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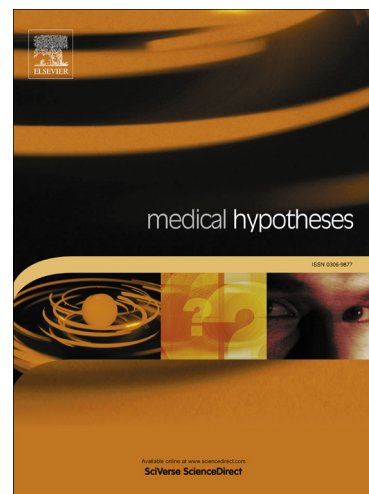Enrico Patrono, Antonella Gasbarri, Carlos Tomaz, Hisao Nishijo

Transitionality in Addiction: a "Temporal Continuum" Hypotheses Involving the Aberrant Motivation, the Hedonic dysregulation, and the Aberrant Learning.

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Abstract

Addiction is a chronic compulsion and relapsing disorder. It involves several brain areas and circuits, which encode vary functions such as reward, motivation, and memory. Drug addiction is defined as a "pathological pattern of use of a substance", characterized by the loss of control on drug-taking-related behaviors, the pursuance of those behaviors even in the presence of negative consequences, and a strong motivated activity to assume substances. Three different theories guide experimental research on drug addiction. Each of these theories consider singles features, such as an aberrant motivation, a hedonic dysregulation, and an aberrant habit learning as the main actor to explain the entire process of the addictive behaviors. The major goal of this study is to present a new hypotheses of transitionality from a controlled use to abuse of addictive substances trough the overview of the three different theories, considering all the single features of each single theory together on the same "temporal continuum" from use to abuse of addictive substances. Recently, it has been suggested that common neural systems may be activated by natural and pharmacological stimuli, raising the hypotheses that binge-eating disorders could be considered as addictive behaviors. The second goal of this study is to present evidences in order to highlight a possible psycho-bio-physiological superimposition between Drug and "Food Addiction". Finally, interesting questions are brought up starting from last findings about a theoretical/psycho-bio-physiological superimposition between Drug and "Food Addiction" and their possibly same transitionality along the same "temporal continuum" from use to abuse of addictive substances in order to investigate new therapeutic strategies based on new therapeutic strategies based on the individual moments characterizing the transition from the voluntary intake of substances to the maladaptive addictive behavior.

1. Introduction

Addiction, from the Latin "addictus" ("slave to debt" or "subjugate"), is a chronic compulsion and relapsing disorder that affects people more psychologically than physically. It is a chronic condition involving several brain areas and circuits, which encode several functions such as reward, motivation and memory. An addict gradually focuses most of his energy on the searching for, finding, and subsequently obtaining and using substances of abuse. This happens even in spite of illness, failures in life and disrupted relationships.

Recently, addiction was defined in DSM-V as a "pathological pattern of use of a substance" characterized by the loss of control on drug-taking-related behaviors, the pursuance of those behaviors even in the presence of negative consequences, and a strong motivated activity to assume substances [1]. The loss of control, the pursuance, and strong motivated activity to assume substances can be analyzed and conceptualized from psychological to biological-molecular level.

Three different theories guide experimental research on drug addiction [2-4]. Each of these theories consider singles features, such as an aberrant motivation [2], a hedonic dysregulation [3], and an aberrant habit learning [4] as the main actor to explain the entire process of the addictive behaviors. The major goal of this study is to present a new hypotheses of transitionality from a controlled use to abuse of addictive substances trough the overview of the three different theories, considering all the single features of each single theory together on the same "temporal continuum" from use to abuse of addictive substances.

Here we overview three major psychological hypotheses that try to explain the passage from casual use to abuse of pharmacological substances: the Incentive-Sensitization Theory, the Hedonic Dysregulation Theory, and the Habit-Based Learning Theory.

1.1 The "incentive-sensitization" theory

In accordance with this theory, repeated drugs of abuse exposition triggers "sensitivity" in the brain making them more attractive or desirables. This can lead to a commitment to obtain drugs even in shortage of drug-induced delight, explaining the phenomenon of relapse.

In psychology, motivation is generally considered the internal condition that guides and modulates the behavior of an individual, toward a goal. The psychological processes guiding addiction behavior can be studied through motivational notions, understanding which brain systems are involved. Compulsive drug seeking/taking behavior and relapse (throughout exposure to stimuli associated with the substance or due to stress) are attributable to a change in the motivational system and the appetitive phase (wanting). Berridge and Robinson explained this phenomenon with the "Incentive-Sensitization Theory" [2]. They suggest that chronic use of a drug leads to increasing neurological change within the reward system, sensitizing the system to drugs and associated stimuli. The enhancement of drug-stimuli pairings increases the incentive value of the stimuli, producing a "transitionality" in drug users that *want* drugs, even though they don't get the *like* from them [5] (Figure 1). Figure 1 shows how *liking* and *wanting* can follow different psychological/brain pathways through the difference in memory comparison. Although this theory explains many aspects of human addiction, such as the excessive search for a drug, intense craving, and relapse, it cannot solely explain the main feature of drug addiction: the inability of addicts to regulate or stop the use of a drug, despite negative consequences and the self-destructive nature of its prolonged use. Drug addiction is a complex psychopathology characterized, at least partly, by drug-induced pleasure, drug-associated memories, and drug-related emotional traits that are connected to the "liking" stimuli [6-7]. An imbalance of both "wanting" (e.g. incentive-sensitization) and "liking" can have a role in the induction of addictive behaviors [8]. However, even though this theory does not reject drug-induced pleasure, withdrawal, or habits as reasons for the drug seeking/taking behavior, it hypothesizes that other factors, such as a sensitized *wanting*, could better explain compulsion and relapse in addiction.

1.2 The "hedonic dysregulation" theory

This theory suggests that the spiral into addiction occurs by passing through three stages: "preoccupation/anticipation", "binge/intoxication", and "withdrawal/negative effect" [9].

The role of "sensitization" in addiction has been explained as a smooth move to an "incentive-

salience" state. Initial use is promoted by the hedonically rewarding properties of the drug, such as a euphoric high, while addictive use is hypothesized to grow by "negative reinforcement" [10]. Negative reinforcement is a process by which discharge of aversive stimuli, such as a negative emotional state of withdrawal, increases the number of drug intake [3]. In order to avoid dysphoria and discomfort, drug users take pharmacological substances [11]. However, drug users proceed from casual use to addiction, and the factors promoting "transitionality" in drug use are hypothesized to shift from impulsivity in the early periods, to compulsivity in last periods. Craving (an intense and powerful desire) has a crucial role in addiction, and is considered a part of the three components: "preoccupation/anticipation", "binge/intoxication", and "withdrawal/negative effect" [10]. The three stages are interactive with each other, deepening in intense, dysregulating the hedonic homeostasis of reward system, and finally bringing the user to addiction [3, 10] (Figure 2). Figure 2 describes the top-down addiction cycle in which the "preoccupation/anticipation" stage as an overwhelming urge to use drugs even if his or her life are plenty of responsibilities and human relationships. The "binge/intoxication" stage specifies the necessity of big amounts of drugs in order to experience the same level of hedonic effects. "Withdrawal/negative effect" refers to the psycho-physical effects induced by the absence of a continuous drug use, that need medical care (e.g. pharmacological use of methadone).

The hedonic dysregulation theory elucidates the passage from use to abuse of drugs such as a "top-down vicious circle", considering the key role of a sort of imbalance in hedonic status of drug users [3]. However, the theory cannot solely explain the role of other main features of drug addiction such as an abnormal sensitization to the substance and the instrumental behaviors to obtain the substance. The mesolimbic reward circuit was originally believed to encode simply the hedonic impact related to drug experiences. Recently, it is considered that this circuit is functionally more complex, encoding attention, expectancy of reward, and incentive motivation [12].

1.3 The "habit-based learning" theory

In the real world, drug users need to stock up on drugs where normally drugs are not easily

available. Neuroscience research has placed special emphasis on this fact [13]. This concept led to the establishment of an animal model of drug-seeking/taking behavior where the sensitivity is due to the relationship between instrumental behavior and drug administration. In fact, drug-associated stimuli with a strong effect on behaviors does play a key role in addiction development [14-15]. Because the drug-seeking behavior occurs before the drug infusion, it has been shown that drug-seeking behavior is not affected by any pharmacological effects of the drug [16]. The fact that the drug seeking behavior can still be present when the drug are not delivered led to the argument that drug-seeking behavior depends instead on the brief presentation of "drug-associated cues". However, drug-seeking/taking behavior depends not only on direct cues, but also on highly complex cognitive processes such as attention, expectancy of reward, disconfirmation of reward expectancy, associative emotional memories, instrumental learning, and incentive motivation. Further, other cognitive processes, such as the evaluation of contexts in which drug-associated-cues are presented [12]. The animal model of drug-seeking/taking behavior provides a chance to study the brain mechanisms of "cue-associated" drug seeking. Furthermore, it is also useful in addressing new potential treatments that would decrease cue-associated drug seeking. The seeking/taking drug behavior and compulsive drug intake, in spite of adverse consequences are the behavioral features that define a "transitionality" idea in drug addiction from use to abuse of substances. When desire becomes a need, the subject acts out a different kind of behavior that leads him or her to take substances. "Goal-directed behavior" and "habit learning" perform two ways of "instrumental learning": the first way is rapidly acquired and tuned by the resulting outcomes; the second way is more intentional, and provoked by antecedent stimuli more than by their aftermaths [17]. The psychobiology of drug addiction identifies a "transitionality" in these behaviors, considering the first one as simply aberrant, and the second one as pathological.

Everitt considers drug addiction the final stage of several transitional steps from the initial and controlled use of a substance [13, 18-19] (Figure 3). Figure 3 describes the following steps through the drug addiction. When the substance is taken voluntarily for its incentive effect, seeking-behavior

progressively becomes a "habit", through a gradual loss of control. Thus, the stimulus-response mechanism plays a crucial role in the maintenance of an instrumental behavior. Finally, the capacity of the stimulus (substance) to act as reinforcement (conditioned reinforcer) exerts a kind of control over the seeking/taking behavior. Thus, drug addiction may start as a "goal-directed behavior"; later, with the maintenance of the "instrumental behavior", it could turn into a "habitual behavior", inducing a form of learning based on the habit (habit-based learning) [13, 16, 18].

2. A "Temporal Continuum" Hypotheses Involving the Aberrant Motivation, the Hedonic dysregulation, and the Aberrant Learning.

Three major theories guide the experimental research in the field of drug addiction. The Incentive-sensitization Theory states that "aberrant motivation" to seek and take drugs could characterize addiction, and considers that "wanting" plays a major role in addiction development. The Hedonic Dysregulation Theory defines a top-down spiraling, from use to abuse of drugs, and focuses on the role of dysregulation in hedonic homeostasis, taking into account a crucial role of a "liking" dysregulation. The Habit-based Learning Theory highlights the role of an instrumental learning behavior that becomes habit, in order to explain the complex use/abuse transition in the drug seeking/taking behavior, and places equal weight on the roles of both "liking" and "wanting".

This study aims to evaluate the three major theories of drug addiction from a new perspective of unity, through the theoretical hypotheses of a unique "temporal continuum" in which an "aberrant motivation", a "hedonic dysregulation", and an "aberrant learning" lie together in order to explain the transition from an occasional use to abuse of drugs (Figure 4). Figure 4 shows a hypothetical time-line in which the three major features are defined as a single "temporal continuum" from the first meet with the drugs to the addiction itself. A large body of literature assessed very well the role of each one of the three theories in drug addiction. Moreover, it has been defined that a progressive shift occurs from habit-driven to motivated-driven drug-seeking/taking behavior in which a hedonic dysregulation is firstly induced during habit learning and continues with the aberrant motivation to use drugs. The Pavlovian-Instrumental Transfer (PIT) design takes into account two conditions: 1)

the Pavlovian processes that define sensitivity to the eventuality between a stimulus (S) and the reinforcers (R); and 2) the instrumental behaviors sensitive to the eventuality between active responses (R), and outcomes (O) [20-21]. Neuro-bio-physiologically, this corresponds to a progressive shift from ventral to dorsal striatal control over drug-seeking/taking behavior [12]. Hence, it is possible to consider a unique "temporal continuum" in which 1) a progressively aberrant "habit-learning" occurs during casual drug use, wherein a "hedonic dysregulation" is activated and 2) lead to a progressively aberrant "salience-incentivation" inducing the drug-taking behavior. However, to our knowledge, there are no evidences of a unitary vision of the three theories through the "temporal continuum" hypotheses. Several human and animal studies have demonstrated that the time of reward has a strong role in reward processing [22-23]. Furthermore, time windows and "reward rates" are of crucial importance for conditioning, and DA neurons are crucially involved in the processing of temporal information about the rewards. At a clinical level, this would also help to understand how and when to intervene along the temporal continuum from occasional use to abuse of pharmacological substances, and to produce new therapeutic strategies in order to avoid the insurgency of the pathological drug-seeking/taking behavior. Finally, motivation, hedonic dysregulation, and habit-based learning can be considered singular parts of a unique and complex drug-seeking/taking behavior.

3. Neuro-bio-physiological background of Drug Addiction "temporal continnum" hypotheses.

Besides the behavioral criteria described above, several studies have drawn a connection between neural circuits activated in the drug-seeking/taking behavior. It is important to note that drug abuse activates several "cortico-subcortical" brain areas and neurotransmission circuits that are involved in the "drug-reinforcement". In order to confirm the hypotheses that the three features enhanced in each single theory can lie in a single "temporal continuum" describing all together the passage from use to abuse of substances, neural basis of a drug-motivated behavior and a drug-habit-learned behavior will be revised.

3.1 The neural basis of a drug motivated behavior

Different studies in the neurobiology of addiction uphold the concept that dopamine (DA) transmission plays an important role in motivational control. The most clearly established mechanism in drug intake is the activation of the DA-associated link in brain reward circuitry [24-26]. The major sites of these neuroplastic changes are thought to be the mesolimbic and nigrostriatal DA-ergic circuits. It has been demonstrated that enhanced DA-ergic transmission in Nucleus Accumbens (NAc) mediates the drug addiction-related rewarding/reinforcing effects [4, 11, 27-29]. The NAc contains two functionally distinct sub-nuclei, termed the "shell" and the "core". Ventral Tegmental Area (VTA) and NAc shell have mutual DA-ergic innervations that are important in the motivational salience modulation and concur to the formation of learned associations between motivate events and contingent environmental perceptions [30]. Neurochemical lesions of the NAc DA-ergic pathways or receptor-blocking drugs reduces *wanting* to eat, but *liking*-related facial expressions for the same reward are not reduced [5, 31-32]. Furthermore, extracellular DA in the NAc is increased by opiates [27] and incentive motivational system in mesolimbic DA-ergic in drug-seeking behavior is reinstates by drug priming [5]. Besides, NAc shell and VTA depletions abolish the reactivation of an extinguished CPP (Conditioned Place Preference) by morphine priming [33], indicating that DA projections from the VTA throughout the limbic system are related to a motivationally relevant event [5, 34]. Adaptive behavioral responses to the motivational situation occur under DA release, inducing cellular changes that establish learned associations with the event [35]. By contrast, in a repeated drug administration, DA release is no longer induced by a particular event, as a motivational event becomes familiar by repeated exposure [36]. For this reason, the behavioral outcomes still "goal-directed" and "well learned", making not necessary further DA-induced neuroplastic changes.

In contrast, the NAc "core" seems to be a crucial site that mediates the learned behaviors expression responding to stimuli that predict motivationally relevant events [30, 37-39]. Moreover, the expression of adaptive behaviors are likely modulated by DA release in NAc core during responses to stimuli predicting a rewarding event [40-41]. In sum, DA might have two functions and might be

crucial in "transitionality" from occasional drug use to abuse. The first alarm the organism to the apparition of new salient stimuli, and after induces learning neuroplasticity. The second is to alert the organism to the imminent apparition of an accustomed relevant event, and motivated on the basis of learned associations previously made through environmental stimuli-event prediction [42]. Finally, a series of parallel cortico-striato-pallido-cortical loops have been defined where the ventral striatum (VS), including NAc core is related to emotional learning; and the dorsal striatum (DS), including NAc shell is related to cognitive and motor functions [43-44].

3.2 The neural basis of a habit-learning drug behavior.

Accumulating evidences suggest that basolateral amygdala (BLA) and the NAc core have a crucial role in separable neurochemical mechanisms underling drug-seeking behavior preserved by conditioned reinforcers [21, 45-48]. The BLA complex performs fundamental roles in memory formation and storage linked with emotional events [49-50]. Moreover, it is involved in appetitive (positive) conditioning [51]. Distinct neurons respond to both positive and negative stimuli, but they do not group into clear anatomical nuclei [52]. Studies report that infusions in BLA of DA receptor antagonists impeded a "CS-induced reinstatement" of after-extinction outcomes [53]. This could mean a key role of DA-ergic transmission in the BLA in drug-seeking/taking behavior. Consistent with these observations, during the response-dependent presentation of conditioned stimuli, DA efflux from NAc core was not increased in a reinstatement procedure [38, 54], whereas glutamate (GLU) efflux was increased in the NAc core of animals during active cocaine-seeking [55]. Finally, a combined "cues+drug-primed" reinstatement conditions showed that increased DA and GLU efflux in the medial prefrontal Cortex (mpFC) and NAc plays a role in promoting reinstatement, and might be an important mediator of "transitionality" in drug-seeking behavior, primed by "multiple relapse triggers" [56]. Taken together, these findings suggest that the transition from use to abuse in drug-seeking/taking behavior could depend on the "drug-associated conditioned reinforcers", which in turn, may depend on DA-ergic transmission in the BLA and GLU-ergic transmission in the NAc core, and together in the mpFC.

This raises the question of whether these selective neurochemical transmissions in the BLA and NAc core are parts of a brain subsystem within "limbic cortical-ventral striato-pallidal" circuitry [57.]. In part, because the technique of the so-called "disconnection", DS and VS interact with each other serially, in a wide range of functional settings, such as PIT on goal-directed behavior [21]. For long time, the VS has been suggested to keep in connection emotion, motivation, and action thanks to its major connections between structures such as the BLA and the orbitofrontal cortex (oFC) [21, 57-58]. The NAc core is important in Pavlovian conditioning, as well as during interactions in "pavlovian-instrumental" learning mechanisms related to involuntary behavior [21, 38, 45]. Conversely, it has been defined that DS has a role in cognitive and motor functions, giving a neurobiological base for both *goal-directed* and *habitual control* of "instrumental learning" [59-62]. Pavlovian-instrumental learning sequential steps could be crucially important in the transitionality from occasional drug use to abuse, that could also involve compulsive drug-seeking/taking behavior [13].

Recently, several experimental and functional observations support the idea of common neural circuits forming a distinct entity into the basal forebrain, termed the "Extended Amygdala". This circuit may be delegated to act on the motivational, emotional, and habitual effects of drug addiction [63-66]. The extended amygdala is comprised of several basal forebrain structures such as the bed nucleus of the stria terminalis (BNST), the central medial amygdala (CeA), and the NAc shell [63-64]. These structures have similarities in morphology, immunohistochemistry, and connectivity [65-66], and they receive afferent connections from limbic structures such as the hippocampus (HP), and BLA. Extended amygdala has key parts that include neurotransmission systems associated with the "positive reinforcing effects" of drugs of abuse, and other major structures related to brain stress systems and associated with the "negative reinforcing effects" of drug addiction [63, 67]. Thus, further studies could investigate the role of extended amygdala in the transitionality from use to abuse of drugs.

4. A new parallel addictive behavior.

Over the past decades, the way of eating has changed dramatically. Among the historical changes that have characterized the last century, Western Countries are assisting to a set of changes in food culture, which have revealed a tendency to consume more frequently and more heavily those foodstuffs once considered rare and valuable. The prevailing tendency to eat more than necessary, often accompanied by significant imbalances between the various components of the diet, has led to a higher incidence of eating disorders (ED). More recently, the hypotheses that several of the same brain systems and neurotransmission circuits are involved in the rewarding effects related to foods and drugs has been suggested. It is conceivable the switching from the same neural systems in food and drugs [68-70], raising the hypotheses that binge-eating disorders could be considered as addictive behaviors. Here, we revised studies showing the possibility to study the key features of eating disorders, such as compulsive eating, with the paradigms used in drug addiction pre-clinical research.

4.1 The legitimacy of the term "Food Addiction"

In the field of the psychobiology of addiction, the number of studies about dependence from both pharmacological and natural substances has significantly increased in the last years. Recently, behavioral/physiological research on addiction has moved the focus on the possibility of different forms of addiction to various stimuli, such as chocolate, sex and gambling [71-74]. On the other hand, some studies pointed out some critical issues about the variety of certain substances addictive potential and the necessity to define specific features of those addictive foods [75]. However, it was observed that in some circumstances, the powerful capabilities of these reinforcing stimuli can lead to behavioral changes (sensitization of brain reward system, increased motor response and motivation) and neurochemical changes (mesolimbic DA-ergic system) similar to those induced by substance abuse [76-78]. Experimental models have been created to study the shift from use to abuse of different kinds of substances [71, 77, 79-82]. In particular, the excessive consumption of foods rich in sugar has contributed, together with other factors, to an increase of cases of obesity [77].

Compulsive eating, is very similar to compulsive drug intake [78], and compulsive eating might be considered an "addiction" in its own right. Studies in humans and laboratory animals showed that, aside to energy balance, eating behavior is regulated by factors unrelated to metabolic control and data from clinical studies suggest that some over-eaters can develop addictive-like behaviors when they consume pleasurable foods [26, 83]. It has been proposed that overeating of palatable food may produce long-term neuroadaptations in the reward and stress networks of the brain [10, 84], similar to those produced by long-term drug abuse [26]. Taken together, these evidences suggest that compulsive eating, as well as compulsive drug-seeking can be explained using the same three major theories driving the experimental research on drug addiction, thus exploring the possibility of a sort of "transitionality" from a moderate use of pleasurable foodstuffs to their abuse.

Recent evidence from mice and monkeys suggest the possibility of producing animal models of eating disorders [71-72, 77, 85-87]. It has been shown that rats with the possibility to assume a calorie-free saccharin solution or to self-administer intravenous cocaine infusions, they irrefutably chose the former solution rather than the second one [77]. This suggests how the macro-nutrients in pleasurable food can activate brain reward systems independently of their caloric load [78]. Furthermore, pleasurable foods can activate brain neurotransmission systems related to reward, motivation, and decision making [69]. Highly palatable foods induce long-lasting memories in non-human-primate models of chocolate preference [86], and the sudden food-reward absence induces anxiety-like behaviors (i.e., exploration), without changes in the levels of stress hormone cortisol [87]. Relying on these findings, eating behaviors related to the learning of food-associated cues seem to be important in the incidence and/or relapse of eating disorders. Finally, since the main features of drug addiction, such as compulsive seeking-behavior and relapse may be reproduced using several animal models, it can be considered the possibility to study food addiction using the animal models that previously defined the main features of drug addiction.

4.2 The neural basis of food addiction.

Besides the behavioral criteria described above, different studies focused on the neurobiology of

addiction also support the idea that overconsumption of certain foods parallels drug addiction [26, 68-71, 88]. Under certain circumstances, the potent rewarding capacity of palatable food may lead to behavioral/neurochemical changes similar to those produced by drug abuse [26, 77].

The activation of the DA-containing link in brain reward circuitry is the most clear and superimposable defined in food and drug-seeking behavior [25-26, 69]. Particularly, DA release seems to correlate with subjective reward from both drug and food use in humans [25, 69]. Repeated mesolimbic DA stimulation induced by expositions to addictive drugs produces brain plastic changes that result in compulsive drug-seeking. In a similar way, a repeated palatable foods exposition can induce compulsive food consumption using the same neurotransmission systems. Moreover, neuroimaging studies have revealed alterations in DA receptor expression in obese subjects that are similar to those found in drug-addicted subjects [69, 78, 89-90].

Eating disorders are characterized by compulsive eating behavior, even in spite of dangerous circumstances. It has been hypothesized that a complex gene-environment interaction may be a key factor of compulsive eating behavior [91-92]. Several studies have implicated DA type2 receptors (D2Rs) in the inclination to compulsive-like behaviors, as its happen in the drug addiction [18, 93]. Moreover, it has been demonstrate a gene-environment interaction in a mouse model compulsive chocolate-seeking/taking behavior using C57 and DBA mice in a Conditioned Suppression Paradigm [88, 94]. In this study, we reproduced a compulsive eating behavior using the paradigm of conditioned suppression of a chocolate-seeking behavior [71] in order to compare the stressed C57 and DBA mice. Moreover, it has been hypothesized that low availability of accumbal D2Rs is considered a genetic risk factor in the incidence of food compulsive-seeking behavior and that the environment can induce a compulsive eating behavior altering the expression of D2Rs in the striatum. To this aim, we measured D1Rs and D2Rs expression in the striatum and D1Rs, D2Rs and NE-ergic α1 receptors (α1Rs) levels in the mpFC, respectively, by western blot [88]. We showed that exposure to a certain environmental condition (food restriction) inducing compulsive eating behavior, depends on genetic background, that is connected with a decreased availability of NAc

D2Rs. Conversely, striatum D2Rs up-regulation and mpFC α1Rs down-regulation are induced during the compulsive eating behavior. These findings confirm the key role of a gene-environment interaction in the compulsive eating behavior, also supporting the idea that low availability of NAc D2Rs is a "constitutive" genetic risk factor for compulsive eating behavior. Finally, striatum D2R and mpFC α1R counteractive regulations are thought to be potential "neuroadaptive responses" paralleling with the transitionality from motivated to compulsive eating behaviors, and consequently in food addiction, as it has been hypothesized in drug addiction [88, 94].

4.3. Electrophysiological basis of food-directed behavior

Parallel to neurobiological studies, electrophysiological studies have enlightened a highly difference in changes in the firing of striatal neurons during a motivated behavior [95-97]. Furthermore, it has been shown that during a sucrose-seeking behavior phasic DA responses selectively modulate the excitatory but not the inhibitory responses of accumbal neurons [98]. Thus, DA rapidly signaled doesn't carry out accumbal global actions but selectively regulates distinct accumbal microcircuits that produce an influence on goal-directed actions. Furthermore, recordings of single neuron activity was recorded from the mesolimbic system (NAc and VTA) in an *in vivo* experiment in which rats were trained to lick water and/or flavored solutions [99]. The results suggested a crucial role of VTA to motivate animals in order to increase the consume of preferred food and fluids. This suggests that VTA appears to be linked to the AMY informations about the hedonic value, via the NAc shell [99]. Moreover, it has been suggested that the taste would be also encoded by the AMY based on the pleasantness of sapid chemicals [100-101].

Interestingly, it has been identified the presence of two neuronal types in the NAc [102-103]: fast spiking interneurons (FSIs) and medium spiny neurons (MSNs). It has been reported that FSIs strongly inhibit MSNs,that exert a control their "spike timing" [102, 104], and that respond differently from MSNs to rewards [102, 105]. These findings suggest that FSIs and MSNs have different roles in those behaviors related to motivation and habit learning. Finally, the NAc plays an important role in the appetitive and consummatory behavior. Commonly, it was found that

subpopulations of neurons in the NAc and VS respond phasically to every single characteristics of appetitive and consummatory phases [97-99, 101]. Since more NAc neurons are inhibited than excited during eating behavior, NAc inhibition manipulations may enhance food-seeking behavior. This not because of the general inactivation of the NAc, but because of the silencing of such neurons whose inhibit the food-seeking behavior. However, many of the same inhibited neurons driving motivated eating behavior are conversely excited during operant responding of environmental food-associated cues. It's arguable if it is electrophysiologically possible to discriminate a dissociable role of mesolimbic structures of reward system in order to investigate a possible transitionality from a normal to compulsive eating behavior.

5. Conclusions

A few interesting questions are brought up in light of all the converging evidences presented here, starting from the theoretical/psycho-bio-physiological conceptualizations of drug addiction, related to the three major theories driving the addiction research, to the last findings about a theoretical/psycho-bio-physiological superimposition between Drug and Food Addiction and their transitionality form use to abuse.

The first question is whether the three theoretical conceptualizations, the "Incentive-Salience Theory", the "Hedonic Dysregulation Theory" and the "Habit-based Learning Theory" are able to individually explain the psychopathological features of drug addiction. Alternatively, it is more likely that these three theories can be considered as parts of a unique general conceptualization that can better explain the psychopathological features of drug addiction. The hypothesis that an "aberrant motivation", a "hedonic dysregulation", and an "aberrant learning" can be sole features that can be included along a unique "temporal continuum" in the complex psychopathological drug-seeking/taking behavior should be considered.

The passage from occasional drug use to abuse is related to a change from a positive reinforcement to a negative one, with changes in motivational baseline [106]. Drug reward is comprised of two components: one appetitive (orienting towards food) and the other consummatory (hedonic

evaluation), which are also referred to as "wanting" and "liking", respectively. It has been explained that "wanting" and "liking" could act independently, defining a psychological and neuroanatomical separation between them [2, 5]. Moreover, it has been defined that craving (intense needing) and continuous neuroplastic changes are involved in the passage from use to abuse [11]. Furthermore, it has been argued that only maladaptive habit-based learning could trigger drug-seeking behavior [4]. However, these three hypotheses are able to explain singular features of the entire complex of drug addiction, such as the compulsive seeking behavior and the relapse. Alternatively, it is possible to consider a unique "temporal continuum" wherein 1) a progressively aberrant habit learning occurs during casual drug use, during which hedonic dysregulation is activated and 2) leads to a progressively aberrant "salience-incentivation" inducing the drug-taking behavior. Finally, motivation, hedonic dysregulation, and habit-based learning can be considered singular parts of a unique and complex drug-seeking/taking behavior; neuroanatomical and neurobiological evidence discussed here are in line with this hypotheses. However, although several studies have investigated how and when these three characteristics are involved in drug addiction, little is known about their possible juxtaposition in a single "temporal continuum". Several human and animal studies have demonstrated that the time of reward has a strong role in reward processing [22-23]. Furthermore, time windows and "reward rates" are of crucial importance for conditioning, and DA neurons are crucially involved in the processing of temporal information about the rewards. DA-ergic neurons in the meso-cortico-limbic system show predictive reward timing with a sensitivity induced by reward-related responses and by the instantaneity of reward probability [22]. This reinforces the hypotheses of a possible single "temporal continuum" from occasional use to compulsive use of substances, mediated by a meso-cortico-limbic DA-ergic circuit. At a clinical level, this would also help to understand how and when to intervene along the "temporal continuum" from occasional use to abuse of pharmacological substances, and to produce new therapeutic strategies in order to avoid the insurgency of the pathological drug-seeking/taking behavior. Moreover, it has been suggested that the so-called "extended amygdala circuit" may be delegated to act on the motivational,

emotional, and habitual effects of drug addiction [63-66]. Brain structures comprised in the extended amygdala have similarities in morphology, immunohistochemistry, and connectivity. Thus, further studies could investigate the role of extended amygdala in the transitionality from use to abuse of drugs [107-109].

A growing body of data hypothesizes the possibility of a behavioral/physiological overlap between drug and food addiction. A recent work of our group has hypothesized that mpFC Norepinephrine (NE) transmission also plays a key role in compulsive chocolate seeking/taking behavior, suggesting that mpFC NE has a role in motivated food seeking/taking behavior, regulated by mesolimbic DA-ergic transmission [71]. Moreover, it has been shown that mpFC NE enhances GABA-ergic neurotransmission via the α1 receptors [110], suggesting a crucial role of NE in the phenomenon of relapse in drug-seeking behavior [111-115]. Thus, further investigations about the role of NE in mediating interneuronal amygdaloid activity are strongly suggested, in order to better understand a possible meso-cortico-limbic pathway in the transitionality of both drug and food addiction [116-118].

The second question is whether the three features presented above (aberrant motivation, hedonic dysregulation and aberrant learning), and underlying drug-addicted behavior could also explain the psychopathological behavior that characterizes eating disorders. Although there are several studies about the behavioral/neurobiological overlap between drug and food addiction, little is known about the possible role of an "aberrant motivation", a "hedonic dysregulation" and an "aberrant learning" in psychopathological behavior characterizing a possible transitionality in food addiction, from normal to compulsive eating behavior. These three theories could contribute to better understanding of the psychopathological features of eating disorders, such as the compulsive use and the relapse to the substances, which resemble characteristics of drug addiction. Thus, future works could aim to better understand the key elements characterizing the psycho-physio-pathological aspects of both drug and food addictions, such as the compulsive use and the relapse.

Authors and contributors

EP wrote the paper. AG, CT, and HN revised the paper.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships.

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Legends

Figure 1: Incentive salience model of incentive motivation. "Liking" and "wanting" correspond to separate psychological and neurological systems. Conditioned Stimuli (CS) and Unconditioned Stimuli (US) produce a memory comparison. DA projections to the NAc and neostriatum generate wanting (incentive- salience aspects of motivation). Conversely, DA does not project directly to the NAc and neostriatum relatively to liking (hedonia) and to associative-learning of rewards. Further cognitive elaborations are required for personal evaluation of pleasure and motivation, in order to have consciousness of emotions underlying "liking" and "wanting".

Figure 2: Spiralling in a top-down vicious circle. Diagram describes the top-down addiction cycle. Craving is crucially involved in the process where a occasional drug use can transitionally lead to abuse, and subsequently to the relapse. This is explained through three factors: "preoccupation/anticipation", "binge/intoxication", and "withdrawal/negative" effect. These three stages interact with each other, becoming more intense, dysregulating the hedonic homeostasis of the reward system, and leading to the pathological state known as addiction.

Figure 3: Following steps from use to abuse of substances. According to Everitt and colleagues, drug addiction is a series of steps that are followed by an initial, voluntary and emotionally activating use of addictive substances up to a loss of control on the consumption of the same substances through a change of the role of conditioned reinforcer. Specifically, when the substance is taken voluntarily for its incentive effect, seeking-behavior progressively becomes a "habit", through a gradual loss of control. Thus, the stimulus-response mechanism plays a crucial role in the maintenance of an instrumental behavior. Finally, the capacity of the stimulus (substance) to act as reinforcement (conditioned reinforcer) exerts a kind of control over the seeking/taking behavior.

Figure 4: Hypothetical timeline of the "temporal continuum" hypotheses. Diagram describing a hypothetical time-line in which the three major features are defined as a single "temporal continuum" from the first meet with the drugs to the addiction. During this time, neurobehavioral changes act on the hedonic dysregulation and on the representation of the value of the drug inducing

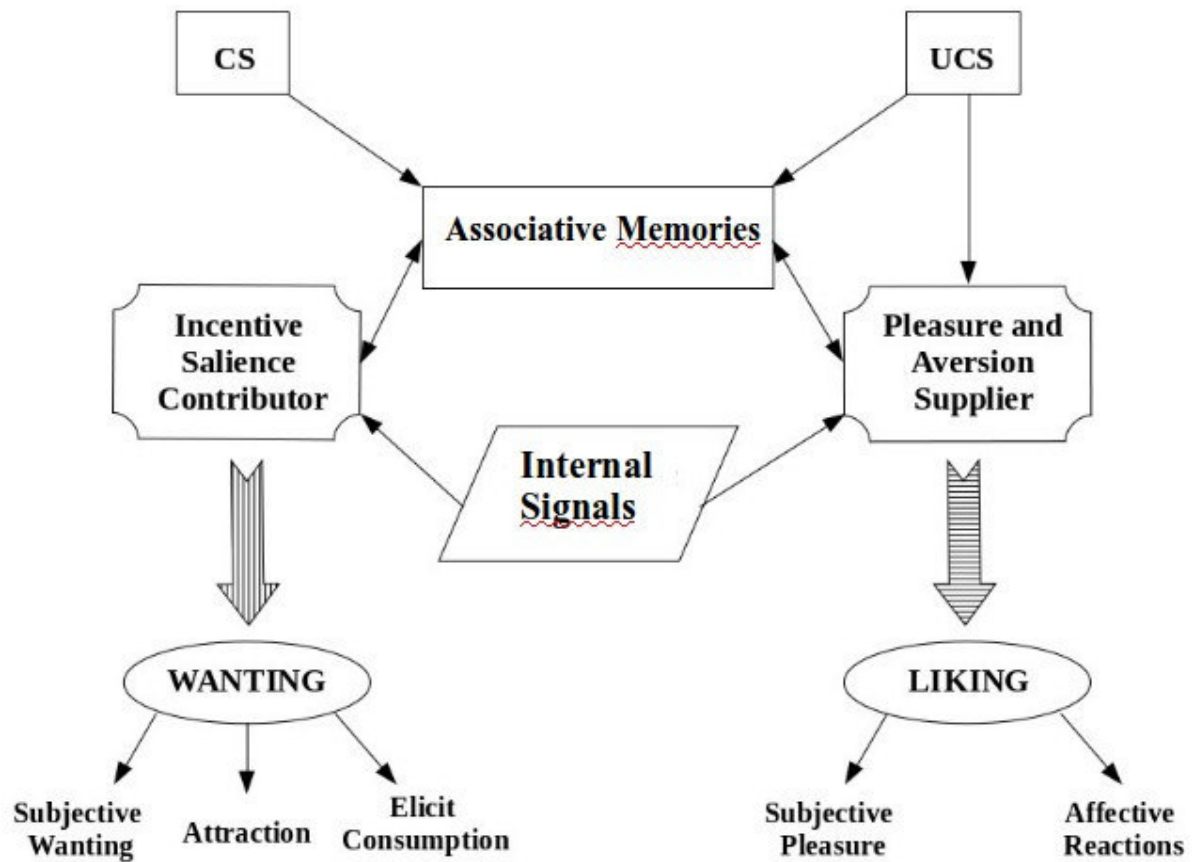a habit-learning, and drastically losing the control over the drug intake.

Fig. 1

Initial Use
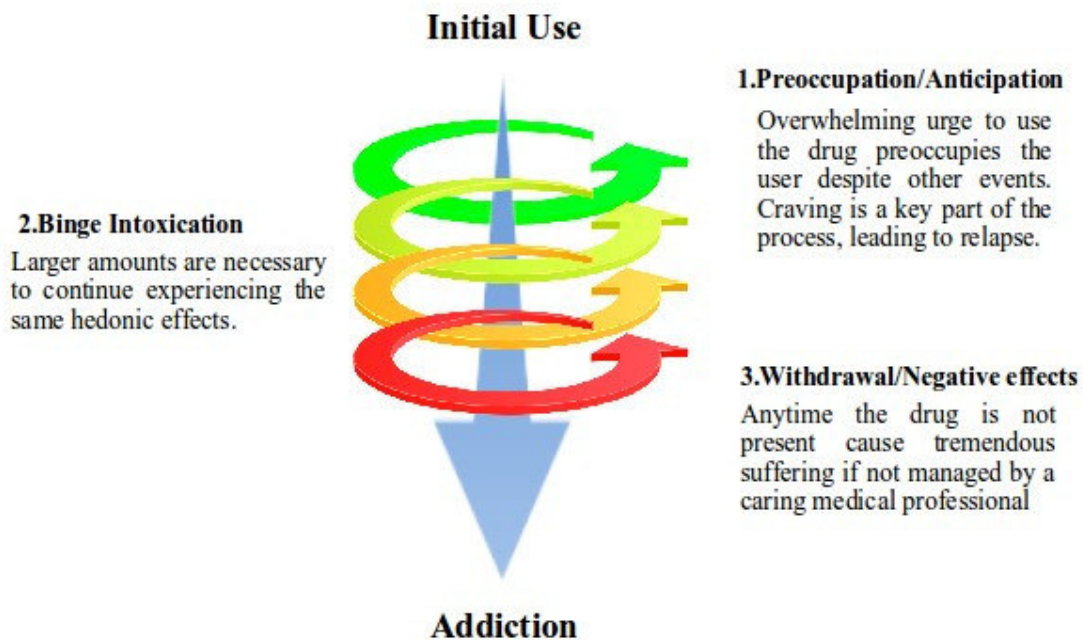
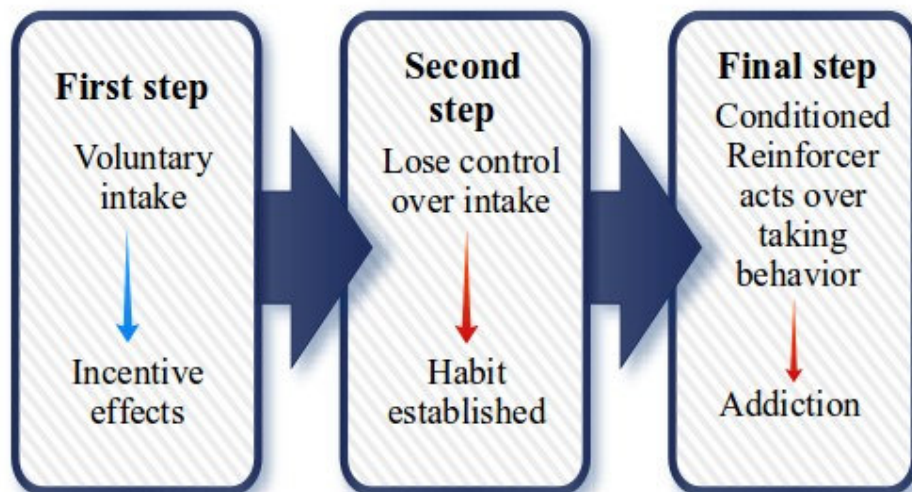**1.Preoccupation/Anticipation**

Overwhelming urge to use the drug preoccupies the user despite other events. Craving is a key part of the process, leading to relapse.

2.Binge Intoxication

Larger amounts are necessary to continue experiencing the same hedonic effects.

3.Withdrawal/Negative effects

Anytime the drug is not present cause tremendous suffering if not managed by a caring medical professional

Addiction

Fig. 2

Fig. 3

Fig. 4