Crisis, what crisis? Addiction neuroscience and the challenges of translation [version 1; peer review: 2 approved with reservations, 1 not approved]

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Abstract
In this article we interrogate the claim that there is an opioid crisis: a dramatic rise in drug overdose fatalities in the United States over the past two decades that is also spreading to other countries. The usual argument is that this crisis is largely explained by errant prescription practices leading to an oversupply of opioids, leading to addiction, premature mortality and drug overdose deaths, both among those prescribed opioids for pain relief, and those obtaining them on the illegal market. We argue, that this view is highly problematic and that it is likely to entrench deeper problems with how substance addiction has been perceived and known. In this article, we develop an alternative picture of the addiction crisis based on four years of research and collaboration with addiction neuroscientists. Drug overdose deaths, we claim, are symptoms of what we term the ‘structural distribution of social despair.’ We argue that this is compounded by a translation crisis at the heart of addiction neuroscience. For all its dominance, the ‘dopamine hypothesis’ of addiction that shaped understandings for some three decades, has still not produced a single effective treatment. However, this translation crisis also represents an opportunity for ‘the memory turn’ in addiction neuroscience as it seeks to translate its emerging conception of addiction as a problem of memory into effective forms of treatment. We conclude by arguing that, for the ‘memory turn’ to underpin effective interventions into ‘the opioid crisis’, a new relation between neuroscientists and social scientists of addiction is needed, one that proceeds from the lived experience of human beings.

Keywords
Drug addiction, opioid crisis, translation, addiction neuroscience, the memory turn, dopamine theory, critical friendship
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Introduction: addiction neuroscience and the opioid crisis

Drug addiction is a disorder of long-term memory

Eric Kandel, The Disordered Mind (2018)

In this article we review the claim that there is an addiction crisis and argue that the crisis represents both a challenge and an opportunity for addiction neuroscience, as it seeks to translate its emerging conception of addiction as a problem of memory into effective forms of treatment. We argue that this requires a neurosocial approach inspired by social medicine; a new relation of 'critical friendship, between neuroscientists and social scientists of addiction.

The crisis concerns the much-discussed rapid rises in drug overdose fatalities in the United States, which are fuelled by an opioid epidemic. This poses fundamental questions of knowledge and translational research that are by no means specific to the United States, or even addiction. This crisis is, fundamentally, one of translation. Most medical and psychiatric research on addiction since the 1970s has been informed by a neuroscientific theory of addiction as excessive pleasure seeking that is yet to produce a single effective treatment. We argue that this concept of addiction has not delivered on its promises, in large part because it does not accord with the human experience of drug dependence or addiction. Further, much addiction neuroscience has depended on neurochemical models and pharmacological interventions that are isolated from social conditions of distress that so often condition lives marked by addiction. The translational crisis in addiction neuroscience thus has deeper epistemological roots in how human problems are perceived and known in our “neurobiological age” (Rose, 2013).

Despite the emergence of a science that claims addiction is not a matter of will or personality but has a biological basis in the brain, and despite decades of research into this neurobiological basis of substance addiction, we do not seem to be able to convert this knowledge into treatment interventions. Thus, proposals to tackle the opioid crisis are dishearteningly familiar. Reduce prescriptions of opioid based pain killers for pain so that they do not leak into the illegal market. Convert those who have become opioid users to alleviate chronic pain to non-pharmacological means of pain control - CBT, mindfulness, acupuncture. Try to mitigate the dangers of illegal use by harm reduction, moving those who have become dependent on opioids onto less addictive drugs such as buprenorphine. Educate prescribers, educate children, educate those experiencing chronic pain, educate actual and potential addicts as to the dangers. And from the social scientists, the familiar critique of ‘medicalisation’ and of the powers of big pharma to influence prescribing practices, as witnessed in the rise and rise of OxyContin.

The first half of this article defines the problem, the second documents a response to it from within parts of addiction neuroscience. Significant changes are taking place in addiction neuroscience that are not yet well-known within social studies of addiction. A new mode of thought has emerged over the last two decades that is changing how addiction neuroscience sees addiction. As Steve Hyman, then director of National Institute of Mental Health, said in 2005: “Based on the available neuroscientific evidence from the molecular to the behavioural, addiction is best explained as a disorder of memory and learning”. Drug memory science is starting to conceptualise how brain and behaviour and pleasure and pain coexist in complex ways in memories that give rise to chronic relapsing addiction. We suggest that this research may offer a way out of the translation crisis in part by creating new collaborations and knowledge-exchange between life and human sciences. Therapeutic hope is starting to be invested in this burgeoning field of enquiry. Drug memory science has begun the difficult transition from lab to clinic. And yet the most telling contribution of drug memory science might be to articulate – at the level of molecular and neural systems – why addiction is so resistant to treatments.

The argument advanced in this article is based upon four years of research and collaboration with addiction neuroscientists (McLean, 2019). Integral to the method was the “history of concepts” (Foucault, 1966 [1991]). This is the study of how concepts emerge within a field of knowledge and how they reshape the ways that researchers within that field perceive and think about their object of enquiry. This research was underpinned by interviews and conversations with addiction neuroscientists and historians, and time spent in a leading neuroscience laboratory in the UK. The analysis was developed in a number of workshops organised by the Neuroscience and Society Network (NSN) based at King’s College London. This is an interdisciplinary network which facilitates collaborations between researchers in the life sciences and the human sciences in the spirit of ‘critical friendship (Rose & Abi-Rached, 2013). Indeed, this article grows out of an international NSN workshop titled Memory/Habit/Addiction that took place in early 2020.

Drug overdose crisis

Disease concepts of human experience tend to have a bad reputation in the social sciences and humanities. And for good reasons. Social conditions of distress, from socioeconomic deprivation to racism and social exclusion, are almost always

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1The terminology is contested (Hasin et al., 2013; O’Brien, 2011). We have, however, chosen to refer to ‘addiction’ rather than ‘dependence’. Dependence is a ‘normal’ adaptive response. Almost everyone who takes psychoactive substances for an extended period becomes dependent, and will experience unpleasant symptoms on withdrawal of the substance in question, but only a small percentage of people develop compulsive, chronic drug-seeking that characterize the clinical category of addiction. ‘Substance use disorder’ is the clinical name for drug addiction in the Diagnostic and Statistical Manual of Mental Disorders IV, but the overall title is “Substance and Addiction-Related Disorders.” (APA, 2013).

2This proceedings of this Workshop are reported at http://somatosphere.net/2020/memory-habit-addiction.html/
reduced to matters of individual pathology. This has the effect of turning our critical attention away from the ways in which power and violence often operate through concepts of health and sickness. That neuroscientific research is often subject to the same kind of criticisms is unsurprising, since concepts of disease and illness are increasingly determined by how neurobiology perceives and knows them. Addiction is no different.

Despite many differences within addiction neuroscience, there are certain beliefs that the majority of addiction researchers can agree upon irrespective of discipline, method, or training. One is that some human beings develop relationships with drugs they wish to change, but have great difficulty doing so ‘organically’ without specialist support. Another is that only a small proportion of drug users experience adverse life-changing problems due to drug use – support networks breaking down, jobs and homes being lost. Few researchers in the field would accept the stereotypical vision of the drug user as a person whose life has been emptied of meaning and value beyond finding the next ‘hit’ or ‘score’. Drug addiction is far less common than domestic drug policy in the United States or United Kingdom would suggest (Garriott, 2011; Nutt, 2012), or one would imagine based on news reporting. This is especially true in the case of ‘hard’ illegal drugs such as heroin, crack cocaine and methamphetamine (Reinarman & Levine, 1997). And yet when debate and theorising about the ‘causes’ of addiction cools down, we are still left with the reality. Human beings suffer from unattended misery they themselves attribute to drug use, and typically desire relief from their affliction. No critique of disease concepts, however justified or well-intentioned, changes this painful truth of social life today.

According to the National Survey on Drug Use and Health, approximately 19.7 million people in the United States, aged 12 and older, battled with “substance use disorder” in 2017 (NSDUH, 2017). The National Institute on Drug Abuse (NIDA, 2018) describes drug addiction as a “national crisis” in the United States. The costs to health, society and economic welfare, NIDA argues, are “devastating”. This crisis is represented most strikingly in drug-related mortality statistics over the past two decades. From 1999 to 2018, 817,000 people are estimated to have died from drug overdoses, making it a leading cause of injury-related death in the United States (Hedegaard et al., 2020). The Centers for Disease Control and Prevention situate the “opioid epidemic” at the heart of this crisis. In the same period of time, opioid-related overdose deaths – those including prescription opioids, heroin, and synthetic opioids like fentanyl – increased almost six times (Hedegaard et al., 2020).

In 2018, opioids were involved in 70% of all drug overdose deaths in the United States, with synthetic opioids (other than methadone) accounting for nearly two-thirds of these drug overdose deaths (Wilson et al., 2020). The total “economic burden” of prescription opioid misuse alone in the United States is estimated at $78.5 billion a year (CDC, 2016). According to the European Monitoring Centre for Drugs and Drug Addiction, although the number of drug overdose deaths is far lower in the United Kingdom, similar trends appear to be developing (EMCDDA, 2017). In 2018, England and Wales recorded the highest number and the highest annual increase in drug overdose deaths since the time series began in 1993 (ONS, 2019). Britain also leads Europe in drug overdose deaths: almost 1 in 3 drug overdose deaths in Europe occurred in the UK in 2018 – twice the number of those occurring in Germany, which is in second place (EMCDDA, 2017).

A social autopsy of drug overdose deaths

Framing the opioid crisis as a “crisis of over prescription” (Nutt, 2012) comes with the danger of inflicting social wounds rather than healing them. Doing so turns critical attention away from the profound social distress at the root of drug overdose deaths. First, it is important to recognise that these deaths are not specific to opioids3, and while the over prescription of OxyContin and other opioids clearly require urgent redress, we argue that they are symptoms of what we might term ‘the structural distribution of social despair’.

This is a conclusion reached by American economists, Anne Case and Angus Deaton in their new book, Deaths of Despair and the Future of Capitalism (2020). Uniquely among high-income nations, life-expectancy in the United States has declined for three consecutive years, for the first time since 1918, which they explain through the dramatic rise of “deaths of despair” as a result of drug overdose, suicide and alcoholism over the past two decades. Case and Deaton draw conclusions that recall those of Durkheim (1897/2002) in his classic sociological study of suicide at the end of the 19th century. The oversupply of opioids, they argue, did not create the conditions for this despair, they filled the gaping hole opened up in white working-class communities by four decades of social and economic exclusion and fragmentation. For those without a college education, not only have median wages declined since 1979, and work security deteriorated, they have found themselves less valued in the economy and disconnected from the ‘American Dream’. Drug overdose deaths, like suicide and self-harm, they propose, follow from a loss of belonging, of self-worth and of hope amidst social and economic upheaval.

Framing drug overdoses as “deaths of despair” is gaining traction. For all the talk of ‘accidental overdose’ from prescription opioids, the relationship between suicide and opioid use is emerging as a significant area of research (Oquendo & Volkow, 2018). Early signs indicate that they are “entangled in multiple ways” (Volkow & Gordon, 2019). A 2017 study based on national survey data found two things of particular importance: that suicidal ideation was 40-60% higher for people who misused prescription opioids than those who do not; and that individuals with a prescription opioid use disorder were twice as likely

3From 2012 through 2018, drug overdose deaths involving cocaine more than tripled. In 2017, cocaine accounted for nearly 1 in 5 overdose deaths. And between 2017 and 2018, there was a thirty-seven per cent increase in overdoses involving psychostimulants such as methamphetamine.
to attempt suicide as those who did not misuse prescription opioids (Ashrafioun et al., 2017).

Isolating the opioid crisis from the wider problem of drug overdose and prescription opioids from illegal drugs not only diverts critical attention away from profound social distress, it threatens to deepen social division by stratifying drug users into two broad groups based, it seems, more on prejudice and discrimination than knowledge and evidence. On the one hand, there are ‘bad addicts’ mixed up with illegal opioids, to be punished with the full force of the law. And on the other hand, ‘unfortunate dependents’ deserving of social and medical support having become unwillingly dependent upon legal opioids. This division has the potential to exacerbate hostile public attitudes towards drugs and those who use them, and to entrench stigma that remains a major barrier preventing people from seeking out and receiving support and treatment for drug-related life-problems (Hadland et al., 2018; Lloyd, 2010; Yang, et al., 2017). It could even fuel already tense racial divisions.

Note, as Chris McGreal does in American Overdose (2019), how the first group is typically associated in the public imagination with African American and Hispanics, and the second group with Whites.

This should not surprise anyone. For dividing opioid users into deserving and undeserving groups helped to create the conditions for a never-ending ‘war of drugs’ that has always had an ugly racial dimension. As David Courtwright (1982: 1) demonstrates in his history of opioid addiction in America, our modern medical concept of addiction emerged in the United States between 1865 and 1935 out of a fundamental change in medical perceptions of the ‘typical addict’. In this period the “addict profile” shifted from the “addicted matron”, middle-aged women of the middle or upper class, to the “street criminal”, lower-class urban men perceived to be African American or Hispanic. Indeed, we might ask if the opioid crisis would be viewed as an urgent public health problem by political and medical elites if problems with Fentanyl and OxyContin addiction were entangled in the public imagination with the lives of African American men in Harlem or Detroit.

Rise and fall of the dopamine hypothesis

Lifting the opioid crisis out of this social and historical context makes it more difficult to understand. Important determining forces are hidden from view, or at the very least, more difficult to perceive. In contradistinction to the reductionism that governs so much of addiction medicine, we argue that the more restricted our perception of a complex phenomenon such as the opioid crisis is, the more limited is the collective capacity of society and addiction research to know and to manage the harms associated with long-term substance addiction.

The dangers of viewing errant prescription practices as the ‘cause’ of the opioid crisis, and this crisis as distinct from the social pathology expressed through drug overdose deaths and suicides are compounded, we argue, by the way substance addiction has come to be seen and known by medical, political and legal institutions in the United States over the three acts of the opioid tragedy. First heroin, then prescription opioids, then synthetics. A way of seeing and knowing addiction in which social conditions of distress and lived human experience are subtracted from its conception of addiction.

The diagnosis of an ‘opioid crisis’ takes for granted an important assumption. That addiction is a neuropsychiatric condition and this condition the underlying cause of the tragedy. And behind the clinical classification of addiction stands a neuroscientific theory, one promoted by the National Institute on Drug Abuse (NIDA) over the past three decades (Campbell, 2007; Courtwright, 2019; Raikhel, 2017; Vrecko, 2010). This is what the historian David Courtwright (2010: 137), writing a decade ago, termed the “NIDA paradigm”. It stands, he writes, for the theory that addiction is a “chronic, relapsing brain disease characterised by a loss of control over drug-taking”. According to this theory, it is high volumes of dopamine (the so-called ‘pleasure molecule’) in the brain’s ‘reward system’ that underlie the loss of self-control said to define addiction. For this reason, neuroscientists sometimes refer to it as the “dopamine theory” of addiction, or the “dopamine hypothesis” (Marsden, 2006; Nutt et al., 2015; Robbins & Everitt, 1999; Wise & Rompre, 1989; Wise, 2018).

In their major review of the “rise and fall of dopamine theory”, Nutt et al. (2015) sharpen the focus of this claim, and in so doing elucidate its most important implication. The humbling truth, they conclude, is that the dopamine-based neuroscience of addiction is yet to produce a “single effective treatment” for addiction. If there is indeed such a translation crisis - a crisis of turning knowledge into treatments able to ameliorate the suffering experienced by the 8-12% of opioid users who develop opioid addiction – then perhaps is not merely because translation is difficult, but because the dopamine hypothesis itself fails to grasp the biological or social nature of addiction.

Translation crisis

The translation crisis addiction neuroscience has struggled to address reflects, we argue, a fundamental conceptual and experimental weakness at the heart of dopamine theory. It is governed by a neurobiological concept of addiction as excessive pleasure-seeking and an over-emphasis on the mesolimbic dopamine pathway at odds with the human experience of addiction, as it is documented in authoritative clinical, neuroscientific, and social studies (Bourgois, 2000; Everitt & Robbins, 2005; Everitt, 2014; Marsden et al., 2018; Volkow et al., 2016). This is particularly true with human opioid addiction. Two brief examples, one neurobiological, the other anthropological, make this point for us.

First: neurobiology. The pleasure-seeking concept is at odds with both George Koob’s (2008, 2008) influential work on stress and the dysregulation of affect, and basic knowledge of the neurochemical function of opioid receptors, first demonstrated by Candice Pert & Solomon Snyder (1973). That opioids function in the nervous system of the body or in specific brain receptors to reduce the intensity of pain. It is also...
radically at odds with the lived experience of heroin addiction. Second: anthropology. In Pastoral Clinic (2010: 5), an affecting ethnography of heroin addiction in New Mexico’s Española Valley, “home to the highest rate of heroin addiction and fatal overdoses in the United States”, Angela Garcia documents in elegiac detail, the motivating power of suffering in human addiction, and the complex ways grief and pain become entwined with memories of pleasure and the uncertain promises they make. The promise not of happiness, nor even satisfaction, but at best, temporal relief from life’s misery.

And yet dopamine theory has proven highly influential in shaping perceptions of addiction neuroscience in the social sciences (Courtwright, 2019). It is how, with few exceptions, social scientists conceive of addiction neuroscience. Indeed, the terms ‘NIDA paradigm’ and ‘brain disease model’ are used interchangeably, as if the National Institute on Drug Abuse represents the field and defines how it perceives and thinks about addiction. There is no doubting the political and economic power of NIDA. But it is a mistake to think this power has translated into epistemic consensus – a shared unified way of seeing and knowing addiction. For there are not only multiple neuroscientific theories of addiction (Campbell, 2011; Raikkel, 2015), there are several competing dopamine models with different concepts of dopamine function. Most notably, perhaps, Wolfgang Schultz’s (2007a, 2007b, 2011) influential work on “prediction error” in the striatum, amygdala and frontal cortex, which accounts for the difference between an “expected reward” based on prior experience (and thus memory of it) and the “actual reward” provided by the drug or behaviour. But more significantly, as we shall see, is that the memory concept of addiction is now at the heart of mainstream addiction neuroscience. In the words of the Director of the National Institute for Alcohol Abuse, George Koob et al. (2017): “The overall hypothesis that addiction persists as a memory or memory-like process long after drug exposure has become the widely accepted position in the field.”

**Beyond the pleasure principle**

As the dopamine hypothesis begins to mutate, it is worth asking why it its epistemic authority was so long-lasting, despite its explanatory and translational failures? Perhaps this is because it linked so well with more general arguments in the neuroscience of psychopathologies that focussed so much attention on the functioning of individual neurotransmitters often seamlessly moving from the experimental reductionism of laboratory based research on animal models to a kind of metaphysical reductionism that extrapolates, without intermediate experimental work, to the vital lives of human beings, whose brains are not only many orders of magnitude greater, whose neural development is not only many orders of time longer, and whose environmental transactions are not only immensely more rich and complex, but whose lives are unintelligible without recognising that the world they inhabit is one of meanings and memories, shaped by myths and stories of lives, their own and others, of hopes and aspirations, of dreams and despair. Perhaps it is also because the dopamine hypothesis retained resonances of the moralistic image of the insatiable quest for the pleasure of the hit overwhelming the will, conscience and the demands of propriety and civility: the science of addiction here retained the sense that what was at stake was a disease of the will (Valverde, 2008).

What, then accounts for the waning of its epistemic authority? No doubt many factors have been involved, as they always are in the overturning of a paradigm, or the mutation in a style of thought. Anomalies certainly accumulated, as we would expect from a reading of Kuhn (1970), and a younger group of research scientists, if not revolutionaries, certainly sought to mutate the old ways of thinking into something new. But not least among the factors that led to the waning of the dopamine hypothesis, we suggest, is its inability to translate, to generate anything significant that could actually intervene positively in the lives of those who it branded as addicts, or as those suffering from a substance addiction.

Let us be clear. We are in no way implying the ‘dopamine theory’ and its influence could explain the translation gap. No theory, however influential or sophisticated, could account for the history of social distress underlying the opioid crisis. We are, however, arguing that ‘dopamine theory’ has significant weaknesses, which have held addiction research back. The theory is reductive in two vital and related ways. First, its pleasure-seeking concept is at odds with the lived experience of human addiction. Second, it deals with neurobiological mechanisms as if they function in isolation from the ‘social’. There is, however, one neuroscientific theory of addiction in particular that is changing the direction of addiction neuroscience – ‘the memory turn’. This is a new way of seeing and knowing substance addiction that helps to address these weaknesses with ‘dopamine theory’. In the remainder of this paper we will sketch out what this new mode of enquiry is, how it may overcome limitations of the ‘dopamine hypothesis’, and why we think it opens up new possibilities for thinking about and perhaps tackling the translation gap that the opioid crisis has brought into sharp relief.

**The memory turn**

By the mid-1990s, neuroscientists and psychologists were already arguing that neurochemical models of dopamine are unable to explain vital neurobiological and psychological features of addiction (Hyman, 2005; Robinson & Berridge, 1998; Robinson & Berridge, 1993; Robbins & Everitt, 2016; White, 1996). Two features in particular posed problems for this model. First, that compulsive drug-seeking persists despite the known harms to health and risk to life. And second, and perhaps most important, that drug-related compulsions and cravings that result in relapses can persist for years even decades after all detectable traces of neurochemicals have left the body.

Around the same time, addiction and memory scientists started to converge on a shared realisation. That addiction and long-term memory share molecular, neural and cellular pathways and systems (Hyman et al., 2006; Kelley, 2004). To understand one, is to know the other. And that this intimate relationship between chronic, relapsing addiction on the one side, and long-term
memory on the other, may provide a basis for exploring and making sense of those vital features of substance addiction (Nestler, 2001; Nestler, 2013; Nestler et al., 1992; Robbins et al., 2008).

This insight formed the basis for of a new field of knowledge – drug memory science – that is organised around three distinct if mutually reinforcing lines of enquiry. The first is neurobehavioral studies of conditioned learning that explain how habitual opioid use turns into addiction over time (Everitt & Robbins, 2015; Robbins et al., 2001). The second is the analysis of how memories associated with drugs – including opioids - underpin compulsive ideation and behaviour and weaken the capacity to acquire new habits (Milton & Everitt, 2010). The third is research on the ways that substance addiction damages the fundamental neurobiological mechanisms involved in long-term memory (Kalivas & O’Brien, 2007; Kauer & Malenka, 2006; Lüscher & Malenka, 2011).

Drug memory science seeks to understand the neurocognitive systems and molecular processes underlying drug memories as well as the memories themselves. Drug memories can be “declarative” – those we can consciously recall. But for the most part, they are “procedural”; unconscious and automatic memories that are primary when it comes to addiction (Squire, 2004). Declarative memories function by strengthening existing associations between drugs and environmental and physiological cues. Drug memories are “maladaptive” (Milton & Everitt, 2012) because they are strongly affective and extremely difficult to disrupt and change once “consolidated” the first time (Troson & Taylor, 2013). Functional, perhaps even structural, changes to memory systems in the brain underlie aberrant drug memories and pathological learning” (Everitt, 2018; Robbins & Ersche, 2008; Robbins & Everitt, 2001).

To make sense of this process, neural, molecular and behavioural knowledge of the “mesolimbic dopamine system” (the pathway connecting the ventral tegmental area in the midbrain to the ventral striatum of the basal ganglia in the forebrain) has been integrated into new knowledge in our understanding of “corticostriatal systems” that connect the striatum to the prefrontal cortex (Graybiel, 2008; Graybiel & Grafton, 2015). This neurobiology of habit gives a new sense to the long-standing description of drug addiction as a ‘habit’. As Barry Everitt & Trevor Robbins (1999) put it: “Bad habits add up.”

From bench to clinic
Drug memory science is also starting to inform the clinical classification of addiction. The latest edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, 2013) included “powerful memories” as part of the core symptomatology of “substance use disorder” for the first-time. The memory turn has also started to make the difficult transition from animal models to clinical human research. So far, clinical research that is informed by the memory concept of addiction is largely focused on pharmacological interventions. In particular, the discovery of chemical “agonists” or “antagonists” to disrupt drug memories, either by introducing states of “reconsolidation” so they can be modified, or “extinction” to break altogether conditioned reactions to cues. (Lee et al., 2005; Merlo et al., 2014; Miller & Marshall, 2005; Torregrossa & Taylor, 2012). This is much like the betablocker propranolol was found to disrupt “fear memories” in posttraumatic stress disorder through a process of reconsolidation (Debiec et al., 2006; Nader et al., 2000).

The rise and fall of dopamine theory show that unless drug memory science can make the transition from knowledge to life, the memory turn will be unable to reduce the translation gap. This requires treating not only chemical dependence, but the long-lasting effects addiction has on cognition and behaviour. There are some positive developments in this direction. One memory-focused human model is the clinical work of Professor John Marsden and colleagues at the Institute of Psychiatry, Psychology and Neuroscience (IoPPN) at King’s College London on cocaine use disorder (CUD) (2018). They have developed and piloted a novel Memory-focused Cognitive Therapy (MFCT) to tackle CUD. Given the enduring effects of cocaine-related conditioning in patients, cue-induction procedures are used to elicit cocaine-related cognitions in patients, with the aim of reducing craving for the stimulant.

Through repeated cue-exposure that goes unrewarded, the strong associations between stimulant-cues-responses established in addiction are broken over time. MFCT also adapts trauma-focused cognitive therapy successfully developed for post-traumatic stress disorder (PTSD) to reduce the intensity of affective responses to trauma-related memories. Crucially, MCFT uses a range of techniques to restructure how patients think about, perceive and relate to the stimulant and its sensory associations. That is to say, to help them grasp the situational dependence of their habits and avoid or reframe those situations that evoke the habitual craving for the substance. In an important way, patients become necessary collaborators in the process of discovering and reducing the social and affective cues that maintain the compulsive use of drugs long after the initial goal has dissipated.

Closing the gap
The memory turn, we are arguing, is an important event in addiction neuroscience. It has given birth to a new way of seeing and knowing substance addiction as a memory disorder. That is to say, an inability to forget drug memories and to learn new habits due to the pathological usurpation of memory systems and processes. But how does the memory theory of addiction advance knowledge of the drug overdose crisis? How does it overcome the conceptual and practical limits of ‘dopamine theory’? And how might it offer a way out of the translation problem?

The memory turn focusses upon explaining how opioid use becomes habitual, dependence develops and in turn how this turn into compulsive, chronic relapsing behaviors that characterise substance addiction. While the ‘dopamine theory’ is certainly effective in explaining some of the important
neurochemical adaptations in the ‘reward system’, the memory turn is thus much better suited to interrogating the more destructive cases of substance addiction that represent the opioid crisis. It is more attuned to the lived experience of human addiction as shown in social and clinical studies referred to above. It taps into the complex nature of motivation in which pleasure and pain coexist in drug memory. It is not simply that the person wishes to ‘feel good’, or to be ‘free of pain’, it is that pleasure and pain become entwined in reinforcing ways. And it does so, by situating the neural, cognitive and affective systems involved within a neuropsychological schema in which the ‘social’ plays a decisive role.

The compulsive, chronic, relapsing hallmarks of substance addiction can be explained through neurochemical maladaptations alone. These behaviors are in part the product of an extraordinary range of unconscious and conscious associations established between drugs and cues in the lived environment that changes in drug memory help to explain. That is to say the ways in which these drug-related associations, the lives people live, and the meanings given to experience are represented in drug memories and memory systems. We call these interactions of brain and life ‘neurosocial relations’. These relations represent a challenge for addiction research: the need to develop conceptual and experimental models of the ways that unconscious and conscious processes interact through memory to undermine human efforts to develop new relationships (cognitive and affective) with drugs.

A recognition of the need to understand these neurosocial relations can underpin a new way forward in addressing the translation crisis. It can open up a creative space for collaborations between social scientists and neuroscientists, a space that the Neuroscience and Society Network has been cultivating. A space in which the hard work of developing these models can take place. Going forward, we argue, these neurosocial collaborations are essential. No one, certainly not the neuroscientists involved, thinks the memory turn alone could possibly address the opioid crisis. This will require not only the full participation of the academic research community; it will depend upon having service users at the heart of these collaborations.

But we should be realistic. Perhaps the major therapeutic insight of the memory turn is to demonstrate the social underpinnings, both in social suffering and in situational memories, that make substance addiction so difficult to overcome. The neurosocial collaborations necessary to advance this way of thinking will take time to develop, and even longer to develop workable responses to substance addiction. In a political context dominated by the never-ending ‘war of drugs’ in which abstinence in the form of ‘drug recovery’ prevails, harm reduction activism (see Campbell, 2020) that is led by service users, but supported by neurosocial collaborations, would be a positive move forward. This approach will not ‘cure’ society of substance addiction – nothing will. Nor will it close the translation gap once and for all. But a renewed commitment to evidence-based harm reduction would save lives and reduce misery, and that at least, would be no small thing.

**Conclusion: Vital life**

Drug memory science taps into an existential truth of memory (see Heidegger, 1978 [1927]; Nietzsche, 1974[1885]) that the human experience of chronic, relapsing addiction discloses. That memories hold us together, but they can also tear us apart – from ourselves, others, and life itself. Such is the paradox of memory.

Twenty-five years ago, memory was a marginal object of enquiry in addiction neuroscience. While drug memory science has multiple starting points, the first attempt to conceptualize substance addiction in terms of ‘multiple memory systems’ can probably be dated to a paper by White (1996), a neuropsychologist based at McGill. Two decades later, the memory concept of addiction has become central to neuroscientific thought. Eric Kandel, the most prominent neurobiologist of memory of his generation, has no doubt. In his recent book, *The Disordered Mind*, he writes “Drug addiction is a problem of long-term memory”. “The memory of pleasure” he continues, “persists long after an addicted person has stopped taking the drug” (Kandel, 2018: 201-2).

As Kandel’s quote shows, addiction neuroscience is not post-pleasure. The memory turn does not represent a straightforward shift from pleasure to memory. It does, however, contradict the Utilitarian concept of pleasure-seeking inherent in dopamine theory of addiction. The human experience of addiction studied by sociologists and anthropologists such as Angela Garcia call into question Bentham’s (2015[1789]) famous dictum that pleasure and pain constitute the two “sovereign masters” of human nature and motivation. The memory turn shows rather that the pleasure of addiction coexists with pain and suffering in memories of drug-related experience. Drug memories which appear to strengthen and become more sensitive to being ‘triggered’ by the associations that build up between drugs and cues over time.

New collaborations between life and human sciences are needed to address the translation weakness in addiction studies. Collaborations forged with the purpose of attending to the affliction of addiction – not the interests or epistemic authority of any one field of knowledge. On this, Nietzsche (1997[1887]) was right – ‘objective’ knowledge means seeing with many eyes. The memory concept of addiction, we argue, makes drug memory science a good candidate for cultivating these collaborations and models. In part because the relations of brain-life and pleasure-suffering are built into the concept itself in ways social scientists and humanities can help develop. If the memory turn is to aid addiction studies in fulfilling this ambition, neurosocial collaborations must develop new models of experimental research that have social life at their heart. Such neurosocial collaborations sustained by “critical friendship” (Rose & Abi-Rached, 2013), must proceed from the vital life of human beings.

**Data availability**

All data underlying the results are available as part of the article and no additional source data are required.
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Yang LH, Wong LY, Grivel MM, et al.: Stigma and substance use disorders: an international phenomenon. Curr Opin Psychiatry. 2017; 30(5): 378-388.
The concept of addiction has never been a single universally accepted one, and various complementary or competing concepts - moral, medical, psychological, social and others - have coexisted over past decades or even centuries. From the mid-twentieth century to the 1970s, the various definitions adopted by the Expert Committee of the WHO were essentially pharmacological in nature, attributing addiction primarily to the actions of the drugs themselves and to individual differences in susceptibility to those actions (Jaffe, 1980; World Health Organization, 1974).\(^1\),\(^2\) In this generally well written and extensively documented conceptual analysis, McLean and Rose raise some important questions about the recent evolution of the concept.

As they point out, the pharmacological concept of addiction was made more specific from the 1970s onward by the neurobiological focus on addiction as pleasure-seeking based on the effects of drugs on a postulated dopaminergic reward system (Wise, 1980)\(^3\) and its offspring, the brain disease concept of addiction (Leshner, 1997)\(^4\). They criticise this focus on the grounds that (i) it is not in accord with the lived experience that distress rather than pleasure predominates in addicted drug use, (ii) the current epidemic of drug overdose deaths cannot be attributed to overprescribing alone because suicidal thinking and attempts are common in overdose cases, (iii) it leads to differentiation between “good” addicts who are the victims of overprescribing and “bad” addicts who seek pleasure from illicit drugs, and (iv) the dopamine hypothesis has not led to any effective new therapy for addiction. They then argue that a much better explanation of addiction is provided by the theory evolved over the last twenty-five years that it is a functional disorder of long-term memory. This model, they believe, is already providing new and more effective approaches to treatment of addiction.

The first two of these points are valuable corrections to commonly held but perhaps erroneous beliefs. The authors present abundant evidence to support them, and readers must give them serious consideration. However, the evidence provided does not make clear whether suicidal thinking preceded the start of addicted use, or was a consequence of it. The authors might wish to clarify that question, since it affects the strength of their argument. The third point is less
convincing, because the differentiation between those who actively seek and use illicit drugs and those who use drugs medically prescribed for them rests on a variety of social and psychological criteria, stereotypes and attitudes, and can not be attributed exclusively to the dopamine theory or other neurobiological models. The fourth point is perhaps debatable. While some reviewers conclude that drug therapy has been of little value in the treatment of addictions (Kalant, 2015)\(^5\), others consider it of significant clinical value (Pierce \textit{et al.}, 2012; Schacht \textit{et al.}, 2017)\(^6,7\). The present authors should consider making their comments on this point less absolute.

The remainder of the paper, dealing with the importance of memory in the development of addiction, is probably the most important part. This is an older concept than the authors imply: the existence of links between learning and memory on the one hand and various elements of the clinical state of addiction on the other, had already been demonstrated well before the 1990s (Finkelberg \textit{et al.}, 1978; Kalant \textit{et al.}, 1971; Lê \textit{et al.}, 1982; van Wimersma-Greidanus \textit{et al.}, 1975)\(^8-11\). Nevertheless, there is great value in this part of the paper, with its detailed and lucid explanation of the role of memory in the generation of addiction, and the extensive documentation of the more recent supporting evidence. Since this is a conceptual review rather than an experimental paper, I do not know how to answer the questions about study design, methods and analysis. Assuming that analysis refers to conceptual analysis rather than to analytical techniques, my answers to question 2 would be "Partly" and to question 3 "Yes". A similar recent review that examines addiction as a maladaptive form of learning draws on much of the same source literature (Lewis, 2018)\(^12\) and should be cited.

The main limitation of this portion of the present paper is the tendency to view the memory theory of addiction and the neurobiologically based concepts as mutually exclusive, rather than to consider the possibility of complementary causal roles of both factors. As expressed elsewhere (Kalant, 2010, 2015)\(^13,15\), in most cases the neurobiological studies identify the mechanisms of brain responses while the behavioral and environmental studies explore the causes that call the mechanisms into play and direct them towards specific targets. However, the prolonged intake of large amounts of drugs of various kinds does lead to functional and even structural changes in the brain that can affect the severity of addiction and its susceptibility to treatment and the risk of relapse. For example, a recent review describes evidence that heavy consumption of ethanol, nicotine and other drugs of addiction can give rise to neuroinflammation and oxidative stress in the brain, which induce increased consumption, thus setting up a self-perpetuating cycle (Berrios-Cárcamo \textit{et al.}, 2020)\(^14\) that can be stopped by administration of anti-inflammatory and antioxidant medications (Israel \textit{et al.}, 2019)\(^15\). McLean and Rose would improve the value of their review substantially if they could discuss the issue of neurobiological and behavioral mechanisms as interacting determinants of addiction rather than as conflicting and mutually exclusive explanations.

A few minor corrections should be made if the paper is revised:

- Page 7, right hand column, paragraph 3, line 6 – MCFT should be MFCT.

- Bottom paragraph, line 3 - “this turn” should be “this turns”.

- Page 8, left hand column, paragraph 2, line 2 - “can be explained” should be “can not be explained”.

- Page 8, paragraph 4, line 8 - “war of drugs” should be “war on drugs”.

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Final paragraph, line 1 - “collaborations between life and human sciences” is inappropriate, because life sciences can also be human sciences. Perhaps better to say “between biological and social sciences”?

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Is the work clearly and accurately presented and does it cite the current literature? Yes
Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
No source data required

Are the conclusions drawn adequately supported by the results?
Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Behavioral Pharmacology. Biological and Behavioral studies of addiction.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.
epidemiologists working on substance use disorders and/or addiction/treatment/outreach/social services.

The “crisis” title and first half of the abstract is something of a red herring. As is the valence of the term “pursuit of pleasure” and the dismissive critiques of existing attempts at translational to effective treatments whether in mainstream medicine or harm reduction services. Those oversimplifications and inordinate valences to discursive power distract from the valuable important (utopian?) primary contribution of the article concerning the potential for the neurosocial dialogue:

1) Crisis “hook”

The article does not provide an argument that there is no “crisis,” as commonly understood, namely a distinct rise in the numbers of opioid death in a defined span of time. On page 4, indeed the authors detail the rapid increase in opioid deaths that begs for response. They are right to emphasize that the increase in mortality is not well described as a simple technical “crisis of over prescription”. There is however a question with respect to: a) what kind of crisis is this, and b) whether or not “crisis language” is counterproductive and distracts from the root causes of the social/existential roots of the problem. Critiques of “the crisis model” (Roitman et al.) argue that “crisis” misconstrues long-standing and socially structurally embedded conditions that are not well described in the sudden language of “emergency” that produces short term palliative measures that are ultimately ineffective. (There is also the more old fashioned longstanding sociology of substance use disorder literature critiquing the stigmatizing/criminalizing effects of “moral panics”.)

2) Overprescription and the novelty of “structural distribution of despair“

The hegemonic model of addiction in the social sciences has already been for some decades a model of the “structural distribution of social despair” long before Case and Deaton’s valuable initial demographic documentation of the drop in life expectancy among least “educated” whites in 2015 (that appears to have been what prompted Deaton’s Nobel prize that same year). Few if any social scientists studying the lived experience of substance use disorders would ascribe the disaster of opioid deaths to something as naïvely technical and reductionist as “over prescription.” The critical ethnographic literature goes back at least to the 1930s in the US.

3) Do neuroscience models have significant impact on stigma and translational science vs old fashioned racism, class power and big pharma profiteering driving translational applications (in the US dominated globalized/medicalized and even the spiritual-religious field) if (in)effective “evidence based” treatments.

I could not help wondering why shifting from addiction being a “brain disease” or “disease of the will” to a model emphasizing “damages” within “the fundamental neurobiological mechanisms involved in long-term memory” would be likely to be less likely to be translationally interpreted into “effective treatments” that are less stigmatizing in racist and/or xenophobic, in highly unequal societies where rapidly rising social inequality has been perversely normalized in popular consciousness (especially the US) as “good for the economy” and the only way to motivate human autonomy and self-realization?
4) Impact of “brain disease pursuit of pleasure” model in the social sciences.

The NIDA paradigm is not the paradigm of most ethnographers and/or critical theory social scientists of addiction. Most have never viewed or have critiqued reductionist interpretations of “addiction is a disease/brain disease” model with a narrow definition of pleasure (or don't even know what that refers to). Many if not most social scientists (who are not psychologists/health services behavioral scientists since at least the 1930s) have treated it as a social and political crisis. Focusing on “pleasure” as a strawman for memory also seems misplaced a false binary. Memory of pleasure is part of the memory prompt which few would reduce to a simple positive bounded definition of pleasure but commonsensically/psychologically/biologically socially might involve relief from pain or flight from suffering distress and traumatic memories. Incidentally the increasingly translational literature on “structural vulnerability” that is going more mainstream into left-leaning reinventions of medical education and clinical practice and addressing so-called “social determinants of health” can be of some use here as it applies to “addiction”.

5) Translational failure of “Effective Treatments”

The trouble with the translational field of treatment (both the neuroscientific and the social quantitative and the social epidemiological) is that in medicalized and non-medicalized addiction treatment fields nothing and almost everything counts as evidence-based treatment from methadone/buprenorphine/naloxone to faith and conversion to CBT psychological therapy to narcotics anonymous to harm reduction. This is because, as the authors argue, addiction is a profoundly social phenomenon of personal existential suffering and population-level despair that is driven by forces and institutional structures. Consequently dismissing the NIDA brain disease pleasure or memory models for that matter which arguably produced or shaped or coincided with/influenced/legitimized biomedical/pharma driven methadone/buprenorphine naloxone treatments and even free spiritual narcotics anonymous treatments. Furthermore the clinicians and medicalized harm reductionists the neurosocial would want to reach out to refer to those as “evidence-based treatments”. Most importantly dismissing them is not consistent with the humility of anticipating that the neurosocial to advance translational effective treatments is to show how resistant to treatment addiction has been. I agree with their take on it overall but it is problematic in their presentation of it.

In conclusion, and sorry for the length of this review. I enjoyed reading the article and I appreciate the authors' optimism over the potential of a neurosocial dialogue and am intrigued and hopeful that the memory turn could possible open up a greater possibility for critically respectful dialogue across the current epistemological/interdisciplinary/disciplinary vacuums that lie between laboratory sciences and in vivo (one currently exists with more bio-psychologically reductionist and narrowly medicalized social sciences that has not been effective). I am not as optimistic as the authors and would like a bit more clarity/detail on how the memory turn will not encounter the same structural reductionist failures of the dopamine/pleasure model and ultimately (in the US at least) are likely to continue to be trumped (ugh) by moralizing populist conceptions of sin/worthiness/racism/carceral punishment/profiteering and genetic/biological reductionism.

**Is the work clearly and accurately presented and does it cite the current literature?**
Yes

**Is the study design appropriate and is the work technically sound?**
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Anthropology/social medicine/social inequality-racism/substance use disorders/violence/homelessness/incarceration/serious mental illness/political economy.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 30 September 2020
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I am sympathetic to several of the themes that run through this paper, particularly the emphasis on “deaths of despair” as determinants of the opioid crisis, and the call for collaboration between neuroscientists and social scientists. I also appreciated the attempt to raise awareness among social scientists of the limitations of relatively simplistic neuroscientific accounts of addiction, and of the limited innovations in addiction treatment that have arisen from dopamine theory.

However, I felt that the linkage between different arguments was unclear or overly speculative (or both), and in particular I was not persuaded by the authors’ argument that recent work on the ‘memory turn’ is likely to yield a solution to the opioid crisis. I elaborate on these arguments below.

1. The authors provide a brief accessible summary of the “rise and fall of the dopamine
hypothesis” (p5). However, contemporary addiction neuroscientists are fully aware that the neurobiology of addiction is complicated, and goes well beyond dopaminergic adaptations. Therefore any attack on the dopamine hypothesis is a bit of a straw man, assuming that the intended purpose was to criticise neuroscience accounts of addiction more broadly. A recent and concise overview of the neurobiology of addiction is provided by Volkow et al. (2016), and the current paper might be strengthened by broadening the coverage of neuroscientific accounts of addiction. The paper would also be strengthened by referring to other reviews which demonstrate that neuroscience research more broadly has failed to deliver novel effective treatments for addiction, and this might be partly because of its inability to model the complexity of addiction, including the importance of social factors (Field & Kersbergen, 2020; Heilig et al.,2016 ; Borsboom et al 2020), the latter includes a relevant commentary by Field et al. (p18) that discusses the opioid crisis and “deaths of despair” in the context of reductionist neuroscience approaches to addiction).

2. Alternatively, perhaps the focus on the dopamine hypothesis was because it has “proven highly influential in shaping perceptions of addiction neuroscience in the social sciences (Courtwright, 2019). It is how, with few exceptions, social scientists conceive of addiction neuroscience” (p6).

If so, the purpose of the criticism of the dopamine hypothesis might be signposted more clearly, along the lines of “the neuroscience has moved on, and it is important that social scientists catch up”.

3. The line of argument in the paper then moves on to argue for the importance of “the memory turn” as a potentially important way to conceive of addiction and to bridge neuroscience with social science. I broadly agree. However, the evidence presented in favour of the notion that a focus on memory may yield new treatments for addiction is selective and rose-tinted. The recent work by Marsden and colleagues on MCFT is preliminary and has not yet been subjected to a definitive clinical trial, therefore the findings from small pilot studies should be interpreted with caution. The authors should also consider other translational addiction interventions that aimed to disrupt drug-related memories, and generally did not translate well “from bench to bedside” (e.g. Das & Kamboj). More recent memory-focussed interventions have also yielded promising findings (e.g. Das et al., 2019). These findings might be discussed. However in the absence of well-powered trials, the clinical promise of interventions translated from “the memory turn” should not be overstated.

4. In my opinion the most significant limitation of the paper is its central argument, summarized on p8: “the memory turn is thus much better suited to interrogating the more destructive cases of substance addiction that represent the opioid crisis. It is more attuned to the lived experience of human addiction as shown in social and clinical studies referred to above. It taps into the complex nature of motivation in which pleasure and pain coexist in drug memory. It is not simply that the person wishes to ‘feel good’, or to be ‘free of pain’, it is that pleasure and pain become entwined in reinforcing ways. And it does so, by situating the neural, cognitive and affective systems involved within a neuropsychological schema in which the social’ plays a decisive role”.

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Where is the supportive evidence for this grand claim? I think that “the social and clinical studies referred to above”, refers to the literature discussed on p5-6 which demonstrate that opioids function as negative reinforcers (they relieve physical and emotional pain in addition to producing euphoria). The notion that negative reinforcement underpins addiction has a long history and indeed the underpinning neuroscience is well described in work by Koob and colleagues, as cited here. It is also plausible that negative reinforcement models of addiction can account for “deaths of despair”, including the opioid crisis. But why does this suggest that memory-based treatment interventions are likely to provide the answer? This link was not clear to me, and the paper would be greatly improved if the authors could spell out the relevant evidence and its implications more clearly. In addition, alternative explanations of the link between social deprivation and drug addiction should be considered, including relative absence of alternative (substance free) reinforcement (e.g. Leventhal et al., 2015; Acuff et al., 2019).

5. The authors made other claims that were not clearly supported by the evidence, for example on p8:

“These relations represent a challenge for addiction research: the need to develop conceptual and experimental models of the ways that unconscious and conscious processes interact through memory to undermine human efforts to develop new relationships (cognitive and affective) with drugs”.

6. Also, I would agree with the following claim, as many would, but I did not understand how this claim is related to the “memory turn”, or how it follows from the arguments presented (p8):

“...harm reduction activism (see Campbell, 2020) that is led by service users, but supported by neurosocial collaborations, would be a positive move forward.”

7. The authors claim that “The compulsive, chronic, relapsing hallmarks of substance addiction can be explained through neurochemical maladaptations alone”. Although this is certainly the conventional view among addiction neuroscientists, the notion of addiction as a chronically relapsing disorder of compulsion has been challenged in recent years (e.g. Heather, 2017) and this debate should be mentioned here.

8. Throughout the paper and particularly on page 7, the authors place technical terms from the neuroscience and memory literatures in quotation marks (e.g. “corticostriatal systems”, “declarative”). I’m not sure what the quotation marks are supposed to achieve here – it would be better to define the terms in a way that would be useful for the intended audience of this paper.

9. On page 7 authors state that “powerful memories” are part of one of the diagnostic criteria in DSM 5. I’m not sure that this is correct. The authors include a footnote in relation to this claim but I could not see the footnote anywhere.

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Is the work clearly and accurately presented and does it cite the current literature?  
Partly

Is the study design appropriate and is the work technically sound?  
Partly

Are sufficient details of methods and analysis provided to allow replication by others?  
No

If applicable, is the statistical analysis and its interpretation appropriate?  
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?  
No source data required

Are the conclusions drawn adequately supported by the results?  
No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Psychology, addiction, behaviour change.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.