Neurobiological and Psychopathological mechanisms underlying addiction-like behaviors:

an overview and thematic synthesis

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Abstract

The term dependency is increasingly being used also to explain symptoms resulting from the repetition of a behavior or legalized and socially accepted activities that do not involve substance assumption. These activities, although considered normal habits of daily life can become real addictions that may affect and disrupt socio-relational and working functioning. Growing evidence suggests to consider behavioral addictions similar to drug dependence for their common symptoms, the high frequency of poly-dependence conditions, and the correlation in risk (impulsivity, sensation seeking, early exposure, familiarity) and protective (parental control, adequate metacognitive skills) factors.

The aim of this paper is to describe addiction in its general aspects, highlighting the underlying neurobiological and psychopathological mechanisms.

Key words: Addiction; Behavioral Addictions, Drug Dependence, Neurobiology, Psychopathology.

Introduction

The World Health Organization (WHO) defines the dependence syndrome as "A state, psychic and sometimes also physical, resulting from the interaction between a living organism and a drug, characterized by behavioral and other responses that always include a compulsion to take the drug on a continuous or periodic basis in order to experience its psychic effects, and sometimes to avoid the discomfort of its absence." (Pigatto, 2003).

Similarly, the Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR (APA, 2000) and the International Statistical Classification of Diseases and Related Health Problems (ICD-10, WHO, 1993) introduced the term "dependence" with reference only to psychoactive substances, highlighting cognitive, behavioral and physiological symptoms due to misuse. Beyond the above meaning, which is largely shared in scientific literature and in clinical practice, the term dependency is increasingly being used also to explain symptoms resulting from the repetition of a behavior or legalized and socially accepted activities that do not involve substance assumption (Shaffer & Kidman, 2003). These activities, although considered normal habits of daily life, can become real addictions that may affect and disrupt socio-relational and occupational functioning. Growing evidence suggests that behavioral and substance addictions share phenomenical similarities: the inability to resist an impulse or the temptation to perform an act (compulsion); tension or arousal before committing the act (craving); pleasure, gratification or relief at the time of

committing the act; feeling of loss of control; persistence of the behavior despite the negative consequences.

To date, no consensus exists about a univocal, shared classification of such conditions that are usually encompassed under the generic term of New Addictions (Ferrini & Rontini, 2011), a definition that generically highlight a problematic behavior.

Dependence has also been defined on the basis of social rules, where social dependencies regard legal drugs (tobacco, alcohol, medications), and socially accepted activities, such as eating, working, shopping, play, browsing the web. Antisocial dependencies include psychoactive drug use and illegal activities (Alonso Fernandez, 1999). This classification highlights the social and cultural nature of dependencies, suggesting that the differences between Substance Use Disorder (SUD) and New Addiction lies in the different focus of addiction. It also should be highlighted the difference between the concepts of Dependence and Addiction, where the first term refers to the physical and chemical dependency, a condition in which the body needs a substance to function, and the second defines a general condition in which there is an unhealthily strong motivation to engage in a particular behavior, usually driven by physiological, psychological, environmental and social factors. Dependence and Addiction, however, does not necessarily occur together.

Evidence suggests considering the behavioral addictions similar to drug dependence, due to the common symptoms, the high frequency of poly-dependence conditions, and the correlation in risk (impulsivity, sensation seeking, early exposure, familiarity) and protective (parental control, adequate metacognitive skills) factors (Alavi et al., 2012). According to these findings, many authors postulate the existence of a real dependence syndrome or "Pathology addiction" (Orford, 2001) caused by the repetition of any conduct which produces short-term reward that may engender persistent behavior for reducing negative affective states and to enhance the positive ones.

The natural evolution of this perspective is not only to admit that several compulsive behaviors, such as gambling, are real addictions comparable to drug addiction, but also to hypothesize the existence of a single addiction syndrome with different expressions. Viewing addiction as a syndrome has several implications for research and treatment (Shaffer et al., 2004). Some authors (Blaszczynski, 1999) take position against the concept of addiction without substance, considering behavioral addictions such as compulsions or elements of the Obsessive-Compulsive Spectrum disorders. Thus, it seems important to highlight the similarities and differences between the two conditions (Alonso Fernandez, 1999): if both disorders are characterized by uncontrolled and inevitable behaviors, they differ in the egosyntonic/egodystonic dimension. Reflection is low or absent in impulse/urge, and excessive in compulsion; dependence involves loss of control, whereas the obsessive-compulsive spectrum is characterized by the reduction of the decisional processes. It has been shown that pathological gamblers also express compulsive and obsessive traits, including excessive worry for intrusive thoughts and difficulty in decisions making (Blaszczynski, 1999). However, despite these findings, the symptoms of the new addictions are better classified into the dimension of impulsivity, rather than into the obsessive-compulsive spectrum disorders.

Consequently, the definition of "dependent" may apply to those individuals whose existence is devoted to hunt for the effects of a substance (legal, prohibited, or prescribed drug) or a behavior (playing, browsing the web, sex or compulsive shopping) with intense physical and/or psychological discomfort (Valleur & Matysiak, 2003). Within this context, for the addicted there is nothing else that matters, and the socio-emotional disinvestment is pervasive. Actually, we can assume that such conducts lie at an extreme pole along a continuum of behaviors that gradually run from normality to pathology (Blaszczynski et al., 2004; Lavanco, 2004).

Congruently with this shift in theoretical perspective, in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders - DSM 5, the Substance Use Disorder (SUD) section has undergone substantial changes,

including the replacement of abuse and dependence categories with a single construct, the "Substance-related and Addictive Disorders" section. Beyond substance-related disorders, the section also includes Gambling Disorder (GD), classified in the previous editions within the Impulse Control Disorder section, whereas Internet Disorder has included in the appendix as a condition that requires further research (APA, 2013).

There is strong evidence suggesting that GD and SUD share several common features that go far beyond behavioral characteristics, as demonstrated by neurobiological and neuroimaging studies showing a substantial overlap between the two disorders (Kober et al., 2016).

The aim of this paper is to describe addiction-like behaviors, highlighting the underlying neurobiological and psychopathological mechanisms.

Neurobiolgy

It is well known that at the basis of addiction there is an alteration of those brain mechanisms which control the reward system and motivational states, as well as other functional systems involved in learning and memory. These systems are interconnected at various levels, from genetic regulation of neurotransmitters synthesis to the affective and cognitive processing of internal urges and external stimuli. From a neurobiological point of view there are not substantial differences between drug and behavioral addictions: a gratification is anyway a gratification, regardless of whether it is induced by a substance, experience or relationship (Brewer & Potenza, 2008), and, where is a gratification, it is possible that a vulnerable individual is caught into an addiction. What seems important is the high frequency of repetition of highly rewarding activities, which parasite those neural circuits evolved to sustain reward activities related to the survival (Potenza, 2006).

The motivation and reward system

The reward system allows us to experience a series of physical and emotional sensations that we consciously recognize as pleasure. Pleasure is an essential aspect of motivational behavior in evolved organisms like mammals: it provides incentive to action. Mammals pursuit two essential biological purposes: their own survival and the preservation of the species. The achievement of these goals is based on the satisfaction of instincts, like hunger, thirst, reproduction, offspring care, which activate the reward system. Each stage of motivated behavior is associated with feelings of pleasure that drive the search for reward (Lang & Bradley, 2010). During the appetitive phase, characterized by a state of excitement that strengthens and supports searching for and approaching to the desired object, seeking behaviors remain flexible and generic; the behavior is driven by distal urges that are perceived through senses (smell, sight, hearing) and does not involve direct interactions with the object. During the consummation phase, rigid behavioral patterns prevail (Di Chiara, 2005).

The brain systems of reward and motivation

Reward and motivation mechanisms are mainly controlled by the limbic system, a set of cortical and subcortical areas involved in the genesis of the emotions, and in learning and memory. The reward brain centers were identified in 1954 by James Olds and Peter Milner. They observed that, when electrodes were placed in certain areas of the brain, rats would repeatedly self-stimulate these areas, often to the exclusion of all other activities, including eating. Further studies provided a more complete comprehension of the different neurotransmitter systems involved in the reward system: first, the dopamine (DA) system that controls the motivational boost to stimulus search, and the opioid system that mediates the processes of gratification arising from substance use. Equally important are the serotonergic system, that influences the activation of the set of

mechanisms by which the different stimuli can induce motor and emotional responses, the glutamatergic system, that modulates the release of dopamine, and the GABAergic system, whose inhibitory activity is thought

to contribute to the development of tolerance and dependence. The DA system consists of a complex of neurons originated at the level of the A9 and A10 nuclei of encephalic trunk. The A9 projects to the caudate and putamen, and the A10 to a complex structure called extended amygdala, including mesolimbic (nucleus accumbens - NAc, stria terminalis, olfactory tubercle) and mesocortical systems. In the opioid system, opioids, endorphins, enkephalins, and dynorphins are the main neurotransmitters. Thus, the reward circuit appears very complex and includes various brain regions, which are needed to characterize the experiences and to drive responses to reward activities such as food, sex, and social interactions.

The mesolimbic pathway connects the ventral tegmental area (VTA) to the NAc, and operates like a switch of gratification, signaling to other brain centers if an activity is enjoyable, and how much.

Higher the reward, greater the possibility of the body to store the action and to repeat it. This same neural circuitry is also active in learning and maintenance of addictive behaviors. In summary, there are three main pathways involved in appetitive behavior and drug seeking:

-       A circuit disrupting the reinforcing effects of a substance (gratification and stress) and integrating the rewarding or negative incentives associated to it. This is the so-called "extended amygdale" circuit that includes the central nucleus of amygdale, the bed nucleus of the stria terminalis and the NAc shell.

-       A circuit involved in relapse, including the prefrontal (PFC), anterior cingulate, orbitofrontal and prelimbic cortices, and basolateral amygdala.

-       A circuit involved in the search for substances ("compulsiveness"), including the NAc, ventral pallidum, thalamus, orbitofrontal and motor cortices. The NAc is thought to be the functional interface between

amygdala and striatum (ventral pallidum, ventral thalamus-cortex-striatum circuit).

Other structures such as the hippocampus, that records the memories of experiences and DAergic and noradrenergic pathways of cortical areas are also involved (Koob & Le Moal, 2006; Gamberana, 2007).

Dopamine, the rewarding hormone

The DA reward pathways progress from the VTA to the nucleus accumbens, olfactory tubercle, ventral striatum and frontal cortex; the release of DA, the main chemical messenger of reward, is the final result of the action of each substance of abuse on this circuit. The release of DA from NAc shell is normally produced by a wide range of stimuli with a physiological, specific range for each subject regarding the amount of released DA and the level of response of mesolimbic DA receptors.

Both neuroimaging studies and animal models have shown that the pleasure associated with the release of dopamine in the NAc is associated with incentive behaviors and provision of acquisition aspects of reward, experienced as urgency, or craving (Di Chiara & Imperato, 1988). Whereas natural rewards induce a rapid adaptive change after a few experiences (habituation), the novelty of the reward should have a major role in the initial response. The strong dopaminergic activation caused by natural reward stimuli decreases upon repetition (even after a single exposure) and learning (Bassareo et al., 1997); this rapid tendency of the system to undergo habituation explains why new stimuli are perceived as more attractive, suggesting a role of associative learning processes. DA release not only promotes research and approach in response to conditioned

stimuli predictive of primary rewarding (incentive-motivational role), but also the acquisition of new conditioned stimuli facilitating associations between neutral and consumer stimuli (Pavlovian incentive learning) (Di Chiara, 2005). Thus, stimuli relevant to survival are marked with a burst of DA producing motivational incentive; the salient features of the context

are recorded, and pleasure is associated to stimuli. In this way, brain transforms a temporal contingency in a causal relation, and makes that context predictor of situations useful for survival. Differently from this basic mechanism, drug and/or behavior-induced reward is not affected by habituation, since each dose of the substance stimulates DA release.

Molecular basis

Important steps have been made in understanding the common molecular mechanisms and substrates shared by addiction, learning and memory (the immediate effect of a stimulus), but it remains unclear which substrates are involved in those stable brain changes leading to permanent behavioral changes that are typical of the advanced stages of addiction. Several transcription factors which regulate the expression or activity of specific genes have been investigated. Substances of abuse increase the concentration of dopamine in the NAc stimulating the D1 and D2 receptors coupled to G proteins. The stimulation of these receptors through the intracellular production of second messengers (cyclic adenosine monophosphate, inositol triphosphate, calcium) triggers the activation of a cascade of phosphorylating (kinase) enzymes that act on specific substrates. Phosphorylation can have immediate effects (acute behavioral effects) via voltage-gated channels, and long-term effects, mediated by proteins that act as transcription factors.

The changes in signal transduction can induce long-term molecular neuroadaptations via transcription factors that modify gene

expression; transcription factors (pCREB, pERK, pELK) trigger immediate early genes (FOS, June, etc.) which in turn activate the transcription of proteins important for neurotransmission (eg., preprodinorphin, a precursor of endogenous opioids). In parallel, the increase of intracellular calcium induces the release of neurotrophins: Brain-derived neurotrophic factor

(BDNF), nerve growth factor (NGF), Glial cell-derived neurotrophic factor (GDNF), Fibroblast Growth Factors (FGF), which act on various protein substrates through tyrosine kinase receptors.

Repeated exposure to rewarding substances and/or behaviors changes the morphology and dendritic spine density in the NAc and hippocampus (Robinson & Kolb, 2004). These effects would be mediated by transcription factors. New connections are responsible for amplification of intercellular signals and overreaction of the brain to stimuli that recall drugs.

Imaging studies

During the recent years, advances in neuroimaging (fMRI, PET and SPECT) have made it possible to study changes in specific brain areas related to behavior; PET have evaluated the acute effects of substances on neurotransmitters such as DA, gamma-Aminobutyric acid (GABA) and opioids, whereas fMRI studies have investigated specific brain areas activity (PFC, amygdala, hippocampus, and NAc) at different stages of addiction (intoxication, craving and withdrawal). PET and SPECT studies showed minor striatal concentration of D2 receptors and blunted DA release and DA functionality in addicts (Schrantee et al., 2015). In addiction, DA dysfunction may imply a lessened sensitivity to natural rewarding stimuli, with substances intake becoming a privileged way to activate the reward circuits. Whereas the acute intake of substances causes an increase in DA transmission, chronic use would result in a reduced DA function which affects orbitofrontal cortex (OFC) and cingulate gyrus activities. These areas are involved in salience attribution and

inhibitory control on dysfunctional behaviors; reduced DA transmission at these levels finally results in compulsive drug seeking. The same areas are hypoactive in withdrawal phase, but are activated when the subject takes the substance or engage in the behavior, is exposed to related stimuli, or experiences a strong desire for it.

New theories of addictions

The above drug and/or behavior-induced changes in the circuits of reward give rise to the clinical phenomena of tolerance, craving and relapse. Drug addiction, especially craving, would be characterized by functional impairment of fronto-striatal system. Chronic drug use causes a DA hypofunction in cortical areas that regulate cognitive functions, including those involved in controlling the compulsive search of the substance (Jentsch and Taylor, 1999). The corticofrontal regions control executive functions that include the ability to make decisions, to make inferences about possible consequences of actions, and to exert inhibitory control of behaviors; the prolonged substance use determines loss of cortical control over subcortical centers such as amygdala and the NAc involved themselves in control of impulses, learning and stress (Hyman & Malenka, 2001). On these data, at present, some theories have been developed (Gamberana 2007).

Abnormal Pavlovian incentive activation

Drugs of abuse stimulate DA transmission in the shell of nucleus accumbens but, differently from primary rewarding stimuli, the release of DA is increased and prolonged, and it is not exposed to adaptive mechanisms that result in a progressive reduction of DA release. This loss of habituation causes an abnormal consolidation of

the associations among the rewarding effects and the stimuli and/or contexts, assuming excessive incentive-motivational properties. Because of this abnormal learning incentive, stimuli associated with substances acquire disproportionate motivational salience. This pathway is also relevant for behavioral addictions.

This is a fundamental aspect of addiction: the abnormal compulsive ability of drug-conditioned stimuli to motivate behavior (craving). According to this hypothesis (Di Chiara et al., 2004), the abnormal motivation of drug addiction is the result of extremely strong associations between the substance and the associated Pavlovian stimuli that strengthen salience through the output of DA in the shell. DA release induced by new and unexpected primary reinforcement would produce an incentive status (euphoria) that would facilitate an instrumental behavior, the acquisition and expression of secondary reinforcement mechanisms, the re-establishment of an instrumental response previously extinguished, and the consolidation of mnemonic traces of salient stimuli associated with emotional states.

Allostatic states and counter adaptive processes among systems.

Whereas the homeostatic systems of the body react to deviations of vital physiological parameters (pH, body temperature, blood sugar, oxygen tension) trying to keep within very narrow limits compared to the base value, the allostasis tends to reach stability through change. Allostatic load involves the price the organism must pay for adapting to an adverse situation (both psychological or physical), reflecting too much demand on the activity of regulatory systems (McEwen, 1998). When the demand of new adaptations becomes excessive, or prolonged over time, the ability to adapt and to reach new set-points of homeostasis may fail, leading to the development of dysfunction and diseases (McEwen, 2005). It is hypothesized that changes in the brain systems associated with the development of affective and motivational states can be a source of potential allostatic changes that support the transition from use to abuse

(Koob & Le Moal, 2001). Affective states, pleasant or unpleasant, are normally modulated by central mechanisms that progressively reduce their intensity (Solomon & Corbit, 1974). Allostatic load from negative affective states may dysregulate reward neurocircuitry within the extended amygdala, resulting in diminished sensitivity to reward and augmented

sensitivity to aversive states. Thus, an allostatic state can be defined as a state of chronic deviation of the regulatory systems from their normal activities (homeostasis) with establishment of a new set point (Koob & Le Moal, 2001). As natural rewards lose their reinforcing value, and negative affects increase under stress conditions, this alteration in reward threshold may cause increased use of substances or repetition of rewarding behaviors, aimed to maintain a hedonic equilibrium. Drug and behavioral addictions may involve a modification in reward set point, reflecting an allostatic, rather than a homeostatic, adaptation. Whereas reward neurotransmitters (DA, opioids) usually have a limited capacity to maintain reward function within homeostatic range, drug intake can extend this capacity, but also leads to neuroadaptation within the DA and opioid peptide systems. The neuroadaptation within the system consists of cellular and/or molecular changes inside the reward circuit that finally reduce its function. These mechanisms of neuroadaptation can completely counterbalance the effects of substances, leading to tolerance. Abrupt discontinuation of the substance causes the emergence of symptoms (withdrawal syndrome) that are expression of these adaptive processes. According to this view, in addiction a dysregulation of reward and antireward systems gradually increases, causing the compulsive use of substances (Koob & Le Moal, 2001).

In animal models of transition to addiction, the reduction of reward precedes and is strongly correlated with drug-intake increase. It has been shown that, whereas repeated dosing of psychostimulants facilitates DA and glutamatergic transmission in the NAc (Ungless et al., 2001), chronic administration is followed by a reduction of the

transmission (Kalivas et al., 2003), causing the hypofunction of the reward system via neuroadaptive changes in opioid receptors in the NAc (Shaw-Lutchman et al., 2002), and in GABAergic transmission (Roberto et al., 2004). Imaging studies in addicts during withdrawal provide similar results

to those of animal models: reduction of D2 receptors (reflecting a dopaminergic hypofunction) and hypoactivity of the OFC infralimbic system (Wilson & Sayette, 2015). It has been suggested that the reduction of the neurotransmitter function of reward significantly contributes to acute negative emotional states associated with abstinence from substances and could trigger long-term biochemical changes that contribute to the syndrome of protracted withdrawal and vulnerability to relapse.

The neurochemical systems involved in stress modulation may be involved in the attempt to restore the normal reward functions, overcoming the deterioration caused by the chronic presence of the drug. The hypothalamic-pituitary-adrenal axis and stress circuits, both mediated by CRF, are disrupted by the chronic administration of substances of abuse, resulting in increases of adrenocorticotropic hormone, cortisone, and CRF levels (Koob & Le Moal, 2005; Kreek & Koob, 1998), in norepinephrine (NE) release in the roof nucleus of stria terminalis, and in the reduction of neuropeptide Y release (Olive et al., 2002).

Anti-reward brain systems modulated by CRF, NE, dynorphin, inducing aversive, stress-like states, are recruited in the processes of dependence and withdrawal (Aston-Jones et al., 1999; Koob, 2003; Nestler, 2001), concomitant with the reduction of reward function in the motivational circuits of the ventral layer of the extended amygdala. This combination provides a powerful negative reinforcement that contributes to the compulsive urge to abuse. Conceptualizing addiction as a simple disruption of those brain homeostatic mechanisms that regulate emotional states is not sufficient to explain the key elements of addiction: it worsens over time, is subject to significant environmental influences, and it leaves a residual neuroadaptive trace which facilitates rapid relapses even after years of detoxification and abstinence.

Sensitization and addiction

The Incentive-Sensitization Theory of Addiction (Robinson & Berridge, 1993) postulates that repeated exposure to substances would result in a hypersensitivity of brain circuits (NAc and ventral striatum) that mediate the incentive motivation function. Sensitization of these neural systems by drugs results in a pathological enhancement of the incentive salience attributed to the act of drug taking, with associative learning mechanisms directing the focus of incentive salience to specific targets associated with substances and drug-related stimuli. The sensitization process involves neuroadaptive changes both in the neurotransmitter systems (serotonin, glutamate, DA, NE, and GABA), and in synaptic plasticity (NAc, cortex), with changes in length, density, and type of dendritic spines. Moreover, the neuroadaptations underlying sensitization are long-lasting and, in some cases, permanent; this persistence of sensitization-related neuroadaptation is thought to make addicts hypersensitive to substances/behaviors and to drug-related stimuli, even after years of abstinence, precipitating relapses. According to this conceptualization of incentive motivation, salience attribution is a process that is activated normally in concurrence with reward and associative learning in the formation of new incentives. Thus, incentive motivation should involve three distinct processes acting together: pleasure, incentive salience, and associative learning, all subtended by distinct, although interacting, neurobiological systems.

Drug addiction as a maladaptive habit

According to this hypothesis, drug addiction would be the final step of a continuum starting from the initial use of a substance, voluntarily assumed for several incentive effects, through a gradual loss of control on behavior

that progressively becomes a habit and, finally, a "compulsion". The evidences in support of this hypothesis are heterogeneous, and in general indicate the dorsal striatum, specifically the dorsolateral part, as a major

influencer of this progression: a goal-directed phase driven by an explicit memory is gradually transformed in a habitual behavior driven by an implicit memory. The maintenance of instrumental behavior in these conditions reveals the degree of control that the stimulus-response mechanism has acquired on the behavior. The transition from voluntary actions (mainly controlled by their consequences) to habits (automatic behavioral responses) in the substance-seeking behavior reflects the switch from a cortical (prefrontal) to a subcortical control involving striatal areas. This hypothesis is partly supported by neuroimaging studies in samples of addicts, showing the reduction of the prefrontal and orbitofrontal cortices activity (Goldstein and Volkow, 2002).

Towards an integration of the different paradigms

As previously reported, substances of abuse and addictive behaviors determine molecular alterations induced by stimulation of DA receptors and changes in plasticity promoted by the expression of new genes (Berke and Hyman, 2000). Furthermore, is reasonably acknowledged that addiction, craving, withdrawal, and tolerance can recognize different neurobiological mechanisms. Actually, it is thought that tolerance and withdrawal are not closely related with persistent drug-induced molecular changes, since they disappear within a few days or weeks after intake. Therefore, the brain areas involved in withdrawal are different from those implicated in addiction. Many of the clinical symptoms in withdrawal are due to neural activation of the locus coeruleus, resulting in release of NE, whereas the reduction of DA transmission in the striatum is involved in motivational disorders (anhedonia) in withdrawal and implicated in determining individual differences in vulnerability to addiction and relapse (Melis et al, 2005). The primary, maybe constitutional, weakness of DA transmission is indicative of more rewarding effects associated with drugs of abuse, a feature related to a heightened vulnerability to addiction; the same feature may account for the higher risk for relapses in abstinent and/or detoxified individuals (Kalivas & Volkow, 2005). All substances of abuse, although belonging to different pharmacological classes, have in common the ability to exploit physiological mechanisms of adaptive

responsiveness of DA in the nucleus accumbens shell, via the abnormal strengthening of stimulus-substance associations; these mechanisms are central both in the transition from habit to addiction and in recovery and relapse processes.

The repeated exposure to the substance entails a reduction of DA transmission, which acts as a powerful motivation for maintenance and relapse. Neuroadaptive changes in subcortical DA transmission derived from chronic exposure to the substance may secondarily impact the functionality of those prefrontal-striatal circuits responsible for the loss of control on behavior (impulsiveness), and the impairment of decision-making that underlie addiction.

However, within a merely neurobiological framework, the increase of DA concentration in the NAc induced by substances cannot explain all the phenomena connected with drug addiction, since each step in the process of addiction could be controlled by different neuroadaptive and neurotransmitter changes in different brain.

Psychological aspects

Psychoactive substances and addictive behaviors have attracted substantial interest in the medical fields of research, and therefore emphasis was put to alleged predisposing biological factors and to the peculiar pharmacological profiles of each class of drugs. Another line of research has evaluated the emotional, cognitive and motivational processes, decision-making, and social influences involved in addiction (Ravenna, 1997). Beyond the biological framework, the complex phenomena of addiction and dependence need to be analyzed also at a psychological level. Cognitive

theories propose that addiction processes and the perceived effects of the different substances are strongly influenced by cognitive-motivational

factors such as attitudes, expectations and beliefs. These beliefs, usually learned within social and relational contexts, provide addicts a range of explanations for interpreting and justify their consumption behavior, where more positive beliefs lead to a greater likelihood that people can begin or continue drug-intake.

Systemic approach.

This approach focuses on systems in which the addicted is involved, primarily the family, focusing on relational and contextual variables more than on intrapsychic factors. Studies carried out in the second half of the '70s by US family therapists have shown that addicts, when compared with healthy controls, are not only drug-dependent, but they also show high levels of dependence from the family unit. In families of addicts a subversion of "traditional hierarchies" was found; the father was absent and emotionally distant, whereas the mother was overinvolved, indulgent and often symbiotic. In many cases, the child-mother-grandmother alliance hindered the parental couple. Drug addiction, viewed as a family symptom, was functional to maintain the stability of the couple, playing a homeostatic role that diverted attention from marriage conflicts by allowing the couple to regain solidarity needed to deal with the addiction problems of the child. On the other hand, the addicted child, recognized as a "patient" affected by a disease, was placed in the center of family. Stanton (1979) introduced the concept of "pseudo-individuation" to explain the prolonged dependence between the addict and his parents; drugs and other transgressive and/or deviant behaviors are means by which the child attempts to separate him/herself from parents, but the drug-intake makes him/her increasingly dependent from the family that provide support, help, and money. The family is so "glued", becoming unable to cope with separation anxieties. According to Cirillo and colleagues (1996), what lies beneath drug addiction is maternal neglect that produces pathological attachment styles in the

child. According to this perspective, addiction is not the result of a mere hyper-maternal involvement along with a distant and marginal father, but the outcome of an intergenerational transmission of deprivation, neglect,

and traumatic experiences not enough elaborated. Within this framework, the families of the addicts may be characterized more by a peculiar "internal quality", a blend of intense, long-lasting, not elaborated traumatic experiences, antecedent the onset of addiction, more than by impairment in social affiliation or in structural cohesion.

Psychosocial perspective.

The difficulty to deal with the demands and pressures from the environment can lead adolescents to identity problems, anxiety, and social isolation. Attempting to prevent or counteract these painful psychic experiences, involving intolerable anxieties of failure and fragmentation of the self, adolescents may look for alternative forms of adaptation, choosing the "addict" identity (Ravenna, 1993). Such perspective integrates the stress-coping model (the occurrence of stressful events increases the likelihood drug use) with the adjustment theories (in poor-skilled subjects, substance abuse and addictive behaviors are way to cope with negative emotional states and severe and prolonged psychological discomfort). Within the modern psychodynamic framework, addiction is not more explained in terms of impulse control and the prevalence of destructive instincts, but rather focusing on identification processes and object relations that characterize identity formation.

Olievenstein (1982) argues that the future addict come into adolescence with a sense of incompleteness derived from the failure of the mirror stage in the first two years of life. The failure of the mother's ability to view the child as a separate individual, and to recognize his/her child's needs, has

significant repercussions on the construction of a stable identity. The mirror is broken, and the result is a deep sense of incompleteness, lessened by the drug which provides a temporary restoration of the whole person through an illusory fusional dynamic with the mother. According to

Bergeret (2001) the addict suffered early in life from repeated frustrations in the primitive relationships, so desires are transformed into simple needs which can be satisfied through acting-out behaviors rather than through mentalization, imagination, and symbolization. Consequently, no symbolic acts can counterweigh the immediate pleasure and the feeling of triumph provided by the satisfaction of needs. These needs tend to rule out the presence of another person and have strong aggressive components. There is a difficulty of integration in childhood and adolescence that remain suspended in a sort of "pseudo-ending latency". The author distinguishes three types of addicts: a neurotic structure (with self-injurious and masochist behaviors), a psychotic structure (taking drugs to contrast or justify the overflow of their imaginary), and depressive structure (undecided, fluctuating and dependent subjects). Kohut (1971) has pointed out the possibility that serious and traumatic deficiencies in the mother-child relationship may cause serious identity disorders in the child. The child removes the disillusion towards the mother by maintaining the first idealized image of the mother-child fusional couple, to relieve the pain of trauma. This gives rise to a weak Ego unable to tolerate frustration, and dependent on a parent (usually the mother) experienced as omnipotent but unable to relieve the pain. The drug as an inanimate, controllable object, moves away the sense of inadequacy and allows the addict to face the reality of growth, with the associated inevitable frustrations. Cancrini (1984), using a psychiatric clinical approach based on the study of symptoms and observable behaviors, considers drug abuse as an attempt to deal with levels of pain perceived as intolerable. Addictions are heterogeneous conditions sharing the common feature of substance use as a way to deal with discomfort. The author classifies them into four types according to the role played by endogenous and exogenous causes on the individuals' psychological organization, and to family organization and communication styles. Type A dependence includes adjustment reactions,

characterized by a close association with traumatic events and addictive behavior, which often develops in the absence of interpersonal relationships perceived as reliable and safe. Type B dependence pertains to the neurotic area; the subject deals with problems of construction of the

self during adolescence, and that can be subtended by psychiatric conditions such as anxiety, mood changes, uncertainty, boredom proneness, dissatisfaction, and dramatization. These are individuals are accustomed to engage in parental conflict and to seek attention and affection in the dramatization of their discomfort. Family dynamics in this case are often characterized by a strong collusion between one parent and the child, with the parent (usually the mother) attempting to hide the child's deviant behaviors, making the educational process ineffective. Type C group includes dependence within the context of limit states and psychosis in which primitive defense mechanisms (split, denial, projective identification) prevail, leading to a diminished ability to experience states of pleasure and comfort. The predisposing factor seems to be the incomplete personality formation, characterized by a strong immaturity and by the inability to form stable emotional bonds. The family system shows a chaotic style in defining roles and borders which remain unstable and fluctuating; moreover, the communication is paradoxical, contradictory, and unclear. In these cases, the drug can briefly alleviate the discomfort, providing a state of inner freedom and rediscovered unity. Finally, Type D dependence refers to antisocial areas, and reflects a lack of social integration and disruptions in early childhood development. Individuals tend to express the conflicts through acting-out and take the drug in a callous, detached way, as a challenge to society, within the context of deviant and violent environments that strengthen such conducts.

Evolutionary-relational model.

A deep understanding of addictive behaviors cannot ignore the individual as a whole, his/her personality traits, and his/her relational history from the earliest years of life. Recent studies have highlighted the role of neglect,

particularly frequent in the family history of addicts, and its possible repercussions on the development of those cognitive and metacognitive skills involved in emotional regulation and necessary for adaptation to social demands. In healthy development, the special attention provided by the caregiver to the child's emotions is expressed through an affective syntonization process (Stern et al, 1987) that makes possible to share positive emotional states, manifested by the child through play and other activities, and that will form the foundation of future affective and relational models. The caregiver's abilities to stay emotionally in tune with the child, to correctly interpret his/her emotional displays, and to promptly adapt behavior accordingly, promote the healthy emotional and cognitive development of the child, forming a relational world in which the child can experience him/herself as a living being who feels, thinks, wants. Normally, the development progresses from a mere sensory experience of reality to a more complex construction of the inner and external world; the essential stage of this process is the progressive emergence of awareness and mentalization. The caregiver's emotional skills help the child to focus on his/her inner emotional experiences, giving them a form: so, emotions become meaningful and manageable (Fonagy & Target, 2001).

Contrarily, the emotionally neglected child, who is not "mirrored" by the caregiver, develops a reduced ability to represent his/her own and others' mental states along with the frequent occurrence of developmental disorders and, in adulthood, may present psychopathological conditions characterized by an inner dimension of affective and cognitive emptiness, which can finally lead to addictive behaviors as a coping strategy (Caretti & Di Cesare, 2005). According to this model, mentalizing deficits are related with pathological dissociative mechanisms that are structured during childhood in response to early relational failures. Dissociation, as a defense mechanism, is a normal function of mind which excludes painful emotions and sensations from consciousness, a locking mechanism

that protects the Ego through the active inhibition of intolerable information and builds a better, although false, reality. The relief arising from this temporary shelter is not pathological, but its excessive recurrence

increases reality distortions, and affects the sense of self and significant relationships, promoting the loss of contact with the reality in favor of compulsive, impulsive, and addictive behaviors. Addiction would represent a dissociative response, able to anesthetize the discomfort generated by the emergence of traumatic memories and emotions, and of splitted states of the Self, under stress conditions. Abuse, emotional neglect and attachment disorders in childhood may increase the psychological vulnerability towards addictive behaviors, in which drug-intake and addictive behaviors promote the achievement of dissociated state of mind. Although dissociation as a defense is central in maintaining personal continuity, consistency and integrity of the sense of Self, avoiding the traumatic dissolution (Bromberg, 2001), in addictive behaviors dissociative withdrawal weakens affects regulation, and increases the compulsive use of psychoactive substances, intensifying pleasant sensations, and reducing the intensity of dysphoric states. Within the context of this model, craving seems to be the core feature in various forms of pathological addiction. Defined as a strong, uncontrollable desire toward a reinforcing stimulus (Janiri et al., 2006), or as a conditioned appetitive motivational state (Franken, 2003), craving may occur in relation to different objects and/or behaviors, and is activated in the presence of environmental stimuli that recall the drug, although it can occur in response to stressful events or aversive emotional states; dissociated mental states contribute to strengthen craving mechanisms.

As mentioned above, if we consider addiction as a disorder based on dissociative defense mechanisms resulting from traumatic childhood experiences, it is easy to understand the role of pre-existing psychopathological conditions, beyond the rewarding properties of substances. According to the self-medication hypothesis formulated

by Khantzian (2003), addiction is an attempt of recovering from aversive states of mind and traumatic memories. In line with these considerations,

McDougall (2003) argues that, although the addict may suffer his/her slavery from psychotropic drugs or compulsive behaviors, the object of dependence is experienced unconsciously as "essentially good" because it brings wellness and, in extreme cases, it can be considered as the only thing that makes life meaningful. Given that craving is reinforced both by rewarding and positive sensations derived from drug effects, and by negative and painful abstinence symptoms, it becomes enough clear that therapeutic approaches based only on rehabilitation and/or pharmacology are expected to be almost ineffective. If the psychopathological and emotional aspects of addiction are not adequately addressed and mentalized, they will always remain in the background, contributing to reduce self-care and abstinence, affecting the detoxification process, and facilitating craving and relapses.

Conclusions

Addiction, whether to substances or pathological behaviors, is an extremely complex phenomenon, that can be considered the outcome of different pathways, derived from the interaction of biological, psychological and social risk factors and vulnerabilities. The contribution of each factor can be very different from case to case, explaining the extreme individual variability in terms of clinical expression, susceptibility, and response to treatment. During the recent years, the study of addictions has rapidly expanded, and this research field has become one of the most challenging and complex. Not differently from other psychiatric disorders, transition to addiction is a multistep process depending on the interaction between a vulnerable individual, in a biopsychosocial sense, and a stimulus (substances of abuse, behaviors) which is not pathogenic in the general population. Psychiatrists and psychologists struggle with a large and differentiated framework of disorders: compulsive shopping, technological dependencies, new drugs of abuse,

emotional and sexual addictions, exercise and work addiction. Many of them have been focused by research and systematic studies, diagnostic criteria and guidelines. A further reason to investigate these forms of psychopathology, which have a significant impact in everyday life, comes from their ability to express and represent, more effectively than other psychiatric disorders, the actual discomfort of civilization. The rapid and profound changes in social life, family structure and organization, consumer styles, cultural patterns and the management of leisure tend to modify the cognitive structure and the regulation of affective states, finally promoting the pathway to addiction. Therefore, research focused on drug and behavioral addictions should expand the knowledge of the multistep process of pathogenesis, with the final aim to find appropriate multidisciplinary models for an optimal prevention and treatment of these emergent, multifaceted conditions

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