

## **Effects of environmental enrichment on recovery from addiction: no disease, no chronic and no relapse**

### **Efectos del enriquecimiento ambiental en la recuperación de la adicción: ni enfermedad, ni crónica ni recidivante**

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Received: 14/02/2022 · Accepted: 11/03/2022

Cómo citar este artículo/citation: Ruiz Sánchez de León, J. M. (2022). Effects of environmental enrichment on recovery from addiction: no disease, no chronic and no relapse. *Revista Española de Drogodependencias*, 47(1), 166-186. <https://doi.org/10.54108/red.10010>

#### ***Abstract***

This paper critically analyses the axioms on which the brain disease model of addiction rests: i) it is a disease, ii) it is genetically determined, iii) it is irretrievably developed by drugs, iv) it is explained by the value placed on reward, and v) it is maintained by abstinence avoidance. It is argued that, in the light of scientific findings and under the prism of common sense, each of its axioms is falsifiable. The commonly held idea that self-administering drugs, eating an excess of palatable foods or persistently playing video games produces an incurable disease in people because their brains undergo irreversible changes after repeated performance of the habit is discussed. Subsequently, the classical definition of addiction as a chronic and relapsing disease is deconstructed by analysing the epidemiological data on the supposed chronicity and relapse, providing evidence of recovery as, in fact, the most probable spontaneous course. Finally, and as a common thread throughout the paper, environmental enrichment is proposed as a therapeutic approach and a precursor of the paradigm shift. It concludes with ideas on the need to build a better biopsychosocial model that substantially optimises the care response offered to people who have developed an addiction.

#### ***Keywords***

Addiction, Brain disease, Chronic disease, Relapsing disease, Addictive behavior, Recovery, Environmental enrichment, Evidence based practice.

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## Resumen

En el presente trabajo se analizan de manera crítica los axiomas sobre los que se apoya el modelo de enfermedad cerebral de la adicción: i) es una enfermedad, ii) está determinada genéticamente, iii) se desarrolla irremediabilmente por las drogas, iv) se explica por el valor que se otorga a la recompensa, y v) se mantiene por evitación de la abstinencia. Se sostiene que, a la luz de los hallazgos científicos y bajo el prisma del sentido común, cada uno de sus axiomas resulta falsable. Se discute sobre la idea -habitualmente sostenida- de que autoadministrarse droga, comer un exceso de comidas palatables o jugar persistentemente a videojuegos produce una enfermedad incurable en las personas porque sus cerebros sufren cambios irreversibles tras la ejecución repetida del hábito. Posteriormente, se deconstruye la definición clásica de la adicción como enfermedad crónica y recidivante analizando los datos epidemiológicos sobre la supuesta cronicidad y recidiva, aportando evidencias de la recuperación como, de hecho, el curso espontáneo más probable. Finalmente, y como hilo conductor de todo el trabajo, se propone el enriquecimiento ambiental como enfoque terapéutico y precursor del cambio de paradigma. Se concluye aportando ideas sobre la necesidad de construir un mejor modelo biopsicosocial que optimice sustancialmente la respuesta asistencial que se ofrece a las personas que han desarrollado una adicción.

## Palabras clave

Adicción, Enfermedad cerebral, Enfermedad crónica, Enfermedad recidivante, Conducta adictiva, Recuperación, Enriquecimiento ambiental, Práctica basada en la evidencia.

## INTRODUCTION

It is true that animals tend to repeat behaviors that bring us closer to the reinforcers offered by the environment. Goats, whenever they can, consume coffee, khat or mescal beans; cats enjoy the pleasurable effects after ingesting thyme or valerian; elephants get drunk on fermented fruit; or dolphins, who capture a puffer fish and consume it in turn, hitting it gently with their snout to force it to release small amounts of its narcotic toxin. We homo sapiens also consume drugs -which only sixty years ago we differentiated between legal and illegal- to obtain pleasurable sensations in a recreational way. And also, like the rest of the animal kingdom, we prefer palatable foods, sugary soft drinks and the company of the

individuals we love. And we use social networks to socialize, and we play games for fun, and we buy some things we don't need for the sheer pleasure of owning them. These behaviors usually develop as habits that we acquire through practice and positive reinforcement; that is, a normal, adaptive learning process. These routines - more or less automated - are implemented in our central nervous system and are triggered by specific stimulus configurations without the need to impose too much cognitive control.

However, we animals can eventually develop an addiction if, after normal incentive sensitization by tolerance (Robinson and Berridge, 1993), a stimulus-impoverished environment is configured around us (Alexander et al., 1978; Galaj et al., 2019; Rosenzweig, 1966; Solinas et al., 2010). Then, the



initial pleasurable sensations following the execution of that behavior are replaced by discomfort in its absence (Solomon, 1980) and we stop executing it for positive reinforcement -to obtain pleasure, because we like it- to execute it for negative reinforcement -to alleviate discomfort, because we need it (Berridge and Robinson, 2016). That is, we stop executing it impulsively and switch to doing it compulsively (Everitt and Robbins, 2005, 2016). Thus, our somatic marker is hijacked (Bechara and Damasio, 2002; Damasio, 1995) and our motivated behavior is reduced to maintaining allostasis (Koob et al., 1989).

Although there is some degree of agreement on the cascade of neurobiological and psychological events underlying the establishment and maintenance of addiction, there is significant controversy about its operational definition. The brain disease model of addiction (BDMA) proposes a definition that is repeated like a mantra: addiction is a chronic, relapsing disease (Leshner, 1997; Volkow and Koob, 2015). That phrase, verbatim, can be read in a multitude of articles in scientific press (e.g. Coffa et al., 2019; Kreek et al., 2012; Le Moal and Koob, 2007; Ryan, 2019; Zoorob et al., 2018; among many). Even obesity, misunderstood as addiction (Hebebrand et al., 2014), has been defined as a chronic and relapsing disease (De Lorenzo et al., 2020). With this statement, the BDMA argues that people who have developed a harmful habit -self-administering drugs, eating palatable foods, or playing video games- and are unable to give it up suffer from an incurable disease because their brains have undergone irreversible changes after repeated performance. Next, we will review the theoretical foundations on which the definition offered by the BDMA, which is assumed by many to be true without being

so, is built. Subsequently, the importance of environmental enrichment in the addiction recovery process will be discussed.

## THE AXIOMS OF THE CONTROVERSY

The BDMA is based on a set of propositions that, as axioms, are considered to be true and accepted without the need to review their evidence: (i) addiction is a disease (Leshner, 1997), (ii) addiction is genetically determined (Goodwin, 1989), (iii) addiction develops irremediably because of the reinforcing effects of drugs (Aigner and Balster, 1978), (iv) addiction is explained by the value placed on reward (Becker and Murphy, 1988), and (v) addiction is maintained by avoidance of abstinence (Lindesmith, 1980). The following paragraphs discuss these ideas under the prism of common sense and in the light of empirical data to reflect on the truth value of the axioms on which the BDMA rests (Volkow and Koob, 2015).

With respect to the first proposal, on considering addiction as a disease, it should be noted that this has never met the criteria to be considered as such. That is, there is no evidence of a measurable primary deviation from the physiological or anatomical norm (Campbell et al., 1979; Kottow, 1980). What variable deviates and differs from the norm? Behavior? In some northern European countries, *surströmming* (in English, fermented herring) is considered a delicious Swedish gastronomic experience. It basically consists of eating rotten fish that gives off an intense stench and tastes the same as it smells. Is the behavior of eating *surströmming* susceptible to be considered a disease for deviating from the norm? And practicing base jumping? Behaviors, no mat-



ter how atypical or self-destructive they may seem, cannot be considered diseases. After all, performing behaviors is not something that can be transmitted or contagious; performing behaviors cannot be considered an autoimmune response, nor is it inherited, degenerative or traumatic (Holden, 2012). There are many works in the scientific literature that have dismantled in different ways the idea of addiction as a disease (Becoña, 2016; Heather, 2017; Levy, 2013; Lewis, 2016 2018; Ruiz and Pedrero, 2014, 2019; Schaler, 2000) without the BMDA having been able to organize a substantiated counter-reply. Addiction is a habit, a behavior learned by repetition. It is established by classical conditioning and maintained by operant conditioning. It is executed automatically, by generalization among similar environments, without the activation of higher behavioral control mechanisms. And although there is very resistant learning behind the addiction, the problematic behavior can be extinguished. But like any extinguished behavior, it can also be reactivated in the face of certain environmental cues (Gifford and Humphreys, 2007; Ruiz and Pedrero, 2019). Smoking cigarettes or drinking alcohol are behaviors that can lead to lung cancer or liver cirrhosis. One must be able to distinguish between smoking and drinking, which are behaviors, and cancer and cirrhosis, which are diseases (Schaler, 2000). Addiction is NOT a disease.

Regarding the second proposal, on genetic determination, indeed, some genes that increase vulnerability to addiction have been identified (López-León et al., 2021) but there are hundreds that have not yet been identified (Hyman, 2018; Duncan et al., 2019). Genetic vulnerability to addiction depends on the configuration of hundreds -if not thousands- of genes (Duncan et al.,

2019). It could be assumed that addiction is only partially heritable, with estimates approaching 50% in twin studies according to the Psychiatric Genomics Consortium; Sullivan et al., 2018). This is, in fact, the reason why some individuals with low genetic vulnerability become addicted (Kendler et al., 2018) and others with higher genetic vulnerability do not (Kendler et al., 2020). Moreover, genetic vulnerability does not seem to be so much related to the drug of choice as to the type of management the individual makes of the social environment (Kendler et al., 2003), along the lines of what we now call epigenetics (Hamilton et al., 2019; Nielsen et al., 2012). Therefore, addiction is NOT genetically determined.

The third proposal, on the reinforcing power of drugs, is based on the original work of Aigner and Balster (1978) in which primates appeared to prefer cocaine to food. However, taking this research result as axiomatic is risky insofar as by slightly modifying the experimental conditions animals prefer food or sugar solution over cocaine (Lenoir et al., 2007). In fact, cocaine generally does not maintain a behavior as effectively as food does (Christensen et al., 2008). On the other hand, common sense tells us that not all individuals who use once, or even for short periods of time, end up becoming hopelessly addicted. Along these lines, O'Brien and Anthony (2005) assessed 114,241 North American participants over the age of 12 and found that a total of 1,081 had used cocaine for the first time in the 24 months prior to the assessment. However, only 5.4% (95% CI [4-7%]) of these recent users had become dependent on cocaine since the onset of use. That is, not everyone who uses a drug becomes subject to its reinforcing power (Reboussin and Anthony, 2006); and common sense tells us that - for-



tunately - not all users become addicted. Therefore, addiction does NOT develop irremediably because of the reinforcing effects of drugs.

The fourth proposition underpinning the BDMA is that consumption is motivated by the value placed on the immediate reward (Becker and Murphy, 1988). This approach asserts that: i) drugs have more value than any other reinforcer since they are chosen even over alternatives that were chosen before addiction, and ii) drugs increase in value with repeated use. We will discuss below the experimental results of environmental enrichment that, in a systematic way since the 1960s, have time and again falsified these two statements (Rosenzweig, 1966; Galaj et al., 2019). In this sense, the environment plays a crucial role in maintaining behavior. For example, if cocaine is available for a long time drinking behavior increases (Ahmed and Koob, 1998) and people with a severe addiction to drinking alcohol may give up drinking to obtain other rewards that they otherwise did not obtain (Cohen et al., 1971; Bigelow et al., 1972). Therefore, addiction is not explained by the value placed on the substance, much less by its pharmacological effect. To understand addiction one must consider how the environment is being unable to restrain the harmful behavior (Lamb and Ginsburg, 2018). Only then can the environment be made more effective in promoting recovery (Banks and Negus, 2017). Therefore, addiction is NOT explained by the value placed on the reward.

Regarding the fifth and final proposition, about addiction as abstinence avoidance, it seems to be applicable in some cases but not in others, a fact that renders it useless as an axiom. For example, the time elapsed from awakening to the first cigarette in the morn-

ing is a powerful predictor of therapeutic success (Baker et al., 2007) and, along these lines, nicotine replacement therapy seems to work as abstinence prevention (Fiore et al., 2008). However, it is common for some addicted to drinking alcohol to undergo long abstinence times, despite having unlimited access to the substance, to consume again in a binge format (Martino et al., 2019; Mello and Mendelson, 1972). Therefore, the role of withdrawal avoidance as an inducer of compulsive behaviors, although a relevant factor, is not sufficient to explain the behavior (Lüscher et al., 2020). Therefore, addiction is NOT explained by abstinence avoidance.

## **ON CHRONICITY AND RELAPSE: EVIDENCE FOR RECOVERY**

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Volkow and Koob (2015) wondered in their famous article why it is so controversial to posit addiction as an incurable brain injury. The controversy is due, among many other reasons, to the fact that there is multiple evidence of neurorehabilitation in people who have suffered head trauma (Magee et al., 2017; Holleman et al., 2018) or stroke (Brady et al., 2016; Legg et al., 2006; Pollock et al., 2014), as well as in people neurosurgically intervened for cancer (Weyer-Jamora et al., 2021). A structurally damaged - but truly damaged - brain is susceptible to rehabilitation through appropriate interventions. There is even evidence of reversal of mild cognitive impairment as a prodrome of Alzheimer's disease (Pandya et al., 2016; Sanz-Blasco et al., 2021). However, the BDMA states that addiction causes more permanent and irreversible changes in the brain than those caused by acquired brain damage or neurodegenerative disease. Addic-

tion injures the brain more persistently than a surgeon's scalpel; the changes are more irreversible than those produced by senile beta-amyloid plaques. This, more than controversial, is irrational. But, moreover, this assertion is defended in multiple supposedly scientific forums against the epidemiological data on recovery.

The National Epidemiological Survey on Alcohol and Related Conditions (NESARC) analyzed a sample of users with dependence on nicotine (n = 15,918), alcohol (n = 28,907), cannabis (n = 7,389) and cocaine (n = 2,259). Table I shows the cumulative probabilities of remission of dependence to the main prescribed and non-prescribed drugs both in the first year since first use, in the first decade and over a lifetime (Blanco et al., 2018; López-Quintero et al., 2010).

As can be seen, more than 65% of people stop using cocaine, cannabis and other prescribed drugs during the first decade of use and more than 95% succeed in quitting during their lifetime. In the case of alcohol and nicotine, being easily accessible substances, recovery rates during the first decade of use

are more modest, although 90% and 84%, respectively, manage to quit dependence during their lifetime. With these figures on the table, it is very difficult to sustain the idea that addiction is chronic and relapsing. In addition, any person with common sense has around him or her multiple evidence of people who have ceased consumption and restarted their lives in such a way that relapse is highly improbable. Undoubtedly, there are also some cases that relapse again and again despite achieving small periods of abstinence. But these account for about 5% of cases so making the minority issue the general definition is perverse. As Peele (2016) rightly points out in the title of his paper, "people can quit their addictions no matter how much the brain disease model indicates otherwise."

Now, how is it possible that the vast majority of drug users manage to stop executing that behavior, in many cases, with hardly any therapeutic intervention? Indeed, it is not difficult to recall people who abused tobacco, alcohol, cannabis or cocaine during their youth and who, as mature professionals with their

**Table I.** Cumulative probability of dependency remission according to the results of Blanco et al. (2018) and López-Quintero et al. (2010)

		First year	First decade	Lifetime
<b>Non-prescription drugs</b>	Cocaine	8,6%	75,8%	99,2%
	Cannabis	4,7%	66,2%	97,2%
	Alcohol	3,0%	37,4%	90,6%
	Nicotine	3,0%	18,4%	83,7%
<b>Prescription drugs</b>	Sedatives	10,2%	71,5%	98,7%
	Tranquilizers	15,2%	74,2%	98,3%
	Opioids	17,7%	67,0%	96,1%
	Stimulants	13,6%	80,7%	99,0%



descendants, now barely retain any of these drugs in a sporadic and totally controlled manner. How is it possible that in the majority of cases drug abuse is spontaneously self-limiting? The answer lies in the environment, which is ultimately responsible for the development of an addiction. That person has new friendships, falls in love, frequents other entertainment venues, gets to know other musical options, and his responsibilities increase; and his age has also changed, an indispensable factor for the maturation that underlies the myelination of the prefrontal cortex to take place (Ernst and Fudge, 2009). In short, over the years new behavioral offers can - and should - appear that will be equally or more reinforcing than drug abuse. Thus, this problematic behavior will cease to be the main behavior and will be relegated to being one more of its repertoire. The passage of time will eventually extinguish it. But if this renewed behavioral supply guided by the environment never appears, the risk of developing an addiction will undoubtedly be high; and once it has been established, it will be increasingly difficult for the environment to promote new behaviors. The importance of the psychosocial environment in the development of addictive behaviors, and thus in the recovery from addictive behaviors, will be discussed below.

## ON ENVIRONMENTAL ENRICHMENT

The first experimental evidence on the effect of environment on behavior appears in the work of Hebb (1947), who described how rats he raised as pets performed better in mazes than rats raised in standard laboratory conditions. Shortly thereafter it was also shown that dogs raised in the company of humans also performed better on problem-solving tasks than dogs raised in simple cages

without environmental stimulation (Clarke et al., 1951). In the 1960s, more systematic research was developed and it was shown that rats reared in groups in large cages filled with toys, ladders, tunnels and running wheels exhibited changes at the histological level (Bennett et al., 1964; Diamond et al., 1964; Krech et al., 1960), with increased mean vessel diameter and increased acetylcholinesterase activity (Rosenzweig, 1966).

Since then, a multitude of papers have been appearing evidencing that environmental enrichment promotes neuronal plasticity through neurogenesis (van Praag et al., 2000, 2005; Hosseiny et al., 2014) and optimization of nerve cell morphology (Diniz et al., 2010; Rosenzweig and Bennett, 1996; Kolb et al., 2003; Viola et al., 2009), long-term synaptic potentiation (Artola et al., 2006; Hosseiny et al., 2014) and altered transcription of certain genes (Greenwood et al., 2011). Exposure to an enriched environment also modifies neurochemical parameters of brain-derived neurotrophic factor (BDNF) (Bakos et al., 2009) and cholinergic (Bennett et al., 1964) and glutamatergic (Melendez et al., 2004) systems, both of which are important for learning and memory.

In light of these findings it was plausible that environmental enrichment would prove beneficial in some neurological diseases (Hannan, 2014; Pang and Hannan, 2013). Neuroprotective effects in neurodegenerative disorders, such as in Alzheimer's disease (Prado-Lima et al., 2018; Ziegler-Waldkirch et al., 2018), Parkinson's disease (Cho and Kang, 2020; Laviola et al., 2008) or Huntington's disease (Kreilaus et al., 2016; Van Dellen et al., 2000), have thus been described. In addition, multiple beneficial effects have been described in animal models of other disorders, such as depression (Renior et



al., 2013; Vega-Rivera et al., 2016), epilepsy (Suemaru et al., 2018; Rutten et al., 2002), stroke (Lin et al., 2020; de Boer et al., 2020), head trauma (Will et al., 2004; Fischer and Peduzzi, 2007), multiple sclerosis (Magalon et al., 2007), schizophrenia (McOmish et al., 2007), autism spectrum disorders (Kondo et al., 2008; Reynolds et al., 2013) and other neurodevelopmental disorders (Martinez-Cué et al., 2002; Sale et al., 2007, 2009).

In the context of addictive behaviors, one of the most revealing papers sought to test whether the isolation conditions of the operant conditioning chamber -the Skinner box- were related to the development and maintenance of addiction. Alexander et al. (1978) showed that animals that had developed an addiction in Skinner's box decreased drinking behavior dramatically to irrelevance when moved to an enriched environment that they called the Rat Park. That is, the animals would rather play sports, play with novel objects, interact with peers or have sex than go near the drug water dispenser. In contrast, animals that were moved from the Rat Park to the Skinner box increased their intake rapidly and developed an addiction (Alexander et al., 1981).

It has since been shown how animals in an enriched environment during periods of abstinence reduce their risk of relapse to cocaine (Chauvet et al., 2012; Ma et al., 2016; Solinas et al., 2008), heroin (Galaj et al., 2016; Imperio et al., 2018), methamphetamine (Hofford et al., 2014; Sikora et al., 2018), alcohol (Li et al., 2015) or nicotine (Hamilton et al., 2014; Sikora et al., 2018). All these findings suggest that the acquisition and maintenance of addictive behavior does not depend so much on the addictive power of the substance but on the environmental circumstances in which it is consumed.

While exposure to different forms of stress promotes the development of addictive behaviors (Goeders, 2002; Marinelli and Piazza, 2002; Sinha, 2001), subjecting animals to an enriched environment protects them and favors the extinction of such a response (Laviola et al., 2008; Nithianantharajah and Hannan, 2006, 2009; Rosenzweig and Bennett, 1996; van Praag et al., 2000).

Along these lines, a unified theoretical framework has been proposed in which environmental enrichment is conceived as a functional opposite of stress given its ability to induce long-lasting neuroplastic changes (Solinas et al., 2010). Indeed, vulnerability studies in humans also place stress as the main risk factor related to addiction (Piazza and Le Moal, 1996; Ruisoto and Contador, 2019). Thus, negative life experiences, a poor relationship with family and friends, low socioeconomic status or school failure are configured as risk factors for developing an addiction or not being able to extinguish it (De Bellis, 2002; Sinha, 2001). In contrast, positive life experiences, good relationships with family and friends, medium-high socioeconomic status or academic success are protective factors (Jessor and Jessor, 1980; Kodjo and Klein, 2002). There is multiple evidence that environmental enrichment simulates positive life experiences and therefore prevents the development of addiction and favors the maintenance of abstinence by reducing the risk of relapse (Solinas et al., 2010).

As Galaj et al. (2019) comment, the advantage of environmental enrichment over other psychotherapeutic interventions is that its success does not depend on the acquisition of new skills or the optimization of deficient abilities. In their opinion, such approaches run the risk of being limited to specific contexts and not generalized. They



add three reasons why they consider that environmental enrichment should be the intervention of first choice: i) it reduces stress, which, as discussed above, is the most potent relapse inducer (Thiel et al., 2012), ii) it modifies the neural circuits responsible for compulsive drug seeking (Spiers et al., 2004; Pinaud et al., 2001), and iii) it reduces drug-seeking behavior by reducing the consequences of reinforcement (Ranaldi et al., 2011; Peck and Ranaldi, 2014).

The first Cochrane Library review of environmental enrichment in acquired brain injury has recently been published (Qin et al., 2021), which it defines as intervention designed to facilitate physical -motor and sensory-, cognitive and social activity through the provision of equipment and the organization of a structured and stimulating environment (Nithianantharajah 2006). That is, an environment designed to foster -without forcing- attractive and interesting, participatory and stimulating activities, which in themselves become reinforcing activities. It is a type of intervention that does not depend so much on the therapist since, in fact, it does not depend on a classic individualized and goal-oriented rehabilitation program. The intervention is the environment, it is right there, and the patient is part of it. Materials may include physical exercise or group sports equipment, rich and varied reading, computers with Internet access, video game consoles, virtual reality and interactive games, board games, access to music and audiobook libraries, art or craft workshops, and any interactive recreational activity of interest depending on the group's interests.

The conclusions of this first historical meta-analysis do not fully endorse environmental enrichment as an evidence-based non-pharmacological therapy, but foresee prom-

ising results in the short term when a number of methodological aspects are homogenized in clinical trials (Qin et al., 2021); and indeed, one of the problems of this biopsychosocial intervention under the magnifying glass of a meta-analysis is undoubtedly the equalization of the intervention environment between countries or cultures. It is estimated that in a few years, with the pooling among researchers, environmental enrichment will dominate the scene in multidisciplinary brain injury neurorehabilitation centers; and likewise, in a few years, we will also have meta-analyses in favor of environmental enrichment as an evidence-based therapy for degenerative dementias (Bourdon and Belmin, 2021; Kok et al., 2017). And despite all this evidence of recovery in people with neurological diseases -real diseases- the BDMA insists on repeating -without demonstrating- that people with addiction are not recoverable.

## CONCLUSION AND FINAL THOUGHTS

Animals learn behaviors and develop them as habits based on their reinforcing power. However, not all acquired habits are healthy and adaptive; some, such as getting high, eating *surströmming*, or base jumping, have the capacity to destroy us. The BDMA argues that people who practice drug self-administration habits-or other behaviors they consider pathological-are incurably ill and, even if they stop performing such behaviors, they will remain so because their brains have been irreparably damaged in the process. The axioms supporting this idea have been analyzed in the light of experimental findings and under the prism of common sense to suggest that addiction is not a disease and there is no data to support that it is chronic, much less relapsing.



It is noteworthy that, to date, addiction has not been documented in goats, cats, elephants or dolphins, nor in any other non-human animal in their habitat, despite the fact that they are all regular users of psychotropic substances. This fact raises a question: why are homo sapiens the only animals that develop addictive behaviors? The answer is multifactorial and therefore complex. But evolution over the last five thousand years has probably made us the only animals capable of restricting our behavioral range to just one habit and surviving by emitting that one behavior. Opium, already in the first civilizations and throughout history, was always on the table. And it was used and abused. But it was in the second half of the twentieth century that its consumption began to be considered pathological, coinciding with political and economic decisions and substantial changes in the model of society that it is not appropriate to analyze in this paper.

Another interesting question in this regard is, why do other animals that are not addicted in their usual environment become addicted in a controlled laboratory situation? That is, what changes to make them addicted? In this case the answer can be offered with a fair amount of certainty: we impoverish their environment to a limit where engaging in addictive behavior is the only possible behavioral offer. And under those circumstances, when the only thing the animal can do is to self-administer the drug, we say that it is addicted because it does not stop self-administering the drug. However, outside the controlled environment of the laboratory, either inside the Rat Park or in its habitat, it ceases to be addicted. Isn't that revealing? We study animals that do not develop addictions in their environment and, to get them addicted, we create a denatured environment in which they can only emit

one behavior. Then, we say that they become sick for emitting it; and we cure them by returning them to their normal environment. What if human addicts live in a big Skinner box in which they can only emit one behavior? If we take them out of that box, won't the addictive behavior subside as their range of possible behaviors increases again? This is precisely what environmental enrichment is all about as a therapeutic approach. Although -ironically- the study of addiction was one of the first to demonstrate its usefulness in animal models, to date there are still very few formal proposals in humans. However, as mentioned above, there is already scientific evidence of its usefulness in the rehabilitation of brain damage and degenerative dementias. In the coming years we expect an exponential growth of this approach, described more than fifty years ago, which was partially eclipsed by the emergence of BDMA and the subsequent pharmacologization of the treatment.

All animals are capable of learning to become addicted if we are faced with the right reinforcer and certain environmental conditions are configured. We can all develop an addiction with greater or lesser difficulty depending on our genetic and neurobiological configurations. In the same way, all animals are capable of learning to stop being addicted if, although the presence of the reinforcer persists, these environmental circumstances change. And we can all stop being addicted with greater or lesser difficulty depending on our genetics and neurobiology. Perhaps this is the best axiom on which to build an authentic biopsychosocial paradigm of addiction; a paradigm that improves the care response offered to people who have developed an addiction and need help to overcome it. Ultimately, they are the ones we should all be thinking about.



## REFERENCES

- Ahmed, S.H., & Koob, G.F. (1998). Transition from moderate to excessive drug intake: change in Hedonic set point. *Science*, 282(5387), 298–300. <https://doi.org/10.1126/science.282.5387.298>
- Aigner, T.G., & Balster, R.L. (1978). Choice behavior in rhesus monkeys: cocaine versus food. *Science*, 201(4355), 534–535. <https://doi.org/10.1126/science.96531>
- Alexander, B.K., Beyerstein, B.L., Hada-way, P.F., & Coombs, R.B. (1981). The effects of early and later colony housing on oral ingestion of morphine in rats. *Pharmacology, Biochemistry, & Behavior*, 15(4), 571–576. [https://doi.org/10.1016/0091-3057\(81\)90211-2](https://doi.org/10.1016/0091-3057(81)90211-2)
- Alexander, B.K., Coombs, R.B., & Hadaway, P.F. (1978). The effect of housing and gender on morphine self-administration in rats. *Psychopharmacology*, 58(2), 175–179. <https://doi.org/10.1007/BF00426903>
- Artola, A., von Frijtag, J.C., Fermont, P.C., Gispen, W.H., Schrama, L.H., Kamal, A., & Spruijt, B.M. (2006). Long-lasting modulation of the induction of LTD and LTP in rat hippocampal CA1 by behavioural stress and environmental enrichment. *European Journal of Neuroscience*, 23(1), 261–272. <https://doi.org/10.1111/j.1460-9568.2005.04552.x>
- Baker, T.B., Piper, M.E., McCarthy, D.E., Bolt, D.M., Smith, S.S., Kim, S.Y., Colby, S., Conti, D., & Giovino, G.A., Hatsukami, D., Hyland, A., Krishnan-Sarin, S., Niaura, R., Perkins, K.A., Toll, B.A. (2007). Time to first cigarette in the morning as an index of ability to quit smoking: implications for nicotine dependence. *Nicotine & Tobacco Research*, 9(4), 555–570. <https://doi.org/10.1080/14622200701673480>
- Bakos, J., Hlavacova, N., Rajman, M., Ondicova, K., Koros, C., Kitraki, E. et al., (2009). Enriched environment influences hormonal status and hippocampal brain derived neurotrophic factor in a sex dependent manner. *Neuroscience*, 164(2), 788–797. <https://doi.org/10.1016/j.neuroscience.2009.08.054>
- Banks, M.L., & Negus, S.S. (2017). Insights from preclinical choice models on treating drug addiction. *Trends in Pharmacological Sciences*, 38(2), 181–194. <https://doi.org/10.1016/j.tips.2016.11.002>
- Becker, G.S., & Murphy, K.M. (1988). A theory of rational addiction. *Journal of Political Economy*, 96(4), 675–700.
- Becoña, E. (2016). Addiction is not a brain disease. *Papeles del Psicólogo / Psychologist Papers*, 37(2), 118–125.
- Bennett, E.L., Diamond, M.C., Krech, D., & Rosenzweig, M.R. (1964). Chemical and anatomical plasticity of brain. *Science*, 146(3644), 610–619. <https://doi.org/10.1126/science.146.3644.610>
- Berridge, K.C., & Robinson, T.E. (2016). Liking, wanting, and the incentive-sensitization theory of addiction. *American Psychologist*, 71(8), 670–679. <https://doi.org/10.1037/amp0000059>
- Bigelow, G., Cohen, M., Liebson, I., & Fail-lace, L.A. (1972). Abstinence or moderation? Choice by alcoholics. *Behaviour Research and Therapy*, 10(3), 209–214. [https://doi.org/10.1016/0005-7967\(72\)90037-x](https://doi.org/10.1016/0005-7967(72)90037-x)
- Blanco, C., Flórez-Salamanca, L., Secades-Villa, R., Wang, S., & Hasin, D.S. (2018).

- Predictors of initiation of nicotine, alcohol, cannabis, and cocaine use: Results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *The American Journal on Addictions*, 27(6), 477-484. <https://doi.org/10.1111/ajad.12764>
- Bourdon, E., & Belmin, J. (2021). Enriched gardens improve cognition and independence of nursing home residents with dementia: a pilot controlled trial. *Alzheimer's Research & Therapy*, 13(1), 116. <https://doi.org/10.1186/s13195-021-00849-w>
- Brady, M.C., Kelly, H., Godwin, J., Enderby, P., & Campbell, P. (2016). Speech and language therapy for aphasia following stroke. *Cochrane Database of Systematic Reviews*, 6, CD000425. <https://doi.org/10.1002/14651858.CD000425.pub3>
- Campbell, E. J. M., Scadding, J. G., & Roberts, R. S. (1979). The concept of disease. *British Medical Journal*, 2(6193), 757-762. <https://doi.org/10.1136/bmj.2.6193.757>
- Chauvet, C., Goldberg, S.R., Jaber, M., & Solinas, M. (2012). Effects of environmental enrichment on the incubation of cocaine craving. *Neuropharmacology*, 63(4), 635-641. <https://doi.org/10.1016/j.neuropharm.2012.05.014>
- Cho, H., & Kang, K. (2020). Effects of Environmental Enrichment on Neurotrophins in an MPTP-Induced Parkinson's Disease Animal Model: A Randomized Trial. *Biological Research For Nursing*, 22(4), 506-513. <https://doi.org/10.1177/1099800420931183>
- Christensen, C.J., Silberberg, A., Hursh, S.R., Huntsberry, M.E., & Riley, A.L. (2008). Essential value of cocaine and food in rats: tests of the exponential model of demand. *Psychopharmacology* 198(2), 221-229. <https://doi.org/10.1007/s00213-008-1120-0>
- Coffa, D., & Snyder, H. (2019). Opioid Use Disorder: Medical Treatment Options. *American Academy of Family Physicians*, 100(7), 416-425.
- Cohen, M., Liebson, I.A., Faillace, L.A., & Allen, R.P. (1971). Moderate drinking by chronic alcoholic: a schedule dependent phenomenon. *The Journal of Nervous and Mental Disease*, 153(6), 434-444. <https://doi.org/10.1097/00005053-197112000-00006>
- De Bellis, M.D. (2002). Developmental traumatology: a contributory mechanism for alcohol and substance use disorders. *Psychoneuroendocrinology* 27(1-2), 155-170. [https://doi.org/10.1016/s0306-4530\(01\)00042-7](https://doi.org/10.1016/s0306-4530(01)00042-7)
- de Boer, A., Storm, A., Gomez-Soler, M., Smolders, S., Rué, L., Poppe, L. et al. (2020). Environmental enrichment during the chronic phase after experimental stroke promotes functional recovery without synergistic effects of EphA4 targeted therapy. *Human Molecular Genetics*, 29(4), 605-617. <https://doi.org/10.1093/hmg/ddz288>
- De Lorenzo, A., Romano, L., Di Renzo, L., Di Lorenzo, N., Cennamo, G., & Gualtieri, P. (2020). Obesity: A preventable, treatable, but relapsing disease. *Nutrition*, 71, 110615. <https://doi.org/10.1016/j.nut.2019.110615>
- Diamond, M.C., Krech, D., & Rosenzweig, M.R. (1964). The effects of an enriched environment on the histology of the rat cerebral cortex. *Journal of Comparative*



- Neurology*, 123, 111-20. <https://doi.org/10.1002/cne.901230110>
- Diniz, D.G., Foro, C.A., Rego, C.M., Gloria, D.A., de Oliveira, F.R.R., Paes, J.M.P. et al. (2010). Environmental impoverishment and aging alter object recognition, spatial learning, and dentate gyrus astrocytes. *European Journal of Neuroscience*, 32(3), 509-519. <https://doi.org/10.1111/j.1460-9568.2010.07296.x>
- Duncan, L.E., Ostacher, & M., Ballon, J. (2019). How genome-wide association studies (GWAS) made traditional candidate gene studies obsolete. *Neuropsychopharmacology*, 44(9), 1518-1523. <https://doi.org/10.1038/s41386-019-0389-5>
- Ernst, M., & Fudge, J.L. (2009). A developmental neurobiological model of motivated behavior: anatomy, connectivity and ontogeny of the triadic nodes. *Neuroscience & Biobehavioral Reviews*, 33(3), 367-382. <https://doi.org/10.1016/j.neubiorev.2008.10.009>
- Everitt, B.J., & Robbins, T.W. (2016). Drug addiction: updating actions to habits to compulsions ten years on. *Annual Review of Psychology*, 67, 23-50. <https://doi.org/10.1146/annurev-psych-122414-033457>
- Fiore, M., Jaen, C., Baker, T., Bailey, W., Benowitz, N., Curry, S., et al. (2008). Treating Tobacco Use and Dependence: Clinical Practice Guideline. US Public Health and Human Services, Washington, DC.
- Fischer, F.R., & Peduzzi, J.D. (2007). Functional recovery in rats with chronic spinal cord injuries after exposure to an enriched environment. *Journal of Spinal Cord Medicine*, 30(2), 147-155. <https://doi.org/10.1080/10790268.2007.11753926>
- Galaj, E., Barrera, E.D., & Ranaldi, R. (2020). Therapeutic efficacy of environmental enrichment for substance use disorders. *Pharmacology Biochemistry and Behavior*, 188, 172829. <https://doi.org/10.1016/j.pbb.2019.172829>
- Galaj, E., Manuszak, M., & Ranaldi, R. (2016). Environmental enrichment as a potential intervention for heroin seeking. *Drug and Alcohol Dependence*, 163, 195-201. <https://doi.org/10.1016/j.drugalcdep.2016.04.016>
- Goeders, N.E. (2002). Stress and cocaine addiction. *Journal of Pharmacology and Experimental Therapeutics*, 301(3), 785-789. <https://doi.org/10.1124/jpet.301.3.785>
- Goodwin, D.W. (1989). The gene for alcoholism. *Journal of Studies on Alcohol and Drugs*, 50(5), 397-398. <https://doi.org/10.15288/jsa.1989.50.397>
- Greenwood, B.N., Foley, T.E., Le, T.V., Strong, P.V., Loughride, A.B., Day, H.E.W. et al. (2011). Long-term voluntary wheel running is rewarding and produces plasticity in the mesolimbic reward pathway. *Behavioural Brain Research*, 217(2), 354-362. <https://doi.org/10.1016/j.bbr.2010.11.005>
- Hamilton, P.J., & Nestler, E.J. (2019). Epigenetics and addiction. *Current Opinion in Neurobiology*, 59, 128-136. <https://doi.org/10.1016/j.conb.2019.05.005>
- Hamilton, K.R., Elliott, B.M., Berger, S.S., & Grunberg, N.E. (2014). Environmental enrichment attenuates nicotine behavioral sensitization in male and female rats. *Experimental and Clinical Psychop-*



- harmacology*, 22(4), 356–363. <https://doi.org/10.1037/a0037205>
- Hannan, A.J. (2014). Environmental enrichment and brain repair: harnessing the therapeutic effects of cognitive stimulation and physical activity to enhance experience-dependent plasticity. *Neuropathology and Applied Neurobiology*, 40(1), 13-25. <https://doi.org/10.1111/nan.12102>
- Heather, N. (2017). Q: Is addiction a brain disease or a moral failing? A: Neither. *Neuroethics*, 10(1), 115-124. <https://doi.org/10.1007/s12152-016-9289-0>
- Hebebrand J, Albayrak Ö, Adan R, Antel J, Dieguez C, de Jong J, et al. (2014). “Eating addiction”, rather than “food addiction”, better captures addictive-like eating behavior. *Neuroscience & Biobehavioral Reviews*, 47, 295-306. <https://doi.org/10.1016/j.neubiorev.2014.08.016>
- Hofford, R.S., Darna, M., Wilmouth, C.E., Dwoskin, L.P., & Bardo, M.T. (2014). Environmental enrichment reduces methamphetamine cue-induced reinstatement but does not alter methamphetamine reward or VMAT2 function. *Behavioural Brain Research*, 270, 151–158. <https://doi.org/10.1016/j.bbr.2014.05.007>
- Holden, T. (2012). Addiction is not a disease. *Canadian Medical Association Journal*, 184(6), 679. <https://doi.org/10.1503/cmaj.112-2033>
- Holleman, M., Vink, M., Nijland, R., & Schmand, B. (2018). Effects of intensive neuropsychological rehabilitation for acquired brain injury. *Neuropsychological Rehabilitation*, 28(4), 649-662. <https://doi.org/10.1080/09602011.2016.1210013>
- Hosseiny, S., Pietri, M., Petit-Paitel, A., Zarif, H., Heurteaux, C., Chabry, J., et al. (2014). Differential neuronal plasticity in mouse hippocampus associated with various periods of enriched environment during postnatal development. *Brain Structure and Function*, 220(6), 3435–3448. <https://doi.org/10.1007/s00429-014-0865-y>
- Hyman, S.E. (2018). The daunting polygenicity of mental illness: making a new map. *Philosophical Transactions of the Royal Society B*, 373(1742), 20170031. <https://doi.org/10.1098/rstb.2017.0031>
- Imperio, C.G., McFalls, A.J., Hadad, N., Blanco-Berdugo, L., Masser, D.R., Colechio, E.M., et al. (2018). Exposure to environmental enrichment attenuates addiction-like behavior and alters molecular effects of heroin self-administration in rats. *Neuropharmacology*, 139, 26-40. <https://doi.org/10.1016/j.neuropharm.2018.06.037>
- Jessor, R., & Jessor, S. (1980). A social-psychological framework for studying drug use. *NIDA Res. Monogr.* 30, 102–109.
- Kempermann, G., Kuhn, H.G., & Gage, F.H. (1997). More hippocampal neurons in adult mice living in an enriched environment. *Nature*, 386(6624), 493–495. <https://doi.org/10.1038/386493a0>
- Kendler, K.S., Ohlsson, H., Sundquist, J., & Sundquist, K. (2018). Familial transmission of externalizing syndromes in extended Swedish families. *American Journal of Medical Genetics B*, 177(3), 308–318. <https://doi.org/10.1002/ajmg.b.32611>
- Kendler, K.S., Ohlsson, H., Sundquist, J., & Sundquist, K. (2020). Facilitating versus inhibiting the transmission of drug abuse



- from high-risk parents to their children: a swedish national study. *Twin Research and Human Genetics*, 23(1), 1–7. <https://doi.org/10.1017/thg.2020.1>
- Kendler, K.S., Prescott, C.A., Myers, J., & Neale, M.C. (2003). The structure of genetic and environmental risk factors for common psychiatric and substance abuse disorders in men and women. *Archives Of General Psychiatry*, 60(9), 929–937. <https://doi.org/10.1001/archpsyc.60.9.929>
- Kodjo, C.M., & Klein, J.D. (2002). Prevention and risk of adolescent substance abuse. The role of adolescents, families, and communities. *Pediatric Clinics of North America*, 49(2), 257–268. [https://doi.org/10.1016/s0031-3955\(01\)00003-7](https://doi.org/10.1016/s0031-3955(01)00003-7)
- Kok, J.S., Berg, I.J., Blankevoort, G.C.G., & Scherder, E.J.A. (2017). Rest-activity rhythms in small scale homelike care and traditional care for residents with dementia. *BMC Geriatrics*, 17(1), 137. <https://doi.org/10.1186/s12877-017-0525-1>
- Kolb, B., Gibb, R., & Gorny, G. (2003). Experience-dependent changes in dendritic arbor and spine density in neocortex vary qualitatively with age and sex. *Neurobiology of Learning and Memory*, 79(1), 1–10. [https://doi.org/10.1016/s1074-7427\(02\)00021-7](https://doi.org/10.1016/s1074-7427(02)00021-7)
- Kondo, M., Gray, L.J., Pelka, G.J., Christodoulou, J., Tam, P.P., & Hannan, A.J. (2008). Environmental enrichment ameliorates amotor coordination deficit in a mouse model of Rett syndrome – Mecp2 gene dosage effects and BDNF expression. *European Journal of Neuroscience*, 27(12), 3342–50. <https://doi.org/10.1111/j.1460-9568.2008.06305.x>
- Kottow, M.H. (1980). A medical definition of disease. *Medical Hypotheses*, 6(2), 209–13. [https://doi.org/10.1016/0306-9877\(80\)90085-7](https://doi.org/10.1016/0306-9877(80)90085-7)
- Krech, D., Rosenzweig, M.R., & Bennett, E.L. (1960). Effects of environmental complexity and training on brain chemistry. *Journal of Comparative and Physiological Psychology*, 53, 509–519. <https://doi.org/10.1037/h0045402>
- Kreek, M.J., Levran, O., Reed, B., Schlussman, S.D., Zhou, Y., & Butelman, E.R. (2012). Opiate addiction and cocaine addiction: underlying molecular neurobiology and genetics. *The Journal of Clinical Investigation*, 122(10), 3387–93. <https://doi.org/10.1172/JCI60390>
- Kreilaus, F., Spiro, A.S., Hannan, A.J., Garner, B., & Jenner, A.M. (2016). Therapeutic Effects of Anthocyanins and Environmental Enrichment in R6/1 Huntington’s Disease Mice. *Journal of Huntingtons Disorders*, 5(3), 285–296. <https://doi.org/10.3233/JHD-160204>
- Lamb, R.J., Stark, H.G., & Ginsburg, B.C. (2021). Implications of there being many paths to addiction and recovery. *Pharmacology Biochemistry and Behavior*, 211, 173299. <https://doi.org/10.1016/j.pbb.2021.173299>. Online ahead of print.
- Lamb, R.J., & Ginsburg, B.C. (2018). Addiction as a BAD, a behavioral allocation disorder. *Pharmacology Biochemistry and Behavior*, 164, 62–70. <https://doi.org/10.1016/j.pbb.2017.05.002>
- Lamb, R.J., Stark, H.G., & Ginsburg, B.C. Implications of there being many paths to addiction and recovery. *Pharmacol Bio-*



- chem Behav* 2021 Nov 12;211:173299. <https://doi.org/10.1016/j.pbb.2021.173299> . Online ahead of print.
- Laviola, G., Hannan, A.J., Macrì, S., Solinas, M., & Jaber, M. (2008). Effects of enriched environment on animal models of neurodegenerative diseases and psychiatric disorders. *Neurobiological Disorders*, 31(2), 159–68. <https://doi.org/10.1016/j.nbd.2008.05.001>
- Le Moal, M., & Koob, G.F. (2007). Drug addiction: pathways to the disease and pathophysiological perspectives. *European Neuropsychopharmacology*, 17(6-7), 377-93. <https://doi.org/10.1016/j.euroneuro.2006.10.006>
- Legg, L., Drummond, A., & Langhorne, P. (2006). Occupational therapy for patients with problems in activities of daily living after stroke. *Cochrane Database of Systematic Reviews*, 4, CD003585. <https://doi.org/10.1002/14651858.CD003585.pub2>
- Lenoir, M., Serre, F., Cantin, L., & Ahmed, S.H. (2007). Intense sweetness surpasses cocaine reward. *PLoS One*, 2(8), e698. <https://doi.org/10.1371/journal.pone.0000698>
- Leshner, A.I. (1997). Addiction is a brain disease and it matters. *Science*, 278(5335), 45–47. <https://doi.org/10.1126/science.278.5335.45>
- Levy, N. (2013). Addiction is not a brain disease (and it matters). *Frontiers of Psychiatry*, 4, 24. <https://doi.org/10.3389/fpsyt.2013.00024>
- Lewis, M. (2016). *The biology of desire: Why addiction is not a disease*. Public Affairs Books.
- Lewis, M. (2018). Brain change in addiction as learning, not disease. *New England Journal of Medicine*, 379(16), 1551–1560. <https://doi.org/10.1056/NEJMra1602872>
- Li, X., Meng, L., Huang, K., Wang, H., & Li, D. (2015). Environmental enrichment blocks reinstatement of ethanol-induced conditioned place preference in mice. *Neuroscience Letters*, 599, 92–96. <https://doi.org/10.1016/j.neulet.2015.05.035>
- Lin, Y.H., Yao, M.C., Wu, H.Y., Dong, J., Ni, H.Y., Kou, X.L., et al. (2020). HDAC2 (Histone deacetylase 2): A critical factor in environmental enrichment-mediated stroke recovery. *Journal of Neurochemistry*, 155(6), 679-696. <https://doi.org/10.1111/jnc.15043>
- Lindesmith, A.R. (1980). A general theory of addiction to opiate-type drugs. *NIDA Research Monograph*, 30, 34–37.
- Lopez-Leon, S., González-Giraldo, Y., Wegman-Ostrosky, T., & Forero, D.A. (2021). Molecular genetics of substance use disorders: an umbrella review. *Neuroscience & Biobehavioral Reviews*, 124, 358–369. <https://doi.org/10.1016/j.neubiorev.2021.01.019>
- Lopez-Quintero, C., Pérez de los Cobos, J., Hasin, D.S., Okuda, M., Wang, S., Grant, B.F., & Blanco, C. (2011). Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Drug and Alcohol Dependence*, 115(1-2), 120-30. <https://doi.org/10.1016/j.drugalcdep.2010.11.004>. Epub 2010 Dec 8.



- Lüscher, C., Robbins, T.W., & Everitt, B.J. (2020). The transition to compulsion in addiction. *Nature Reviews Neuroscience*, 21(5), 247-263. <https://doi.org/10.1038/s41583-020-0289-z>
- Ma, Y.Y., Wang, X., Huang, Y., Marie, H., Nestler, E.J., Schluter, O.M., & Dong, Y. (2016). Resilencing of silent synapses unmasks anti-relapse effects of environmental enrichment. *Proceedings of the National Academy of Sciences of the United States of America*, 113(18), 5089-5094. <https://doi.org/10.1073/pnas.1524739113>
- Magalon, K., Cantarella, C., Monti, G., Cayre, M., & Durbec, P. (2007). Enriched environment promotes adult neural progenitor cell mobilization in mouse demyelination models. *European Journal of Neuroscience*, 25(3), 761-71. <https://doi.org/10.1111/j.1460-9568.2007.05335.x>
- Magee, W.L., Clark, I., Tamplin, J., & Bradt, J. (2017). Music interventions for acquired brain injury. *Cochrane Database of Systematic Reviews*, 1, CD006787. <https://doi.org/10.1002/14651858.CD006787.pub3>
- Marinelli, M., & Piazza, P.V. (2002). Interaction between glucocorticoid hormones, stress and psychostimulant drugs. *European Journal of Neuroscience*, 16(3), 387-394. <https://doi.org/10.1046/j.1460-9568.2002.02089.x>
- Martínez-Cué, C., Baamonde, C., Lumberras, M., Paz, J., Davisson, M.T., Schmidt, C. et al. (2002). Differential effects of environmental enrichment on behavior and learning of male and female Ts65Dn mice, a model for Down syndrome. *Behavioural Brain Research*, 134(1-2), 185-200. [https://doi.org/10.1016/s0166-4328\(02\)00026-8](https://doi.org/10.1016/s0166-4328(02)00026-8)
- Martino, F., Caselli, G., Fiabane, E., Felicetti, F., Trevisani, C., Menchetti, M. et al. (2019). Desire thinking as a predictor of drinking status following treatment for alcohol use disorder: A prospective study. *Addictive Behaviours*, 95, 70-76. <https://doi.org/10.1016/j.add-beh.2019.03.004>
- McOmish, C.E., Burrows, E., Howard, M., Scarr, E., Kim, D., Shin, H.S. et al. (2007). Phospholipase C-beta1 knockout mice exhibit endophenotypes modeling schizophrenia which are rescued by environmental enrichment and clozapine administration. *Molecular Psychiatry*, 13(7), 661-72. <https://doi.org/10.1038/sj.mp.4002046>
- Melendez, R.I., Gregory, M.L., Bardo, M.T., & Kalivas, P.W. (2004). Impoverished rearing environment alters metabotropic glutamate receptor expression and function in the prefrontal cortex. *Neuropsychopharmacology*, 29(11), 1980-1987. <https://doi.org/10.1038/sj.npp.1300507>
- Mello, N.K., & Mendelson, J.H. (1972). Drinking patterns during work-contingent and noncontingent alcohol acquisition. *Psychosomatic Medicine*, 34(2), 139-164. <https://doi.org/10.1097/00006842-197203000-00007>
- Nielsen, D.A., Utrankar, A., Reyes, J.A., Simons, D.D., & Kosten, T.R. (2012). Epigenetics of drug abuse: predisposition or response. *Pharmacogenomics*, 13(10), 149-60. <https://doi.org/10.2217/pgs.12.94>
- Nithianantharajah, J., & Hannan, A.J. (2006). Enriched environments, experience-de-



- pendent plasticity and disorders of the nervous system. *Nature Reviews Neuroscience*, 7(9), 697-709. <https://doi.org/10.1038/nrn1970>
- O'Brien, M.S., & Anthony, J.C. (2005). Risk of becoming cocaine dependent: epidemiological estimates for the United States, 2000–2001. *Neuropsychopharmacology*, 30(5), 1006–1018. <https://doi.org/10.1038/sj.npp.1300681>
- Pandya, S.Y., Clem, M.A., Silva, L.M., & Woon, F.L. (2016). Does mild cognitive impairment always lead to dementia? A review. *Journal of the Neurological Sciences*, 369, 57-62. <https://doi.org/10.1016/j.jns.2016.07.055>
- Pang, T.Y., & Hannan, A.J. (2013). Enhancement of cognitive function in models of brain disease through environmental enrichment and physical activity. *Neuropharmacology*, 64, 515–28. <https://doi.org/10.1016/j.neuropharm.2012.06.029>
- Peck, J.A., & Ranaldi, R. (2014). Drug abstinence: exploring animal models and behavioral treatment strategies. *Psychopharmacology*, 231(10), 2045–2058. <https://doi.org/10.1007/s00213-014-3517-2>
- Peele, S. (2016). People Control Their Addictions: No matter how much the “chronic” brain disease model of addiction indicates otherwise, we know that people can quit addictions - with special reference to harm reduction and mindfulness. *Addictive Behaviors Reports*, 4, 97-101. <https://doi.org/10.1016/j.abrep.2016.05.003>
- Piazza, P.V., & Le Moal, M.L. (1996). Pathophysiological basis of vulnerability to drug abuse: role of an interaction between stress, glucocorticoids, and dopaminergic neurons. *Annual Review of Pharmacology and Toxicology*, 36, 359–378. <https://doi.org/10.1146/annurev.pa.36.040196.002043>
- Pinaud, R., Penner, M.R., Robertson, H.A., & Currie, R.W. (2001). Upregulation of the immediate early gene arc in the brains of rats exposed to environmental enrichment: implications for molecular plasticity. *Molecular Brain Research*, 91(1-2), 50–56. [https://doi.org/10.1016/s0169-328x\(01\)00121-8](https://doi.org/10.1016/s0169-328x(01)00121-8)
- Pollock, A., Baer, G., Campbell, P., Choo, P.L., Forster, A., Morris, J., et al. (2014). Physical rehabilitation approaches for the recovery of function and mobility following stroke. *Cochrane Database of Systematic Reviews*, 4, CD001920. <https://doi.org/10.1002/14651858.CD001920.pub3>
- Prado Lima, M.G., Schimdt, H.L., Garcia, A., Daré, L.R., Carpes, F.P., Izquierdo, I. et al. (2018). Environmental enrichment and exercise are better than social enrichment to reduce memory deficits in amyloid beta neurotoxicity. *Proceedings of the National Academy of Sciences of the United States of America*, 115(10), E2403–E2409. <https://doi.org/10.1073/pnas.1718435115>
- Qin, H., Reid, I., Gorelik, A., & Ng, L. (2021). Environmental enrichment for stroke and other non-progressive brain injury. *Cochrane Database of Systematic Reviews*, 11(11), CD011879. <https://doi.org/10.1002/14651858.CD011879.pub2>
- Ranaldi, R., Kest, K., Zellner, M., & Hachimine-Semprebom, P. (2011). Environmental enrichment, administered



- after establishment of cocaine self-administration, reduces lever pressing in extinction and during a cocaine context renewal test. *Behavioral Pharmacology*, 22(4), 347–353. <https://doi.org/10.1097/FBP.0b013e3283487365>
- Reboussin, B.A., & Anthony, J.C. (2006). Is there epidemiological evidence to support the idea that a cocaine dependence syndrome emerges soon after onset of cocaine use? *Neuropsychopharmacology* 31(9), 2055–64. <https://doi.org/10.1038/sj.npp.1301037>
- Renoir, T., Pang, T.Y., & Hannan, A.J. (2013). Effects of environmental manipulations in genetically targeted animal models of affective disorders. *Neurobiological Disorders*, 57, 12–27. <https://doi.org/10.1016/j.nbd.2012.04.003>
- Reynolds, S., Urruelam, M., & Devine, D.P. (2013). Effects of environmental enrichment on repetitive behaviors in the BTBR T+tf/J mouse model of autism. *Autism Research*, 6(5), 337–43. <https://doi.org/10.1002/aur.1298>
- Rosenzweig, M.R. (1966). Environmental complexity, cerebral change, and behavior. *American Psychologist*, 21(4), 321–332. <https://doi.org/10.1037/h0023555>
- Rosenzweig, M.R., & Bennett, E.L., 1996. Psychobiology of plasticity: effects of training and experience on brain and behavior. *Behavioural Brain Research* 78(1), 57–65. [https://doi.org/10.1016/0166-4328\(95\)00216-2](https://doi.org/10.1016/0166-4328(95)00216-2)
- Ruisoto, P., & Contador, I. (2019). The role of stress in drug addiction. An integrative review. *Physiology & Behavior*, 202, 62–68. <https://doi.org/10.1016/j.physbeh.2019.01.022>
- Ruiz Sánchez de León, J.M., & Pedrero Pérez, E.J. (2014). *Neuropsicología de la adicción*. Editorial Médica Panamericana.
- Ruiz Sánchez de León, J.M., & Pedrero Pérez, E.J. (2019). *Neuropsicología de las conductas adictivas*. Editorial Síntesis.
- Rutten, A., van Albada, M., Silveira, D.C., Cha, B.H., Liu, X., Hu, Y.N. et al. (2002). Memory impairment following status epilepticus in immature rats: time-course and environmental effects. *European Journal of Neuroscience*, 16(3), 501–13. <https://doi.org/10.1046/j.1460-9568.2002.02103.x>
- Ryan, S.A. (2019). Substance Abuse in Pregnancy. *Clinical Obstetrics and Gynecology*, 62(1), 112–117. <https://doi.org/10.1097/GRF.0000000000000427>
- Sale, A., Berardi, N., & Maffei, L. (2009). Enrich the environment to empower the brain. *Trends in Neuroscience*, 32(4), 233–9. <https://doi.org/10.1016/j.tins.2008.12.004>
- Sale, A., Maya Vetencourt, J.F., Medini, P., Cenni, M.C., Baroncelli, L., De Pasquale, R., & Maffei, L. (2007). Environmental enrichment in adulthood promotes amblyopia recovery through a reduction of intracortical inhibition. *Nature Neuroscience*, 10(6), 679–81. <https://doi.org/10.1038/nn1899>
- Sanz-Blasco, R., Ruiz-Sánchez de León, J.M., Ávila-Villanueva, M., Valentí-Soler, M., Gómez-Ramírez, J., & Fernández-Blázquez, M.A. (2021). Transition from mild cognitive impairment to normal cognition: Determining the predictors of reversion with multi-state Markov models. *Alzheimer's & Dementia*, Sep 5. <https://doi.org/10.1002/alz.12448>. Online ahead of print.



- Schaler, J. A. (2000). *Addiction Is a Choice*. Open Court.
- Sikora, M., Nicolas, C., Istin, M., Jaafari, N., Thiriet, N., & Solinas, M. (2018). Generalization of effects of environmental enrichment on seeking for different classes of drugs of abuse. *Behavioural Brain Research*, 341, 109-113. <https://doi.org/10.1016/j.bbr.2017.12.027>
- Sinha, R. (2001). How does stress increase risk of drug abuse and relapse? *Psychopharmacology (Berl.)* 158(4), 343-359. <https://doi.org/10.1007/s002130100917>
- Solinas, M., Chauvet, C., Thiriet, N., El Rawas, R., & Jaber, M. (2008). Reversal of cocaine addiction by environmental enrichment. *Proceedings of the National Academy of Sciences of the United States of America*, 105(44), 17145-17150. <https://doi.org/10.1073/pnas.0806889105>
- Solinas, M., Thiriet, N., Chauvet, C., & Jaber, M. (2010). Prevention and treatment of drug addiction by environmental enrichment. *Progress in Neurobiology*, 92(4), 572-92. <https://doi.org/10.1016/j.pneurobio.2010.08.002>
- Spires, T.L., Grote, H.E., Varshney, N.K., Cordery, P.M., van Dellen, A., Blakemore, C., & Hannan, A.J. (2004). Environmental enrichment rescues protein deficits in a mouse model of Huntington's disease, indicating a possible disease mechanism. *Journal of Neuroscience*, 24(9), 2270-2276. <https://doi.org/10.1523/JNEUROSCI.1658-03.2004>
- Suemaru, K., Yoshikawa, M., Aso, H., & Watanabe, M. (2018). Environmental enrichment alleviates cognitive and behavioral impairments in EL mice. *Epilepsy Behaviour*, 85, 227-233. <https://doi.org/10.1016/j.yebeh.2018.06.016>
- Sullivan, P.F., Agrawal, A., Bulik, C.M., Andreassen, O.A., Børglum, A.D., Breen, G. et al. (2018). Psychiatric genomics: an update and an agenda. *American Journal of Psychiatry*, 175(1), 15-27. <https://doi.org/10.1176/appi.ajp.2017.17030283>
- Thiel, K.J., Painter, M.R., Pentkowski, N.S., Mitroi, D., Crawford, C.A., & Neisewander, J.L. (2012). Environmental enrichment counters cocaine abstinence-induced stress and brain reactivity to cocaine cues but fails to prevent the incubation effect. *Addiction Biology*, 17(2), 365-377. <https://doi.org/10.1111/j.1369-1600.2011.00358.x>
- van Dellen, A., Blakemore, C., Deacon, R., York, D., & Hannan, A.J. (2000). Delaying the onset of Huntington's in mice. *Nature*, 404(6779), 721-2. <https://doi.org/10.1038/35008142>
- van Praag, H., Kempermann, G., & Gage, F.H. (2000). Neural consequences of environmental enrichment. *Nature Reviews Neuroscience*, 1(3), 191-198. <https://doi.org/10.1038/35044558>
- van Praag, H., Shubert, T., Zhao, C., & Gage, F.H. (2005). Exercise enhances learning and hippocampal neurogenesis in aged mice. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 25, 8680-8685. <https://doi.org/10.1523/JNEUROSCI.1731-05.2005>
- Vega-Rivera, N.M., Ortiz-López, L., Gómez-Sánchez, A., Oikawa-Sala, J., Estrada-Camarena, E.M., Ramírez-Rodríguez, G.B. (2016). The neurogenic effects of



- an enriched environment and its protection against the behavioral consequences of chronic mild stress persistent after enrichment cessation in six-month-old female Balb/C mice. *Behavioural Brain Research*, 301, 72-83. <https://doi.org/10.1016/j.bbr.2015.12.028>
- Viola, G.G., Rodrigues, L., Americo, J.C., Hansel, G., Vargas, R.S., Biasibetti, R. et al. (2009). Morphological changes in hippocampal astrocytes induced by environmental enrichment in mice. *Brain Research*, 1274, 47-54. <https://doi.org/10.1016/j.brainres.2009.04.007>
- Volkow, N.D., & Koob, G. (2015). Brain disease model of addiction: why is it so controversial?. *Lancet Psychiatry*, 2(8), 677-679. [https://doi.org/10.1016/S2215-0366\(15\)00236-9](https://doi.org/10.1016/S2215-0366(15)00236-9)
- Weyer-Jamora, C., Brie, M.S., Luks, T.L., Smith, E.M., Hervey-Jumper, S.L., & Taylor, J.W. (2021). Postacute Cognitive Rehabilitation for Adult Brain Tumor Patients. *Neurosurgery*, 89(6), 945-953. <https://doi.org/10.1093/neuros/nyaa552>
- Will, B., Galani, R., Kelche, C., & Rosenzweig, M.R. (2004). Recovery from brain injury in animals: relative efficacy of environmental enrichment, physical exercise or formal training (1990-2002). *Progress in Neurobiology*, 72(3), 167-182. <https://doi.org/10.1016/j.pneurobio.2004.03.001>
- Ziegler-Waldkirch, S., Marksteiner, K., Stoll, J., d'Errico, P., Friesen, M., Eiler, D. et al. (2018). Environmental enrichment reverses Abeta pathology during pregnancy in a mouse model of Alzheimer's disease. *Acta Neuropathologica Communications*, 6(1), 44. <https://doi.org/10.1186/s40478-018-0549-6>
- Zoorob, R., Kowalchuk, A., & Mejia de Grubb, M. (2018). Buprenorphine therapy for opioid use disorder. *American Academy of Family Physicians*, 97(5), 313-320.