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Disease or Developmental Disorder: Competing Perspectives on the Neuroscience of Addiction

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Abstract Lewis' neurodevelopmental model provides a plausible alternative to the brain disease model of addiction (BDMA) that is a dominant perspective in the USA. We disagree with Lewis' claim that the BDMA is unchallenged within the addiction field but we agree that it provides unduly pessimistic prospects of recovery. We question the strength of evidence for the BDMA provided by animal models and human neuroimaging studies. We endorse Lewis' framing of addiction as a developmental process underpinned by reversible forms of neuroplasticity. His view is consistent with epidemiological evidence of addicted individuals 'maturing out' and recovering from addiction. We do however hold some reservations about Lewis' model. We do not think that his analysis of the neurobiological evidence is clearly different from that of the BDMA or that his neurodevelopmental model provides a more rigorous interpretation of the evidence than the BDMA. We believe that our understanding of the neurobiology of drug use is too immature to warrant the major role given to it in the BDMA. Our social research finds very mixed support for the BDMA among addicted people and health professionals in Australia. Lewis' account of addiction requires similar empirical evaluation of its real-world implications.

Keywords Addiction · Brain disease · Neuroplasticity · Neurodevelopment · Learning

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Introduction

There have been numerous critiques of the brain disease model of addiction (BDMA) in recent years (e.g. [1–7]). Marc Lewis' critique is unusual in being from the perspective of a neurobiological researcher rather than that of a social scientist or clinician [8]. In what follows we outline the key criticisms that Lewis makes of the BDMA, indicate where we agree and disagree with his criticisms, and critically analyse his alternative developmental interpretation of neurobiological research on addiction.

Is the BDMA Unchallenged within the Addictions Field?

We do not accept Lewis' claim that the BDMA is "nearly unchallenged" by medical, psychiatric and

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research communities, research funding bodies and professional organisations. We agree that the BDMA does dominate official discourse in the USA, as promulgated by the National Institute on Drug Abuse (NIDA), National Institute on Alcohol Abuse and Alcoholism (NIAAA), American Society for Addiction Medicine (ASAM), and the American Medical Association (AMA). However, the BDMA has not gone unchallenged in the USA [3, 6, 9, 10] and it enjoys much less support from international addiction researchers, 94 of whom signed a letter to the editor of *Nature* dissenting from an editorial promoting the BDMA [11]. Our interviews with addiction scientists and clinicians in Australia have not found universal support for the BDMA.

We agree with Lewis that political factors have played a major role in the apparent dominance of the BDMA in the USA. The primary political factor has been the funding and institutional clout of the leading institutional advocates of the BDMA in the USA, Nora Volkow and George Koob, the Directors of NIDA and NIAAA, respectively. These NIH Institutes fund most of the research on alcohol and other drugs in the USA. Applications that support the BDMA are more likely to be funded given the NIH's bias towards funding neuroscience and biological research on addiction [6, 12]. As Lewis argues, NIAAA and NIDA funding decisions minimise the volume and impact of research findings that contradict the BDMA.

These Institutes have also conducted well-funded high public profile education and advocacy efforts in favour of the BDMA over the past 20 years. The Directors have published pieces advocating for the BDMA in the *Journal of the American Medical Association* [13] and *New England Journal of Medicine* [14]. They have also sponsored special issues in leading science journals like *Nature* [15] to promote their views as the consensus in the field. They have been very reluctant to engage in debate with their critics, preferring to simply reiterate their views when challenged [16, 17].

The chronicity of addiction entailed by the BDMA is also congenial to the private rehabilitation sector in the USA, which provides expensive, long-term residential treatment for addicted persons who can afford it [18]. A chronic model of addiction provides a strong rationale for intensive residential services, in the absence of evidence of long-term clinical efficacy. The pharmaceutical industry has been less supportive of the BDMA; indeed it has been criticised for its lack of interest in developing new drugs to assist addicted persons to remain abstinent [18, 19].

Lewis' Account of the BDMA

According to NIDA, addiction is: "a chronic relapsing brain disease" characterised by compulsive drug seeking and use, despite harmful consequences [20, 21]. The key evidence presented for this assertion is that chronic drug use produces changes in dopamine (DA) activity and transmission over time, affecting motivation, goal-directed behaviour, attention and memory. It is also claimed that DA rewires the brain in the striatum, amygdala, hippocampus and prefrontal cortex (PFC), "hijacking" the brain [21, 22].

Most of the evidence for the BDMA comes from animal studies, which receive some support from neuroimaging studies, that report differences in brain structure and function between addicted and non-addicted individuals that are assumed to be caused by chronic drug use. According to the BDMA, chronic drug use produces a progressive shift in voluntary control of behaviour away from the PFC and ventral striatum towards compulsive behaviour controlled by the dorsal striatum. The claim is that chronic drug use and addiction change the way the brain works much like diabetes changes the functioning of the pancreas. These changes in brain function are what make addiction a brain disease.

Lewis identifies a number of advantages of the BDMA. He says that it helps to understand why it can be difficult for addicted individuals to achieve abstinence by simple act of will; it invokes neurogenetic vulnerabilities to explain individual differences in addiction liability and response to environmental factors; it promises to provide a basis for developing new drugs to reduce withdrawal and craving; and it counters the common perception that addicted individuals are morally deficient and self-indulgent.

Lewis' Critique of the BDMA

Lewis' criticisms of the BDMA echo those of others [3, 6, 7, 23]. He stresses, for example, that the BDMA clashes with the experiences of many former 'addicts' who do not accept that they were sick and have been cured. The BDMA ignores the fact that most people who develop an addiction do recover, often without any formal treatment, and with very few using the pharmacological treatments rationalised by the BDMA.

We strongly agree with Lewis that the BDMA provides an unduly pessimistic view of the prospects of recovery from addiction. We have noted before [6] that

there are no analogues of recovery in the animal models of addiction described by Koob and Moal [24]. The BDMA gives rise to a pessimistic outlook because it mistakenly equates all forms of addiction with the severe cases of relapsing addiction seen in specialist addiction treatment centres (from which the research subjects in neuroimaging studies are usually recruited). Proponents of the BDMA misleadingly cite epidemiological data on the prevalence of the common forms of addiction in community surveys as if the addiction of individuals described in those surveys was the same as that in the minority of severely addicted individuals whom neuroimaging researchers study [6]. They fail to note that their pessimistic view of addiction chronicity is at odds with the same epidemiological evidence that they cite in showing very high rates of recovery from addiction in adulthood [25] in the absence of treatment, as a result of positive changes in life circumstances [3].

We are less impressed than Lewis by the research evidence offered in support of the BDMA. The identification of the neural pathways on which drugs of dependence act is heavily reliant on animal models of the effects of chronic drug exposure on brain function; these models are of doubtful relevance to addicted humans [9, 26, 27]. Human neuroimaging studies typically compare small samples of severely addicted persons with equally small samples of non-drug using controls. These studies have low statistical power and report too many positive findings for their estimated size of effect and typical sample size [28]. A recent study has also called into question the validity of the statistical methods used in some 40,000 fMRI research studies to identify areas of brain activation. It suggests that these methods result in false-positive rates of up to 70% in identifying "activated" brain regions [29]. The case-control design also means that neuroimaging studies are unable to determine to what extent the differences found between the brains of addicted individuals and controls are causes or consequences of chronic drug use (or more likely some combination of the two). For a more detailed discussion of our points, see [6].

Lewis' Alternative Interpretation – Entrenched Habit rather than Disease

Lewis proposes that patterns of addictive drug use should be thought of as deeply entrenched habits rather than as *diseases* [30]. He argues that there is no clear dividing line in personal experience or brain function between an addiction and the repeated pursuit of other rewarding activities. If dopamine release makes addiction a disease then, he suggests, all goal-directed behaviours pursued to excess can be classified as diseases. He argues, for example, that romantic love would qualify as a disease on this definition because it involves dopamine release and it can become compulsive and dysfunctional when the 'sufferer' becomes preoccupied with spending time with the object of their affection, with little regard for the long term consequences of their behaviour or its effects on their ability to perform other roles [8].

We are sympathetic to the alternative explanations that Lewis offers for the cortical changes in animal models of addiction and neuroimaging studies of persons with severe addictions. According to the BDMA, these structural cortical changes comprise the anatomical basis for the brain disease model, especially the reduced connections between the prefrontal cortex and striatum that are reflected in a loss of grey matter in persons with long term addiction. The BDMA implies that these changes are either irreversible or, at least, very hard to reverse.

Lewis interprets these changes as evidence of neuroplasticity, that is, the ability for neural connectivity to adapt in response to changes to behaviour or the environment. He is accordingly more optimistic about the possibility that sustained abstinence can reverse these changes. Indeed, he cites neuroimaging studies in which persons with many forms of severe addiction appear to show a full recovery of cortical connections between the frontal and striatal areas after prolonged abstinence. His interpretation of the neurobiological evidence fits better with the epidemiological evidence on the recovery of the majority of persons with the more common, less severe forms of addiction. It also suggests that we can successfully use treatment approaches (in addition to pharmacological ones) that enhance the prospect of recovery (e.g., lifestyle interventions such as exercise).

Lewis' Developmental Approach to Addiction

The major challenge for critics of the BDMA is in providing a more plausible model that does justice to our understanding of the effects that addictive drugs have on the brain while taking into account evidence that behavioural, social and economic factors also affect

drug use and addiction. As Harold Kalant has argued, this evidential synthesis has barely begun because neuroscientists see their work as ontologically more fundamental than that of other disciplines [9, 27]. The major challenges in producing a convincing synthesis makes it easier to settle for the simplified, NIDA version of the BDMA.

According to Lewis, addiction is a form of learning that is underpinned by dopamine signalling. Addictive drug use accelerates learning and makes the learned behaviour more deeply ingrained because drugs are potent activators of the brain's dopaminergic reward system. This form of learning, he suggests, becomes stronger and more invariant over time through a confluence of social, cultural, societal and economic factors that act in concert with these neurobiological adaptations.

Lewis hypothesizes that three mechanisms increase our attraction to the rewarding effects of addictive drugs and thereby entrench addictive patterns of drug use, none of which makes addiction a brain disease in his view. The first is the phenomenon of delay discounting in which humans (and other animals) give a higher priority to immediate over delayed rewards. This biases our attention towards the short term rewarding effects of drugs (and other activities such as the consumption of high calorie foods) that produce greater than normal dopamine release.

The second mechanism is the motivational amplification of the behaviour that precedes drug use. According to Lewis, the frequent repetition of a behaviour that is boosted by strong motivation is one of the most effective drivers of synaptic shaping.

The third mechanism is that the rewarding effects of many drugs are short lived and their rapid dissipation whets the appetite for more. The rewarding effects of drugs disappear quickly, leaving frustration, loss and depression in their wake, prompting more drug use. These dysphoric feelings may be amplified by a sense of shame when a person sees him or herself, and is seen by others, as selfishly using drugs. These painful feelings may be relieved by more drug use, producing a vicious cycle. The fact that using drugs also relieves the symptoms of drug withdrawal increases the difficulty that many drug users experience in trying to stop using drugs. Lewis also suggests that the drug-induced relief of anxiety and depression in persons who are prone to develop these disorders forms synaptic configurations within which addictive behaviour fits well [30].

On Lewis' analysis, then, addiction is "motivated repetition that gives rise to deep learning" [30]. Addictive patterns of drug use grow more quickly and become more deeply entrenched than other, less compelling habits, because the intensely positive drug effects, and avoidance of dysphoric states, motivate drug users to repeat the experience. The emotional turmoil of childhood and adolescence can initiate patterns of personality development that "anchor" the person in a search for addictive drugs as sources of relief and comfort [30].

Critique of Lewis' Neurodevelopmental Model of Addiction

We prefer Lewis' neurodevelopmental approach to that of the BDMA because it recognises that addiction emerges during the process of human development. For example, addiction is more likely to develop in adolescence in young men who had conduct disorders during primary and secondary school, in young women and men who have anxiety and depressive disorders, and in psychologically vulnerable individuals who have experienced emotional or physical trauma during childhood [3].

A developmental approach is also more consistent with the most common outcome of addiction, namely, that young adults "mature out" of addictive drug use as they enter the workforce and develop positive personal relationships. This approach encourages the search for social strategies to assist young people to disengage from drug use. For example, Lewis' view encourages the use of social groups to support skill development and foster socially positive outcomes rather than focusing on pharmacological treatments to modify neurotransmitter systems in the brains of the minority of persons who become severely addicted.

Most significantly, Lewis' emphasis on addiction as a reversible, neuroplastic developmental process provides a more optimistic view of the prospects of recovery than the BDMA. This is an important difference between Lewis' account and that of the BDMA because the latter emphasises the persistence of drug-induced changes in the brain and the need for medical interventions to overcome addiction. Consequently, the BDMA view, which is characterised by persistent brain changes, may have detrimental effects on drug addicted individuals' hope for the future and on their motivations for recovery. It may also increase stigmatisation of people with drug problems.

We nonetheless have a number of reservations about Lewis' neurodevelopmental model. First, it is not clear how distinct Lewis' model is from the BDMA as it shares many similarities with the interpretations of neurobiological studies provided by supporters of the BDMA. For example, Steve Hyman, former Director of the National Institute of Mental Health, and prominent addiction researcher [31, 32], also emphasises the role of overlearning in the development of addiction. He argues that learning in addiction is underpinned by adaptations at the molecular and neural levels that are driven by dopamine release produced by chronic drug use. The role of negative affect in maintaining addiction is also consistent with George Koob's allostatic model of addiction [33, 34]. According to Koob, adaptations to the stress system (produced by interactions between dopamine and the hypothalamopituitary axis) motivate addictive drug use and produce relapse when the addicted individual ceases drug use. Koob's account also emphasises that these changes are the result of plastic neural adaptations [34, 35].

Second, we think that Lewis' model shares a major weakness with the BDMA, namely, both rely on the use of metaphors to bridge the explanatory gaps between neurobiological evidence (from animal studies and human neuroimaging studies) and the addictive patterns of behaviour that the neuroscience models are supposed to explain. Thus in Lewis' model the "hijacking" of the brain is replaced by metaphors about drugs "leaving footprints in the brain" and "entrenching and anchoring" behaviour in the brain. These metaphors simply re-describe the addictive behaviour that the neurobiology is supposed to explain. In our view, both types of metaphors exhibit features of the *mereological fallacy* described by Bennett and Hacker (after Aristotle) [36], namely, they ascribe the behaviour of addicted persons to patterns of activity in brain regions and assume that this somehow explains the addictive behaviour. The persistent use of addictive drugs clearly produces important changes to the neural activity within key regions of the brain. However, a large explanatory gap remains between these neural changes and the behaviour and intent of people who use addictive drugs. It is beyond the scope of this article to determine whether such an explanatory gap will be bridged in the future, although the complex role of psychological and social factors in driving drug use leave us doubtful.

Third, we think that our understanding of the neurobiology of drug use and addiction is too immature to support the BDMA. Neuroscience has provided suggestive evidence that the chronic use of drugs changes brain functioning in ways that make it more difficult for severely addicted persons to desist from using drugs in the absence of substantial social and pharmacological support to remain abstinent. The role of these neurobiological changes in brain function seems most plausible in explaining the cognitive and motivational impairments often seen during drug intoxication and drug withdrawal. Our improved understanding of these processes has helped to alleviate the symptoms of drug withdrawal but we believe that a preoccupation with the neurobiology of drug effects focuses too much attention on the use of pharmacotherapies to reverse the neurobiological changes that advocates of the BDMA claim are central to addiction.

The Social Impacts of Neurocentric Models of Addiction

The focus on neurobiology in both the BDMA and Lewis' model distracts attention away from the important roles played by interpersonal, social and economic factors in addiction. These factors need to be addressed in treatment if we are to assist addicted persons to live more productive and happier lives; the best ways of preventing relapses to drug use [37]. Although Lewis makes brief mention of social factors implicated in addiction, such factors do not play a central part in his alternative model. Additionally, whilst social factors are given lip service by proponents of the BDMA [17, 38], their importance is not reflected in either the funding of NIDA and NIAAA or the policy solutions that they offer.

In 1997, Alan Leshner confidently predicted that the BDMA would deliver more effective and targeted pharmacological treatments that would substantially improve addiction treatment outcomes. We do not think that the BDMA has delivered on these promises [6]. The main drug treatments derived from neuroscience research are modestly effective and the most efficacious of these (methadone maintenance) preceded the proclamation of the BDMA [6, 7, 27]. These drugs represent a very small return on a large and sustained research investment in neurobiological research and drug development. The failures of a long list of "promising" new drugs and drug vaccines to move beyond clinical trials have been quickly forgotten as attention has shifted to the next great hope.

Leshner also claimed that a wider social acceptance of the BDMA would reduce the stigma of addiction, discrimination against people with an addiction, and the use of incarceration as a first line treatment of addiction. It would do so, he suggested, by convincing a sceptical public that addiction is a real (meaning neurobiologically-based) disorder. There is very little evidence that the BDMA has reduced stigma or discrimination. A growing body of social research on public attitudes and understanding suggests that portraying mental and substance use disorders as brain diseases may entrench rather than reduce negative public attitudes towards persons with these disorders [39]. Indeed, a disease model may reinforce public fears of addicted persons by suggesting that their behaviour is an uncontrollable consequence of permanent changes in their brains produced by their drug use [40].

Our social research in Australia has found very mixed support for the BDMA among addicted people and health professionals. In our interviews with 44 people in treatment for drug and alcohol addiction, essentialist biological explanations of addiction were rarely offered by participants [41]. They favoured multi-dimensional accounts that emphasised the role of social relationships and environmental factors in the origins of their addictions. Some narratives described the experience of addiction as a form of pleasure-seeking rather than as a 'sickness' or disease. Participants were ambivalent about the idea of addiction as a (brain) disease because many saw this as a synonym for 'brain damage' and understood the BDMA to imply that addiction was incurable. Unsurprisingly, many believed that the brain disease label was very stigmatising.

Additionally, our research also found that most Australian addiction treatment providers did not wholeheartedly support the BDMA [42, 43]. Whilst the BDMA was seen as potentially increasing treatment-seeking because pharmacotherapy may be viewed more favourably, treatment providers feared that a focus on medical interventions would discount the role of social and environmental factors in addiction and recovery. These clinicians identified both positive and negative clinical impacts for addicted individuals if they came to see addiction as a brain disease. On the positive side, the BDMA may increase addicted persons' insight about the reasons for their drug use and reduce their sense of guilt. In contrast, it may increase feelings of helplessness and fatalism, undermining people's ability to change.

Lewis' model is more optimistic about the prospects of recovery and avoids the loaded term 'brain disease' but it is not clear what impact his neurobiological developmental model may have on stigma, self-efficacy or addicted individuals' self-understanding. We conjecture that many of the positive and negative implications raised about neurobiological understandings of addiction would also apply to Lewis' neurodevelopmental model. Most notably, Lewis' model still privileges neurobiological explanations of addiction in ways that may not integrate with the phenomenological experience of different people affected by addiction. Further empirical research is needed on the real-world impact of Lewis' model.

Conclusions

Lewis' assertion that the BDMA has been widely unchallenged within the addictions field has been overstated. The BDMA is primarily a North American view that owes its promotion to the leaders of the major US research funding bodies. Furthermore, it is nowhere near as widely endorsed among researchers and clinicians outside the USA and dissident views are expressed by leading US clinicians and researchers.

Second, the neurobiological evidence base for the BDMA is weaker than its advocates acknowledge. The BDMA is heavily reliant on animal models and small sample case-control neuroimaging studies with highly selected samples of severely addicted persons. We argue it is premature for advocates of a BDMA to insist upon the pre-eminence of their neurobiological accounts of addiction.

Lewis' developmental approach is more consonant with the research evidence from epidemiology, social science and economics than the BDMA of the NIH. His model more reasonably frames addiction as a disorder that develops over time, and from which most affected individuals can recover, often without formal treatment.

Lewis' model nonetheless shares some of the weaknesses of the BDMA. He also relies on animal models and evidence based on weak neuroimaging research designs. Lewis' neurobiological explanations of addiction also attempt to smuggle descriptions of the behaviour of addicted individuals into his descriptions of neuroimaging studies. We also contend that Lewis' model underplays the role that social and interpersonal factors play in the origins of and recovery from addiction.

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