

From concepts to treatment: a dialogue between a preclinical researcher and a clinician in addiction medicine.

Running title: A dialogue on addiction

Vandaele Youna¹, Daeppen Jean-Bernard.¹

¹Addiction Medicine, Department of Psychiatry, Lausanne University Hospital, Lausanne, Switzerland

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Abstract:

The debate surrounding the brain disease model and the associated questioning of the relevance of animal models is polarizing the field of addiction, and tends to widen the gap between preclinical research and addiction medicine. Here, we aimed at bridging this gap by establishing a dialogue between a preclinical researcher and a clinician in addiction medicine. Our objective was to evaluate animal models and the neuroscientific conceptualization of addiction in light of alcohol or drug dependence and treatment in patients struggling with an addiction. We sought to determine how preclinical research influenced addiction medicine over past decades, and reciprocally, what can preclinical researchers learn from addiction medicine that could lead to more effective approaches. In this dialogue, we talk about the co-evolution of addiction concepts and treatments from neuroscientific and medical perspectives. This dialogue illustrates the reciprocal influences and mutual enrichment between the two disciplines and reveals that, although preclinical research might not produce new pharmacotherapies, it does shape the theoretical conceptualization of addiction and has considerable implications for the implementation of therapeutic approaches

Keywords: Addiction, animal models, medicine, compulsion, choice, ambivalence, motivational interviewing

Introduction

YV: The relevance of animal models of alcohol, tobacco and substance use disorder (referred to as addiction hereafter) is being increasingly questioned (1). Notably, there is a growing awareness of a translational crisis, evidenced by the poor predictive validity of animal models of addiction (2). Despite decades of research and considerable progress in our understanding of the neurobiological processes mediating the transition to addiction, most of the promising pharmacotherapies developed in animals failed to prove effective in the treatment of addiction in humans (1). Besides these unsuccessful efforts, sometimes characterized as a waste of time and resources, preclinical research significantly contributed to the predominance of the Brain Disease Model of Addiction (BDMA) (3), increasingly criticized in the scientific community (1,4,5). In fact, it has even been suggested that viewing addiction as a brain disease could hinder recovery from addiction and promote social injustice (6–8). This criticism seems to imply that using animal models to study the neurobiology of addiction is not only useless but could even be counter-productive for the treatment of this disorder.

As a preclinical researcher and neuroscientist, I have come to question the relevance and usefulness of my own work in understanding and, more importantly, in treating addiction. However, the influence of the BDMA worldwide, dominating thinking and practice and driven by the neuroscience of addiction, highlights the importance of preclinical research in affecting societal attitudes toward addiction. Preclinical research may not have led to the development of new pharmacotherapies, but it has generated neurobiological theories that have significantly shaped our conception of addiction with many clinical and societal implications (for better or for worse). My goal here is not to advocate for or against the BDMA, a topic already extensively covered in the literature (1,4,9–11). Instead, I am specifically interested in determining how preclinical research has influenced addiction medicine over past decades and reciprocally, what can preclinical researchers learn from addiction medicine to help develop more effective therapies. To address these questions and to evaluate my models and conceptualization of addiction in light of drug use and treatment in patients struggling with an addiction, I contacted Dr. Jean-Bernard Daeppen, head of the addiction medicine unit at Lausanne University Hospital. We exchanged ideas about the reciprocal influences between preclinical research, neuroscience and addiction medicine and the co-evolution of addiction conceptualization and treatment. We wanted to share this dialogue in the hope of establishing more fruitful translational research in the field of addiction to optimize beneficial therapeutic outcomes.

From theoretical concepts of addiction to the implementation of therapeutic strategies

YV: The current neuroscientific conceptualization of addiction is the result of several decades of preclinical research on the brain mechanisms underlying loss of control over drug¹ use in animal models of addiction. Much of the progress in preclinical research on addiction emerged in the '60s from the development of intravenous drug self-administration techniques in monkeys (12) and rats (13). It was rapidly demonstrated that all drugs abused in humans could be administered in nonhuman animals (14,15). Researchers realized that under controlled conditions in which drug intoxication does not interfere with other natural behaviors (i.e. eating and drinking), rats learned to regulate their drug intake and titrate their consumption to reach the desired level of intoxication (16,17). Thus, it became evident that drug self-administration was not sufficient to model addiction,

¹ For ease of reading, the term “drug” includes alcohol as well as any pharmaceutical psychoactive substances subject to abuse.

and additional tests were required to assess loss of control over drug intake. Preclinical models of addiction were developed to evaluate “addiction-like” behaviors, based on diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM) (18–20).

Building on these multiple models, different theories posit that transition to addiction results from a disruption of brain reward circuits with: an overvaluation of the drug reward relative to alternative nondrug rewards, accompanied by a shift from positive to negative reinforcement (i.e. opponent process theory)(21–23); aberrant habitual learning (24,25); and heightened sensitivity to drug-associated cues (i.e. incentive sensitization) (26,27). On the other hand, impairments in top-down executive control resulting from disruption in the prefrontal cortex can contribute to a loss of goal representation or to deficits in inhibitory control over problematic drug use (28–30). One common factor between these theories is the central place of compulsion, defined as an irresistible desire or a “force” driving persistent drug use despite negative consequences (31,32). This “force”, outside of voluntary control, is sometimes hypothesized to result from the abnormal persistence, dominance and expression of maladaptive habits (24,25). In this framework, drug use is automatically triggered in familiar situations or in response to drug-associated cues, without any deliberation, conscious expectation of drug effects or anticipation of negative consequences (i.e. absent goal-directed control). In addition, clinical and preclinical research converge to demonstrate functional disruptions in the prefrontal cortex associated with reduced inhibitory control and broad impairment in executive functions (28,32), leading some researchers to describe compulsive drug use as resulting from a “defect of the will” (29,33).

Jean-Bernard, what is your view, as a clinician, on the influence of this compulsive account of addiction on treatment?

JBD: In the '60s and '70s, the clinical approach to addictions was dominated by Alcoholics Anonymous (AA) and Narcotics Anonymous (NA), who consider loss of control and automaticity as landmarks of addiction. AA and NA are built on the belief that individuals are powerless over alcohol and drugs and need the help of a Higher Power to restore control over consumption (34,35). The AA/NA model and the brain disease model appeared in the scientific literature when the social and political views on addictions were dominated by the moral view that addiction results from the desire for the hedonic effect of alcohol or drugs and from a lack of will to control this desire (36–39). We can hypothesize that the compulsive account of addiction proposed by neuroscientists was influenced by the AA/NA model of addiction. This model assumes a complete loss of control over drug use and a lack of responsibility in individuals with addictions, and the compulsive account of addiction depicted in the BDMA justifies this claim by providing neurobiological evidence supporting the AA/NA model.

If addiction is conceptualized as a brain disease, characterized by compulsive drug use and a defect of free-will, the logical consequence is that individuals do not have the ability or the responsibility to change. It suggests that external pressures should impose change. In the '70s, there was a very strong belief that the remission of an addiction was possible only through abstinence, even when the affected individual did not agree (40). Treatments proposed for alcohol dependence were long hospital stays and disulfiram, while opiate addiction treatment did not consider alternative solutions to withdrawal; both of these reflected some sort of psychological, chemical or physical control imposed on individuals. These confrontational approaches were actually justified by the brain disease concept originating from preclinical research.

Clinical research with experimental treatments testing confrontational counseling styles, including various types of constraint and pressure, became very popular. But despite this popularity, the

efficacy of these approaches has not been conclusive (38,40). A systematic review identified 12 studies published between 1972 and 2000 evaluating the efficacy of confrontational counseling for alcoholism treatment; all of them reported no demonstrated benefits (38).

In summary, my impression is that the compulsive account of addiction described in the BDMA appeared to justify that individuals had no responsibility for the occurrence and maintenance of their addictions. However, evidence in my daily practice suggests otherwise. In fact, my patients do not behave like automatons compelled to consume alcohol or drugs, but can instead exert some degree of control over their consumption.

Youna, is there any evidence of a total loss of control over drug use in animal models of addiction?

YV: There is currently no satisfying evidence of a complete loss of control over drug use in preclinical research. The illusion of compulsion, as defined by an absence of free will (31), may have arisen from an important limitation in most animal models of addiction (41–43). In standard ethanol or drug self-administration settings, animals have no other choice but to use the substances available. In these conditions, is drug use symptomatic of a pathological compulsive state or merely an expectable response to lack of choice (43)? The landmark ‘Rat Park’ study of Bruce Alexander and colleagues, demonstrated that replacing small cages with large naturalistic parks where animals have access to food, play and sex resulted in the preference of plain water over morphine-laced water (44,45). Following this finding, numerous studies have demonstrated that providing alternative nondrug rewards during drug self-administration is sufficient to reduce (or even suppress) drug self-administration (46–50). This was shown with a wide range of drugs (cocaine, methamphetamine, nicotine, alcohol, and heroin) and nondrug rewards (sweet water, food pellets, social interaction, and plain water) under a large array of experimental conditions (46–54). These findings suggest that drug seeking can be considered as a voluntary goal-directed behavior, sensitive to changes in environmental contingencies such as the dose, the price, the delay or the availability of alternative rewards. Thus, theories of addiction viewing maladaptive habits and compulsions as central concepts in the etiology of this disorder are now being questioned in both clinical and preclinical literature (55,56). Instead, addiction is now increasingly conceptualized as a disorder of choice (57,58).

Jean-Bernard, is there clinical evidence that echoes these findings from preclinical research?

JBD: Transposed to humans, the “Rat Park” and choice experiments suggest that remission of addiction in humans is possible when the environment offers interesting alternatives to drug use. There is a large body of research on humans suggesting that the motivation to stop using alcohol or drugs results from the anticipated benefits. For example, in contingency management experiments, subjects receive a financial incentive to stop smoking or reduce alcohol and drug use with positive and robust results across numerous studies (59–61). These studies suggest that patients can exert some degree of control over drug or alcohol use, if circumstances and environmental conditions offer worthwhile alternatives. However, in my experience, contingency management strategies are rarely used to treat addiction. Besides the practical difficulty of implementing them in outpatient settings, part of the problem resides in the fact that, although addiction can be conceived as a disorder of choice, the choice to use or to abstain from using drugs is hard. In my opinion, patients with addictions are prone to strong ambivalence, which is a cardinal feature of addiction.

Ambivalence is characterized by vacillation between the desire to use alcohol or drugs, on the one hand, and regrets when suffering the adverse consequences, on the other hand. In contrast to animals, humans with addictions can verbalize to some degree the feelings and thoughts they experience at different moments in the history of their addiction. In the beginning, subjects do not fight against their progressively increasing consumption. They tend to justify it cognitively (e.g. “I

drink like the others, like everyone else, I love wine, it is part of the social life, etc.”). During this period, consumption is part of a routine, the adverse effects are subtle and the motivation to use alcohol or drugs dominates. As the addiction progresses, the desire for drugs becomes stronger in parallel with the increasing costs experienced (i.e. the social, professional, legal and health issues). Therefore, an internal conflict emerges from the opposition between the desire to use and accompanying negative consequences, which finally results in an ambivalence between using or stopping, as expressed by a patient:

« I like to drink. When I don't have my drink, I miss it and it's all I can think about. But sometimes I think I should stop. I can't stand feeling like this, it's like I have no control. But drinking helps me to relax, it makes it easier for me to talk to people. I don't know what to do, I feel stuck. I want to, but it's driving me crazy»

In the example above, the patient manifests this ambivalence, with immediate advantages of using and not getting into treatment, opposed to the delayed costs of doing it. The ambivalence of using fluctuates rapidly during the day, depending on the level of intoxication or symptoms of withdrawal. Typically, the decision to stop and get into treatment is associated with symptoms of withdrawal, while the decision to use typically follows craving. Therefore, the ambivalence could be illustrated by sinusoidal waves with varying amplitudes and periods. In the above case, we observe that the period of the sinusoidal wave is very short, since the patient expresses in the same sentence that he both wants and does not want to use or to stop using alcohol. Therefore, although addiction can be conceived as a disorder of choice where the drug is preferred over alternative activities, it is probably more precise to conceive of addiction as arising from conflicting decisions resulting in an internal fight, and experienced as feelings of ambivalence.

Youna, do you think that we can explain the neural bases of ambivalence as an opposition between disruption in the brain reward system which explains craving, on the one hand, and alterations in the prefrontal cortex resulting in deficits in top-down executive control, on the other hand?

YV: In fact, the opposition between brain reward circuits and the prefrontal executive system has been suggested to underlie compulsive drug use (29,30,33). Thus, in my opinion, it cannot explain the internal conflict and ambivalent feelings of your patients. In this framework, repeated exposure to addictive substances alters dopamine signaling in mesolimbic and mesocortical circuits, which results in an overvaluation of the drug at the expense of alternative nondrug rewards. In parallel, alterations in the prefrontal cortex result in impairments of top-down executive functions and reduce inhibitory control over drug use (30,32,62). According to this model, alterations at both cortical and subcortical levels contribute to compulsive drug use at the expense of alternative activities and despite negative consequences (Figure 1A). There is no place for ambivalence in this model.

Ambivalence refers to the simultaneous existence of contradictory feelings and attitudes, where individuals feel torn between two alternatives (to use or to abstain). In the choice model presented in Figure 1B, the ambivalence results from competing motivations for the drug and nondrug alternatives, and recurrent choices are made between using and abstaining. Although the positive effects of the drug are immediate, certain and predictable, the benefits of abstinence are hidden to the individual and involve significant delay and uncertainty. This will tilt the balance toward drug use (63). Several regions of the prefrontal cortex are implicated in weighing the options, based on rewards' magnitude, cost, uncertainty and delay, to compute their relative value and carry out a decision (Figure 1B) (64–67). However, when individuals face the negative consequences of their addiction, they experience a mix of positive and negative feelings about their consumption. These emotions of positive and negative valence are encoded in the amygdala (68,69), integrated in the

anterior insula, and transmitted to other prefrontal cortical regions, notably the lateral prefrontal cortex and the anterior cingulate cortex, which in turn contribute to the subjective experience of internal conflict (70).

Importantly, although brain alterations induced by repeated drug exposure are likely involved in the development and maintenance of addiction, they are not required to explain ambivalence in the choice model presented here. Instead, it seems that the characteristics of drug positive effects and the direct experience of negative consequences, combined with the anticipation of long term benefits of abstinence are responsible for ambivalent feelings.

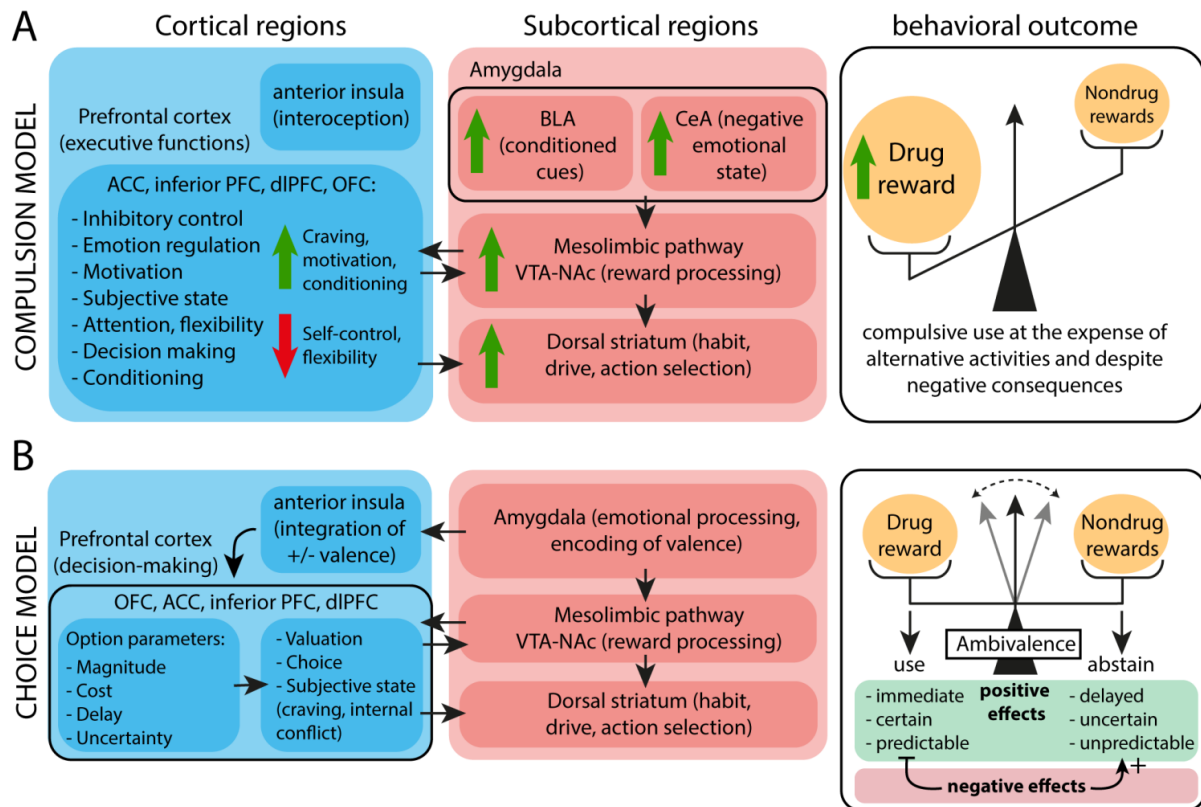


Figure 1. Simplified diagram of neural circuitry associated with compulsion and ambivalence.

A. Compulsion model. Compulsive drug use at the expense of alternative activities and despite negative consequences may involve reward processing and associative mechanisms in the amygdala, striatum and mesolimbic pathway and engages stimulus–response habits that depend on the dorsal striatum. In the amygdala, conditioned reinforcement is processed in the basolateral amygdala (BLA) while the negative emotional state of withdrawal notably engages the central nucleus (CeA). At the cortical level, the anterior insula is involved in interoception, and executive functions depend on the prefrontal cortex. Notably, the OFC, ACC, inferior PFC, and dlPFC are involved in inhibitory control, emotion regulation, motivation, and representation of subjective state, attention, flexibility, decision-making and conditioning. Compulsion is mediated by an imbalance between enhanced reward expectation in the reward, motivation, and memory circuits and reduced self-control in top-down prefrontal circuits, together with impairments in decision-making and emotion regulation. Green and red arrows indicate drug-induced brain alterations.

B. Choice Model. In the choice model, the ambivalence between competing motivations (to use or abstain) could emerge from the imbalance between the positive effects of use and abstinence combined with the experience of negative consequences. Emotions of positive and negative valences are notably encoded in the amygdala at the subcortical level, and integrated in the anterior insula at the cortical level. The anterior insula

projects to different regions of the prefrontal cortex, optimized for options valuation (based on magnitude, cost, delay and uncertainty) and decision-making. Prefrontal regions are also involved in the representation of subjective states such as craving or the feeling of internal conflict. BLA -basolateral amygdala; CeA -central nucleus of the amygdala; VTA -ventral tegmental area, NAc -nucleus accumbens, OFC -orbitofrontal cortex, ACC -anterior cingulate cortex, PFC -prefrontal cortex, dlPFC -dorsolateral prefrontal cortex.

Jean Bernard, would it be possible to target this process and highlight the negative consequences of drug use while emphasizing the positive long-term benefits of abstinence in a therapeutic approach?

JBD: Yes, indeed. This is one of the principles of Motivational Interviewing (MI), which represents another step in the development of therapeutic strategies to address addictions, by focusing on the notion of motivation to change (71). The concept underlying MI is that ambivalence about change – concurrently wanting to make a change while also feeling reticent to do so – is normal and central in addictions. An important consequence of the presence of ambivalence is that clinicians should avoid confronting and voicing arguments in favor of change directly, because this would result in patients showing reticence or voicing arguments for continuing drug or alcohol use, thus reinforcing their current behavior. Recognizing ambivalence allows the clinician to explore it, bringing patients to evoke arguments both favoring change (change talk) and opposing change (sustain talk). The strategic emphasis in MI is on purposefully evoking and reinforcing change talk (i.e. reasons, desire, ability and commitment to change), but also responding to sustain talk in a way that respects it, but does not strengthen or encourage it.

The therapeutic hypothesis of motivational interviewing is that patients need to hear themselves voicing the advantages of change and to encounter their own behavior and personal values in order to develop enough motivation to change. The therapists avoid confrontation and do not force abstinence (confrontational model), nor do they prematurely teach behavioral strategies to avoid craving and relapse (cognitive and behavioral treatment model). Instead, they act as a guide, eliciting patient aspirations and strengths, listening to them in the spirit of acceptance and non-judgement, and supporting their autonomy in decision making. Research indicates that MI technical skills are associated with a higher proportion of change talk, which is predictive of actual change in behavior (72).

It is worth noting that the principles of MI imply that the patients have some ability and therefore some responsibility to change. When the moral perspective on addictions was predominant, the AA/NA philosophy and the brain disease model issued from neurosciences developed a symmetrical counterargument, pointing out the limitation or absence of responsibility to change in individuals suffering from addictions. Currently, a more balanced perspective on the treatment of addiction is possible, in which some degree of autonomy coexists with the ability and responsibility to change. This brings a positive therapeutic perspective, but also has important moral implications. Responsibility to change carries the risk that the person feels guilty for not changing, thus complicating the interactions with significant others and health care providers. In turn, those trying to help someone suffering from addiction, because of this responsibility and ability, might adopt MI non-adherent and counterproductive attitudes such as pressure, threats or constraints. MI therefore requires not only empathy, acceptance and autonomy support from the provider, but also, simultaneous acceptance that the person is responsible for deciding to change, or not.

To conclude our discussion, I think that a better understanding of the physiological processes explaining ambivalence, and, more generally, the mechanisms underlying addiction, is essential for clinicians in allowing them to provide “gentle” psychoeducation to patients. It also permits patients to better understand their ability to resist the strong pathophysiological processes underlying addiction.

Conclusion

Youna, what did you get from this exchange?

YV: Our dialogue reveals that while neurobiological theories of addiction influenced the rationale for addiction treatment, the medicine of addiction can enlighten neuroscience on the reality of drug use in addicted individuals and the interventions most effective at promoting remission. Therefore, this exchange allowed me to more fully comprehend the reciprocal influences and mutual enrichment between the preclinical research and addiction medicine. Furthermore, through this dialogue, I learned about the motivational interviewing approach, which has aroused my interest in the cognitive and neurobiological bases of ambivalence, a topic largely overlooked in preclinical research on addiction. Perhaps this could be explained by the fact that non-human animals cannot report their feelings, as can humans. However, in my opinion, the progress already made in our understanding of decision-making processes using animal models can be extended to the investigation of ambivalence. We can already infer from their behavior whether rodents deliberate (73) or regret (74), and I am sure that future research can find a proxy for ambivalence. It was recently suggested that the translational validity of animal models could be improved with a reverse translational approach consisting of mimicking successful treatment in animals, in order to study the development and recovery from addiction in ecologically-relevant settings (2). In that respect, investigating the neurobiology of ambivalence could represent a new promising avenue for future research. But would it be useful for the treatment of addiction?

Two years ago, Field and Kersbergen published an opinion article in the journal *Addiction*, questioning the relevance of animal models of addiction (1). The authors suggest that preclinical research has “not served us well in understanding and treating addiction in humans”, notably because of the poor translational predictive validity of animal models and the prevailing conceptualization of addiction (emerging from preclinical research) as a disorder of habit and compulsion. Although I agree to some extent with the first point, I strongly disagree with the second, and my opinion is supported by the dialogue presented herein. The compulsive account of addiction conveyed by neurobiological theories of addiction emanating from preclinical research appeared to justify that individuals had no responsibility for the occurrence and maintenance of their addictions; this belief was already in place in addiction medicine, when the brain disease model was first introduced in 1997 (3). Ironically, preclinical research studies often bolster the arguments used by the detractors of the brain disease model to support their claim (43,51,75,76). As for the question “are animal models of addiction useful?”, my answer is yes. Animal models are useful in understanding and explaining the neurobiological and cognitive processes involved in the development and recovery from addictions. Perhaps preclinical research does not contribute to the development of new treatments, but it does play a role in shaping theoretical conceptualizations of addiction and has considerable implications at individual, philosophical and societal levels. It can help improve clinical care, guide the implementation of therapeutic approaches, and strengthen the enactment of drug policies that optimize the desired beneficial outcomes.

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