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COMMENTARY

Negative reinforcement via motivational withdrawal is the driving force behind the transition to addiction

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Piazza and Deroche-Gamonet have significantly contributed to the field of addiction and published several pioneering articles that have had a major influence on the field. The latest article by Piazza and Deroche-Gamonet is a position paper, in which they argue that they provide a foundation for the first general theory of the transition to addiction. Their theory is composed of the following three principles: (1) The transition to addiction depends on an interaction between individual vulnerability and drug exposure. (2) The transition to addiction involves at least three steps (i.e., recreational/sporadic drug use, intensified/sustained/escalated drug use, and loss of control/full addiction). (3) Addiction is a true psychiatric disease. Piazza and Deroche-Gamonet propose to test their "first" general theory of addiction by providing three predictions that can be used to validate or invalidate their theory. The review by Piazza and Deroche-Gamonet represents an excellent opportunity to discuss critical aspects of the transition to addiction. In this article, we attempt to test point by point the validity of their statements based on the current state of the field, with the hope that a better understanding of the addiction process will lead to better treatments for drug addiction.

To test the validity of their claims, as suggested by Piazza and Deroche-Gamonet, it is important to define the criteria that need to be fulfilled for a novel theory to be valid. A scientific theory is a well-substantiated explanation of a phenomenon based on knowledge that has been repeatedly confirmed through observation and experimentation. Its strength is related to the diversity of phenomena it can explain and the accuracy in predicting outcomes. A scientific theory should allow for falsifiable predictions. Finally, a new theory should better explain experimental observations than previous theories and result in further testable predictions that can be confirmed. We will review each principle proposed by Piazza and Deroche-Gamonet based on each of these criteria.

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Principles

First principle

"The transition to addiction results from an interaction between individual vulnerability and the degree/amount of exposure." Although we understand that the topic of individual vulnerability vs. the degree/amount of drug exposure might have been a matter of debate a few decades ago, this relationship has been extensively tested and investigated to the point that it now is safe to say that this is actually not a theory anymore but a law of behavioral neuroscience. Extensive research has repeatedly demonstrated that behavioral phenotypes, including drug-related behaviors, are modulated by the interaction between individual vulnerability (whether genetic or not) and the environment, including drug availability/exposure (e.g., Crabbe et al. 1999; Hughes et al. 2011; Redolat et al. 2009; Verweij et al. 2010; Spanagel 2009; Nielsen and Kreek 2012; Agrawal and Lynskey 2008; Ellenbroek et al. 2005; Caprioli et al. 2007; Nader and Czoty 2005; Ahmed 2005; Volkow and Li 2005).

Second principle

"The transition to addiction is composed of at least three steps: recreational sporadic (ReS), intensified, sustained, escalated (ISuE), and loss of control (LoC)." Although the acronyms

used by Piazza and Deroche-Gamonet are novel, the concept behind them is not. Numerous authors have theorized that the transition to addiction involves the same three steps of *use* (i.e., the initial first step of reinforcement that is recreational and social and involves learning the reinforcing effects of the drug), *abuse* (i.e., the second step of increased seeking, consolidation of learning, and escalation of drug intake), and *dependence* (i.e., the third step with maintenance of escalated intake with loss of control, full addiction, or Dependence). Numerous epidemiological studies have used these three steps of use, abuse, and dependence to characterize the transition to addiction (for details, see Chapter 1, "Definitions of Addictions: Drug Use, Drug Abuse, and Drug Addiction," of Koob and Le Moal 2006). Additionally, below is a non-exhaustive list of authors who have not only included these three steps using different terms but also provided additional steps to better explain the addiction process, including withdrawal and relapse that are essential to the transition to addiction.

- Kreek et al. (2002): (1) initial use of drug, (2) sporadic intermittent use, (3) regular use, (4) addiction, (5) early withdrawal/relapse, (6) protracted abstinence/relapse/sustained abstinence.
- Koob and Le Moal (2006): (1) acute reinforcement/social drug taking, (2) escalating/compulsive use, (3) dependence, 4) withdrawal, (5) relapse/recovery.
- Everitt et al. (2001): (1) vulnerability; (2) the maintenance of drug-taking/seeking behavior, which might be viewed as a dynamic product of the gradual strengthening or "consolidation" of behavior that arises from the reinforcing action of drugs, supplemented by a recurrent shaping of drug-related memories; (3) the eventual progression of addiction to a form of habit-based learning through which voluntary control over drug use is lost; (4) the propensity for relapse of drug seeking/taking, which often occurs after protracted abstinence.
- Kalivas and O'Brien (2008): (1) social use, (2) regulated relapse, (3) compulsive relapse.

Thus, a more reasonable argument is that the general theory proposed by Deroche-Gamonet embraces a concept that has indeed (a) been with us for a long time and (b) evolved substantially. Indeed, the recent elimination of the "abuse" designation in DSM-V is a reflection of the evolution of the hypothesis that addiction represents a continuum of excessive drug-taking, from recreational use to severe Substance Use Disorder.

Third principle

"The transition to addiction is a true psychiatric disease." The overwhelming majority of neuroscientists would agree that addiction is a true psychiatric disorder. The debate between the iatrogenic and psychiatric views of addiction as outlined by Piazza and Deroche-Gamonet has added value, however, in elegantly applying multiple arguments with which to persuade those few academic holdouts and the general public.

In summary, our only objection to the general theory that addiction is a psychiatric disorder that results from an interaction between the individual and the environment that progresses along at least three steps of use, abuse, and addiction with loss of a control over drug intake, is that it is not particularly novel, has already been proposed in numerous articles, and been accepted by the most prominent scientists in the field. Therefore, it is difficult to see how it can better explain experimental observations than previous theories. Piazza and Deroche-Gamonet's general theory provides a well-substantiated explanation of the importance of individual differences, and this specific hypothesis has been repeatedly confirmed through observation and experimentation. The notion of "protection" or what we might call "resilience" is definitely an area for future research.

Predictions

Despite the fact that the three principles proposed by Piazza and Deroche-Gamonet are already well-known facts that are accepted by the overwhelming majority of scientists, let us assume that these principles are novel and test the validity of the three predictions as suggested by Piazza and Deroche-Gamonet. As mentioned by the authors, for a theory to be valid it must provide *falsifiable predictions*; however, when a falsifiable prediction is not possible to be proven wrong by definition, such as "no human lives forever," or is only falsifiable in theory but not in practice, such as "it will be raining here in one billion years," it invalidates the falsifiable prediction and makes a theory unscientific (Popper 2005).

First prediction

"The transition to addiction depends on an interaction between individual vulnerability and drug exposure." The authors specifically state, "variation in the degree of these interactions cannot be seen as a fundamental fallacy of the theory," and that one must prove "that one of these two variables is not necessary in the development of pathological drug use." If variation in the degree of interaction is not a fallacy, then for this prediction to be falsifiable one must demonstrate that drug addiction can occur in an individual without access to the drug or that drug addiction can occur without an individual. By definition, drug addiction requires an individual who has or had access to a drug; therefore, this prediction is unfalsifiable.

Second prediction

"The transition to addiction is a process that develops along at least three steps (recreational, intensified, loss of control)." A

transition is the process of changing from one state to another. There is a minimum of two steps that describe a transition, the original state and the final state. Therefore, for this prediction to be falsifiable, one would have to demonstrate that the transition from drug use to drug addiction is instantaneous without a transition state. While this prediction is falsifiable in theory, it is not falsifiable in practice because chemical and biological phenomena involved in neuronal activity exhibit transitional states. From a simple chemical reaction, such as the change from adenosine triphosphate to adenosine diphosphate, to more complex phenomena, such as the activation of neurotransmitter receptors, the generation of action potentials, the release of neurotransmitters, or neuronal remodeling, all of these phenomena exhibit transitional states.

Third prediction

"The transition to addiction is a true psychiatric disease." The authors add that to falsify their theory, one must "demonstrate that in most conditions drug exposure is both necessary and sufficient to induce addiction." "Most conditions" is a vague term that cannot be tested experimentally; therefore, this prediction is not falsifiable.

As mentioned by the authors, for a theory to be valid, it must provide *falsifiable predictions*, unfortunately the predictions provided by Piazza and Deroche-Gamonet do not appear to be falsifiable. However, the fact that the predictions provided by Piazza and Deroche-Gamonet are not falsifiable does not mean that they are not relevant. We agree with the statements that addiction results from the interaction between the individual and the drug, that it develops along at least three steps, and that it is a true psychiatric disease, but these are not falsifiable predictions, and we encourage the authors to elaborate more specific predictions that can be tested experimentally.

Where we disagree … somewhat

Embracing hedonic allostasis but discarding "withdrawal"

Piazza and Deroche-Gamonet state, "we have not proposed as relevant models of transition to addiction important drug–induced physiological adaptations, such as tolerance or withdrawal, which are diagnostic criteria for SUD but are not necessary or sufficient conditions for a diagnosis of the disease." While we agree that these adaptations are not necessary or sufficient for the diagnosis of Addiction, it is important to realize that the diagnostic criteria in the DSM-IV or DSM-V are not relevant to the understanding of the mechanisms that underlie the progression of a disease. One can imagine that the best clinical symptom(s) to identify an individual with a specific disease may be a mere consequence of reaching the ultimate stage of the disease and unrelated to the cause of the transition to the ultimate stage of the disease. Clinicians know that the earlier a disease is treated, the better the outcome. By focusing on only a sufficient criterion (loss of control) and excluding neuroadaptations and behaviors that are critical for the pathological process (tolerance, withdrawal, and bingeing), one risks missing the unique neuroadaptation that is actually causing the transition to addiction before the clinical symptoms have fully developed and that could be the target of novel treatments, particularly for individuals who have a history of abuse, but fail to meet the diagnostic criteria for severe substance-use disorder. The National Institute of Mental Health (NIMH) already recognized the fallacy of excluding biological adaptations based on DSM criteria by no longer funding research projects that rely exclusively on DSM criteria, and we strongly encourage researchers to investigate phenomena that precede the loss of control over drug intake. Moreover, tolerance and negative emotional states during withdrawal are particularly important phenomena that deserve special attention. Even if they are not sufficient or necessary criteria to characterize addiction, they are phenomena that represent a powerful driving force to increase the motivational properties of drugs of abuse. While we agree with the authors that physical withdrawal is not necessarily observed in all drug addicts, it is important to understand that withdrawal is a multifaceted phenomenon that includes both physical and emotional symptoms and that drugs of abuse that were considered to be associated with very little if any physical withdrawal, such as cocaine or marijuana, are now known to be associated with a very strong emotional withdrawal, including anxiety, irritability, and hypohedonia (D'Souza and Markou 2010; Budney et al. 2004) that not only provide a driving force to loss control over drug intake through negative reinforcement (Cohen et al. 2013) but also represent potential vulnerability for individual differences for the transition to addiction (Koob et al. 2013, 2014; George and Koob 2010). Disregarding animal models that emphasize emotional withdrawal would be a critical error that would most likely delay progress on the neurobiological mechanisms that underlie drug addiction and the development of novel therapeutic strategies. Indeed, we would further argue that the state of loss of reward in hedonic allostasis to which Piazza and Deroche-Gamonet refer and the state of "mourning" to which they refer are indeed simply what we have hypothesized for over 15 years as "motivational withdrawal." While Koob and colleagues have been unable to extricate the colonic

blockage of "physical withdrawal" from the metabolism of theories of addiction, we keep trying. Indeed, we are heartened to see it replaced by hedonic allostasis and mourning.

What happened to the brain stress systems?

Piazza and Deroche-Gamonet repeatedly invoke negative reinforcement in the form of self-medication as a mechanism for enjoying the pleasures of drug taking in the human population. However, they fail to bridge this construct to the transition to addiction. For example, they wrote, "One of the most easily identified functions of drugs is their stress relieving and anxiolytic effects, which certainly have an important role in helping individuals function in most human societies that are largely very demanding, often unjust, and practically never egalitarian." While they elegantly and correctly outline the allostatic view of addiction of Koob and Le Moal, they leave out half of the story. We have argued, with some substantial evidence, that as dependence and withdrawal develop, brain anti-reward systems, such as corticotropin-releasing factor (CRF), norepinephrine, and dynorphin, are recruited in the extended amygdala to produce a negative emotional state from the side of stress, malaise, and pain that we believe also accounts for a significant amount of motivational withdrawal or what Piazza and Deroche-Gamonet call "mourning." For example, extracellular CRF in the extended amygdala is increased during acute withdrawal from drugs of abuse. Critically, CRF receptor antagonists injected into the extended amygdala block the anxiety-like effect of drug withdrawal and blunt excessive drug taking during escalated drug taking with extended access (Koob 2003). We have hypothesized for over 15 years and demonstrated that the brain stress neurotransmitter CRF, which is known to be activated during the development of excessive drug taking, comprises a between-system opponent process. This activation is manifest when the drug in removed, producing anxiety, hyperkatifeia, and irritability symptoms associated with acute and protracted abstinence (George et al. 2007; Edwards et al. 2012; Cohen et al. 2013). Recent data show that blockade of the κ opioid system can also block the aversive stimulus effects of drug withdrawal and stress, and excessive escalated drug self-administration can also be blocked by κ antagonists (Koob 2013; Chartoff et al. 2012; Walker et al. 2011; Wee et al. 2009; Schlosburg et al. 2013). These effects may be mediated by the shell of the nucleus accumbens (Nealey et al. 2011; Schlosburg et al. 2013) and central nucleus of the amygdala (Gilpin et al. 2013; Kallupi et al. 2013). These results suggest a within-/between-system neuroadaptation that was originally hypothesized by Carlezon and Nestler (Carlezon et al. 1998), in which activation of CREB by excessive dopamine and opioid peptide receptor activation in the nucleus accumbens trigger the induction of dynorphin to feedback to suppress dopamine release. Thus, anti-reward circuits are recruited as between-system neuroadaptations (Koob and Bloom 1988; George et al. 2012a, b) during the development of addiction, producing aversive or stress-like states (Nestler 2001; Koob 2003; Aston-Jones et al. 1999) via two mechanisms: direct activation of stress-like, fear-like states in the extended amygdala (CRF–norepinephrine) and indirect activation by suppressing dopamine (dynorphin).

Classification of the model of escalation of drug intake as an animal model that precedes the transition to loss of control

Piazza and Deroche-Gamonet define the animal model of escalation of drug intake after extended access to the drug developed by Ahmed and Koob (1998) as being an animal model of "intensified–sustained–escalated use" that has no relevance as a model of "loss of control of drug use or full addiction." If we follow the authors' own *logic*, then an animal model of the full addiction stage must meet the criteria for drug addiction developed in the DSM-IV and now in the DSM-V. By analogy, the escalation model in our laboratory and other laboratories has been shown to exhibit seven of the seven items in the DSM-IV and seven of the 11 items in the DSM-V, including most of the criteria required for severe use disorder: (1) tolerance (Ben-Shahar et al. 2005), (2) withdrawal (Ahmed et al. 2002; Vendruscolo et al. 2011), (3) substance taken in larger amount than intended (Ahmed and Koob 1998), (4) unsuccessful efforts to quit (Ahmed and Cador 2006; Lenoir and Ahmed 2007), (5) considerable time spent to obtain the drug (Wee et al. 2008), (6) important social, work or recreational activities given up because of use (George et al. 2008; Vendruscolo et al. 2011; Lenoir et al. 2013), (7) continued use despite adverse consequence (Xue et al. 2012; Vanderschuren and Everitt 2004; Vendruscolo et al. 2011; Vendruscolo et al. 2012; Seif et al. 2013; Lenoir and Ahmed 2007; Ahmed 2012). Clearly, after significant escalation of drug intake, this is an animal model of loss of control over drug intake. Even more than that, we believe that when taken as a whole it is one of the most useful animal models to date to study the transition to addiction as one can investigate the three different steps of use (initial limited access), abuse (escalation of intake), and addiction (escalated intake) in the same paradigm. However, and in contrast to Piazza and Deroche-Gamonet, we do not believe that our animal model is the only relevant model to study the compulsive aspect of drug addiction or is a perfect model of drug addiction in humans. Other groups, including Piazza, Ahmed, Wise, Roberts, and Miczek, to name a few, have generated very interesting animal models that capture different aspects of

compulsive drug intake (Morgan et al. 2005; Ahmed 2012; Tornatzky and Miczek 2000; Deroche-Gamonet et al. 2004).

We agree with Piazza and Deroche-Gamonet that the transition to addiction requires two types of vulnerability, one for the abuse of drugs and one for the loss of control of intake. We predict that these two types of vulnerabilities can be detected by analyzing the change in cocaine intake in rats during the transition from limited to extended access to drugs. Contrary to Piazza's theory, we predict that the escalation of drug intake in this animal model will be associated with not only a quantitative change but also a qualitative change in drug intake. We also predict that escalation in drug intake is not attributable to an increase in the initial vulnerability to take the drug but rather in the loss of this initial vulnerability and development of a new vulnerability of loss of control over drug intake that follows the switch from positive to negative reinforcement.

A somewhat myopic view of the biological bases of loss of control

The authors state, "the only biological modification yet specifically associated with loss of control of drug intake is a loss of synaptic plasticity." We have demonstrated above that rats in the escalation model exhibit all of the criteria required for addiction, including loss of control. The authors ignore a vast amount of literature showing neuroadaptations in animals that exhibit the escalation of alcohol, nicotine, cocaine, methamphetamine, and heroin intake. For instance, 100+ articles from at least 19 different laboratories, including G.F. Koob, T.E. Robinson, J. Mantsch, K.A. Miczek, C.M. Weiss, R.E. See, S.R. Jones, R.M. Carrelli, M. Marinelli, P.J. Kenny, M.T. Bardo, M. Roberto, A. Ettenberg, L.H. Parsons, S. H. Ahmed, B.M. Walker, N.W. Gilpin, C.D. Mandyam, P.V. Piazza, V. Deroche-Gamonet, and O. George, have been published using the escalation model, including biological measures also observed in humans, such as reduced dopamine function (Briand et al. 2008; Schwendt et al. 2009), hypofrontality (George et al. 2008; Briand et al. 2008; George et al. 2012a, b; Meinhardt et al. 2013), and most importantly from our perspective, changes in extrahypothalamic and neuroendocrine stress systems (Adinoff et al. 1990; Vendruscolo et al. 2012). Indeed, the finding that gabapentin, a drug that was first found to be effective in reducing alcohol drinking in rats with escalation of alcohol drinking in a dependence model and had a profile in the central nucleus of the amygdala similar to a CRF_1 antagonist (Roberto et al. 2008), was recently found to also be effective in humans with alcohol dependence (Mason et al. 2013) demonstrates the predictive validity of the escalation model for the loss of control over drug intake. Piazza and Deroche-Gamonet missed this literature. While we all focus on our own piece of the addiction cycle, general theories of addiction need to cast a broader net of conceptual frameworks.

Percentage of vulnerable individuals

The authors state that their animal model of loss of control exhibits the same percentage of vulnerable animals (~15–20%) as in humans. This fact is used as a powerful argument for face validity. Moreover, they argue that extending access to the drug (escalation model) does not increase the percentage of rats that show loss of control, making it an argument in favor of their theory that escalation of drug intake is not associated with loss of control. Unfortunately, there are two major problems with their analysis. First, the percentage of animals with loss of control is mathematically predetermined by the fact that they use three behaviors that are highly correlated with each other (typically with R=0.80–0.90) and that they use a cut-off of the upper ~35 % to diagnose a positive criterion. Therefore, the percentage of animals with loss of control is mathematically restricted to a very narrow range of values. To demonstrate this point, we generated normally distributed random numbers using the Box–Muller transformation (Mayes 2010) and simulated the percentage of animal with loss of control (LoC) depending on the correlation coefficients between the three behaviors using the same threshold (35 %) used by Piazza and Deroche-Gamonet. The results are the following: R=1.0, LoC=35 %; R=0.97, LoC=29 %; R=0.87; LoC=22 %; R=0.35, LoC=10 %. Our simulation found a very similar level of LoC animals (~22 %) when using correlation coefficients similar to Piazza and Deroche-Gamonet's studies (R=0.87). Combining this simulation with a χ^2 power analysis (power=0.8, alpha=0.05), one would require 626 rats per group to obtain a significant difference between 22 % and 29 %. Therefore, it is virtually impossible to demonstrate any increase in the percentage of rats with loss of control using their model. The fact that resistance to punishment may follow a bimodal distribution will not change this fact. The reason why Piazza and Deroche-Gamonet found this percentage to be very resistant to changes, including extending access to the drug, is not because the escalation model is not associated with loss of control, and it is not because it is a true measure of who is vulnerable to the loss of control. It is because it is a biased measure that is mathematically constrained to produce a very restricted range of values close to what the authors believe to be the percentage of individuals who are vulnerable to loss of control in humans. The second problem is that we believe that the authors are incorrect when they compare the percentage of users who become addicted in humans and rats while having two completely different environments. If humans were locked inside their homes with legal and free chronic daily access to drugs as the only daily activity, with no access to any alternative reinforcers other than water and bland food, then it would be extremely surprising if the percentage of drug-addicted users would stay at ~20 %. Moreover, recent statistics indicate that the percentage of individuals who meet the criteria for Substance Use Disorders of

those who ever used during the past year ranges from 9.8 % for alcohol to 65.5 % for heroin. The only drug in the 20 % range is cocaine (Koob et al. 2013, 2014).

In conclusion, the theory developed by Piazza and Deroche-Gamonet is not exceedingly novel. Indeed, its major premise is widely accepted in academia in the United States. While we agree with most of their analysis of the literature, we strongly disagree with their view that only animal models that reflect the DSM-IV/V are relevant for the transition to addiction. The key to solve the enigma of drug addiction is not whether we can produce addiction in every single individual, whether there is more than two steps in the transition to addiction, or whether addiction is a psychiatric disorder. All of these questions have already been answered. The keys to solve this enigma are (1) to investigate neuroadaptations associated with different aspects of the transition to addiction, including incentive-salience, tolerance, motivational withdrawal, escalation, cognitive impairment, and loss of control, not only over drug intake but also loss of control over emotion, stress, and pain; (2) to determine the neuronal networks and plasticity (or lack thereof) that mediate the vulnerability to seek and take drugs at every single step of the addiction process as well as relapse after abstinence; (3) to develop novel therapeutic approaches that can reduce compulsive drug seeking and taking in individuals with addiction and return the brain motivational systems to homeostasis; and (4) to use various animal and human models for every stage of the addiction process to identify resistance to the transition to addiction and provide an evidence-based approach to prevention.

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