) a neurogenetic mechanism shared with substance addictions [4]. The observations of Kotyuk *et al.* [6] led the authors to assert that there are large areas of commonality between the occurrence of these substance addictions and addictive behaviors. Kotyuk *et al.* found associations between 1) smoking and "exercising, eating dis-

orders, gambling and addictive internet use"; 2) alcohol consumption and "gambling, and eating disorders, problematic Internet use, and online gaming", and; 3) cannabis use and 'gambling and problematic online gaming [6]. These data lend support to the Reward Deficiency Syndrome concept [4].

3. Alcoholics Anonymous and Abstinence

Indeed, it is fair to suggest that, unlike other chronic diseases like diabetes, the novel spiritual intervention and fellowship provided by the 12-step self-help programs in addiction/dependence recovery is beneficial and works on a neurobiological and neurogenetic basis [7].

Kelly *et al.* [8] evaluated Alcoholics Anonymous (AA) and other Twelve-Step Facilitation (TSF) interventions using the Cochrane Central Register of Controlled Trials to determine abstinence, reduced drinking intensity, reduced alcohol-related consequences, alcohol addiction severity, and healthcare cost offsets. They found that rates of continuous abstinence at 12, 24, and 36 months were improved compared to with other interventions, such as motivational enhancement therapy (MET) or cognitive behavioral therapy (CBT), TSF treatment variants, or no treatment (risk ratio (RR) 1.21, 95% confidence interval (CI) 1.03 to 1.42; 2 studies, n = 1936 with high-certainty evidence). They also found that regarding the longest period of abstinence, drinking intensity, alcohol-related consequences, alcohol addiction severity, and cost-effectiveness, AA performs as well as other clinical interventions [8].

However, we propose that better outcomes may occur if the addiction treatment arena considers combining Genetic Addiction Risk Severity (GARS) testing and pro-dopamine regulation with precision KB220 variants [9]-[22] to treat reward deficiency behaviors (addiction/dependence). This therapeutic combination is "Precision Behavioral Management", the restoration of neurotransmitter deficits with nutraceuticals [23]. The exhaustive literature involving the neurobiology of drug and non-drug addictive behaviors includes 51,890 papers listed in PubMed in the arena of behavioral genetics, providing a basis for the disease model of addiction [24] [25].

4. The Neurobiological and Neurogenetic Foundation of Addiction—Indicates That Addiction Is a Brain Disorder

Our overall question is what exact science can Lewis [1], Peel [26], and others [27] make to support arguments against this large body of data indicating the neurobiological and neurogenetic underpinnings of RDS that include all addictive behaviors? Despite sobering disconfirmations, advocates of controlled drinking continue to promote non-abstinent treatment goals and procedures for alcoholics. Claims by Stanton Peele that favor controlled drinking against "the disease model" have been mainly based on inadequate scholarship, misrepresentations of the literature, inappropriate comparisons, and generalizations [28].

While it is true that some people carry genetic antecedents that set them up

for these unwanted behaviors, not everyone carries these risk alleles. Blum *et al.* [28] pointed out that neuroimaging studies indicate that neurobiological recovery can take years. Like a "double-edged sword", SUD has a biological bi-directional (bio-directional) effect on the brain reward circuitry. It is reasonable to suggest that the acute intake of psychoactive drugs results in heightened dopaminergic activity, while the opposite, hypodopaminergia, occurs following chronic abuse [28]. Patients with SUD can have a genetic predisposition [29], compounded by stress [30], and neurotoxically induced [31], epigenetic insults that impact recovery due to protracted abstinence [32]. Relapse will usually occur if post-short-term recovery hypodopaminergia is not treated with attempts at epigenetic manipulation of compromised brain neurochemistry using pro-dopamine regulation [33].

5. Viewing Addiction as a Brain Disorder Calls for Better Management

It is well-known that the Federal Drug Authority (FDA) has approved medications for the treatment of Alcoholism, Nicotine dependence, and opioid dependence, although as yet nothing for psychostimulants and cannabis. Finding treatment strategies that focus on the well-known, highly characterized biochemical pathways that regulate the DA systems involved in mediating rewarding experiences is challenging. As mentioned earlier, to curtail psychoactive drug abuse and dependence, in the United States (US), FDA-approved pharmaceutical agents are known as Medication-Assisted Treatment (MAT) (see **Table 1**).

While these agents have helped many patients, they have not entirely prevented cravings and relapse. This fact is highlighted by drug urine testing data from the sophisticated Comprehensive Analysis of Reported Drugs (CARD) [34]. The study revealed a lack of "abstinence" from psychoactive drug use in inpatient and outpatient treatment settings.

The US FDA-approved pharmaceuticals either reduce craving or suppress the pleasurable effects of drugs. Anti-reward mechanisms seem to predominate the listing of existing FDA-approved drugs to treat all types of addictive behaviors (**Table 1**). Briefly, it is well-known that narcotic antagonists (in any form) attenuate euphoria via opioid receptor blockade. Buprenorphine/naloxone does not affect the cingulate gyrus or prevent relapse and, when used chronically, has significant anti-reward characteristics that include a flat emotional effect due to lack of dopamine homeostasis. Bupropion may block DA re-uptake but does not increase extracellular dopamine in man. Acamprosate calcium regulates chemically induced dopamine release in the Nucleus Accumbens (NAc). This reduced activation of the dopaminergic system and the failure to release adequate mesolimbic dopamine at the NAc site over the long term can result in depression and potential suicide ideation. N-methyl-D-aspartate (NMDA) receptor antagonists inhibit glutaminergic drive in the Ventral Tegmental Area (VTA) and reduce dopamine release at NAc. The neurological science of reward neurotransmitter

Table 1. United states Federal Drug Authority (FDA) approved pharmaceutical agents.

Drug	Company	Purpose	Date
Zubsolv®. Zubsolv® (buprenorphine and naloxone)	Orexo AB	treatment of opioid dependence	July 2013
Vivitrol® extended-release naltrexone	Alkermes	prevention of relapse to opioid dependence	October 2010
Vivitrol® Naltrexone	Alkermes	treatment of alcohol dependence	April 2006
CHANTIX® (varenicline),	Pfizer	treatment of nicotine addiction	May 2006
acamprosate calcium	Campral	treatment of alcoholism	2004
Suboxone® (buprenorphine/naloxone) Subutex® (buprenorphine)	Reckitt Benckiser	treatment of opiate dependence	October 2002
NicoDerm CQ ® Nicorette®	Glaxo-SmithKline	for smoking cessation	
Naltrexone Hydrochloride oral tablets	Dupont	tablet form (50 mg taken daily) for the treatment of alcoholism	1994
Antabuse® (disulfiram)	Odyssey Pharmaceuticals	Treatment of alcohol dependence	1951

dysfunction related to RDS implicates reduced dopaminergic activity and may be understood as a trigger to self-medication or process non-substance addictions [35]. While based on epigenetic insults to reward gene expression, it is known that certain developmental events may cause hyperdopaminergia in teens, and this dopamine abundance provides for a more intense quanta release following each action potential [35]. Specifically, Renard *et al.* [36] found adolescent THC exposure induced behavioral abnormalities mirroring positive and negative schizophrenia-related endophenotypes and a state of neuronal hyperactivity in the mesocorticolimbic dopamine (DA) pathway. Renard *et al.* also found profound alterations in several prefrontal cortical molecular pathways consistent with sub-cortical dopaminergic dysregulation [36].

Nevertheless, genetic data utilizing a Genetic Addiction Risk Severity (GARS) test shows the opposite in many teenagers [37] [38]. As a scientific community, we must at least provide alternative scientifically based objective explanations. We agree that many people do not have the chronic disease of addiction (genetic trait) and can easily succeed at controlling their substance intake. However, un-

fortunately, at least in America, many unsuspecting individuals carry reward gene risk polymorphism, leading to, for example, low dopamine release at the reward site of the brain [39]. This reduced resting-state functional connectivity (rsFC) at the mesolimbic and orbital frontal cortex (*i.e.*, anterior cingulate gyrus) sets people up for addiction-related seeking behaviors [40] [41]. Understanding the potential importance of differential rsFC, Febo *et al.* [42] found that the pro-dopamine regulator KB220Z significantly enhances, above placebo, functional connectivity between reward and cognitive brain areas in the rat. Specifically, these include the nucleus accumbens, anterior cingulate gyrus, anterior thalamic nuclei, hippocampus, prelimbic and infralimbic loci. Significant functional connectivity, brain connectivity volume recruitment (potentially neuroplasticity), and dopaminergic functionality increased across the brain reward circuitry. Moreover, increases in functional connectivity were specific to these regions and were not distributed broadly across the brain. While these initial findings were observed in drug naïve rodents, this robust yet selective response implies clinical relevance for dependent subjects at risk for relapse, who show reductions in functional connectivity after protracted withdrawal. Other work from Blum's group reveals similar clinical benefits involving enhanced rsFC in heroin-dependent subjects [43].

6. Summary

Finally, taking away the drug, for example, does not stop the inborn error or maybe evolutionary adaptive altered dopamine and other brain neurotransmitter dysfunction (one's genetic trait) [44]. The take-home message is to develop tools like gene therapy [45] that bring about balance or homeostasis even in the face of indulgence. For some people, RDS addictive behaviors, substance, and non-substance may occur without any DNA risk polymorphic alleles, potentially induced by epigenetic insults. They may have an easier time recovering through remediation. However, for those carrying reward gene risk polymorphisms as displayed by the GARS test, this is not the case, and for them, addiction must be considered a chronic brain disorder.

Moreover, we are cognizant that others have argued for free choice and not determinism by genetics or epigenetic insults, as discussed by Heyman [46]. However, we are not entirely in agreement with this theory. A very high percentage of people that stop using substances early on in life due to societal pressures are known to relapse after 50 years of age, possibly due to reduced D2 receptors [47]. Finally, in support of our insistence that arguing against the "disease concept of addiction" is harmful, the most recent paper by Heilig *et al.* [48] stated, "We acknowledge that some of these criticisms [against the disease model of addiction] have merit but assert that the foundational premise that addiction has a neurobiological basis is fundamentally sound. We also emphasize that denying that addiction is a brain disease is a harmful standpoint since it contributes to reducing access to healthcare and treatment, the consequences of which are

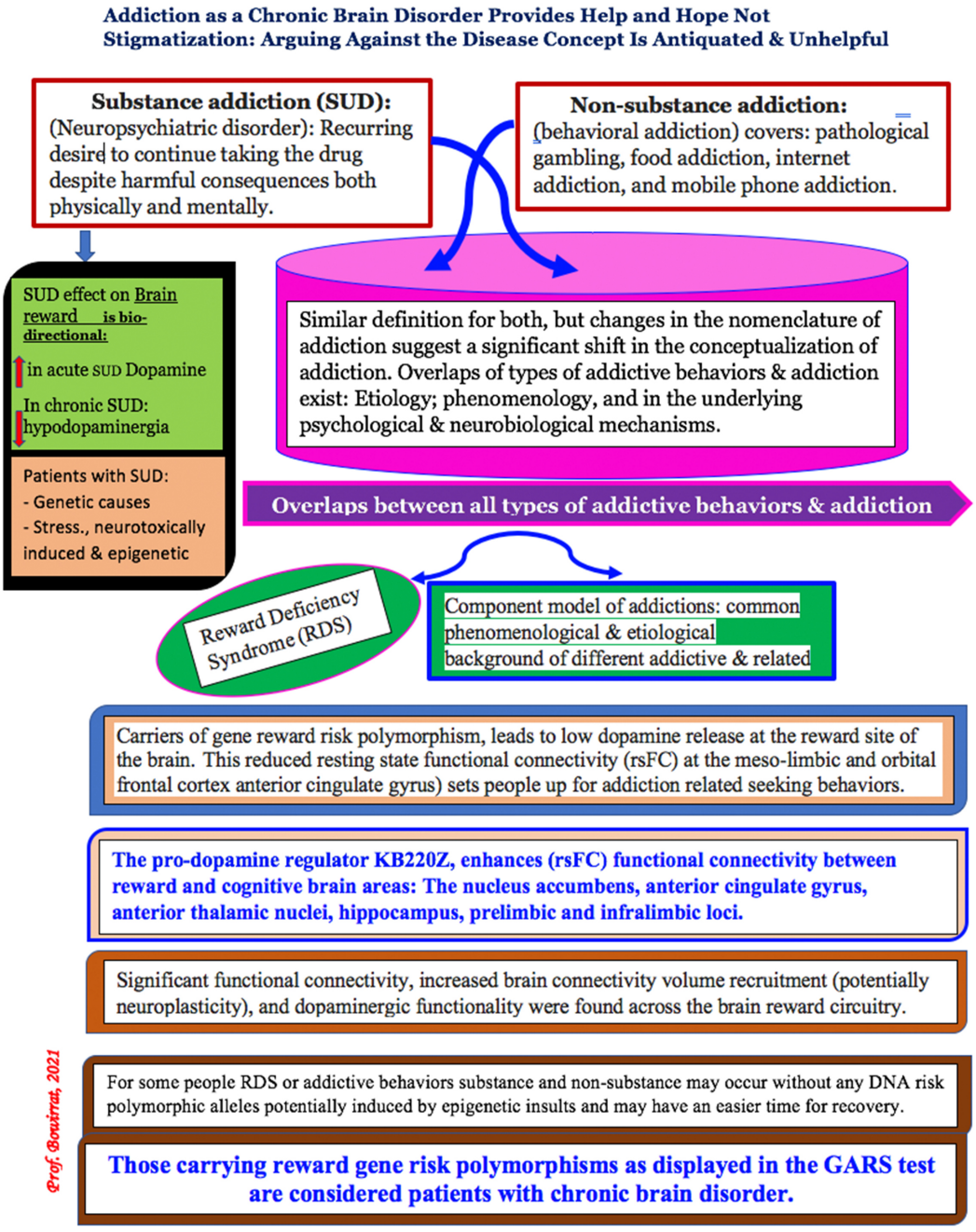

Figure 1. Is a schematic of the reward deficiency syndrome disease model.

catastrophic" p. 1 [48].

De-stigmatization of smoking behavior resulted in increased smoking rates across the globe. However, following the stigmatizing knowledge that tobacco cigarette smoking is addictive and harmful, smoking rates decreased dramatically [49].

7. Conclusion

Acute intake of psychoactive drugs results in heightened dopaminergic activity,

while the opposite, hypodopaminergia, occurs following chronic abuse. Patients with SUD can have a genetic predisposition, compounded by stress and epigenetic insults that impact recovery. Post-short-term recovery, relapse will occur if dopaminergic dysfunction is not treated using some manner of DNA-directed pro-dopamine regulation. We agree that for some people, RDS substance and non-substance addictive behaviors may occur without any DNA risk polymorphic alleles. These individuals may have an easier time in recovery from SUD induced by epigenetic insults. However, those carrying reward gene risk polymorphisms, as displayed in the GARS test; require treatment for a chronic brain disorder. Finally, we conclude that the disease model of addiction (**Figure 1**) provides better access to medical treatment and allows opportunities to manage relapses more effectively.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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