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Highlighting the role of cognitive and brain reserve in the substance use disorder field.

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Abstract: ***Background:*** *Cognitive reserve (CR) refers to the ability of an individual to cope with brain pathology remaining free of cognitive symptoms. This protective factor has been related to compensatory and more efficient brain mechanisms involved in resisting brain damage. For its part, Brain reserve (BR) refers to individual differences in the structural properties of the brain which could also make us more resilient to suffer from neurodegenerative and mental diseases.* ***Objective:*** *This review summarizes how this construct, mainly mediated by educational level, occupational attainment, physical and mental activity, as well as successful social relationships, has gained scientific attention in the last years with regard to diseases, such as neurodegenerative diseases, stroke or traumatic brain injury. Nevertheless, although CR has been studied in a large number of disorders, few researches have addressed the role of this concept in drug addiction.* ***Methods:*** *We provide a selective overview of recent literature about the role of CR and BR in preventing substance use onset. Likewise, we will also discuss how variables involved in CR (healthy leisure, social support or job-related activities, among others) could be trained and included as complementary activities of substance use disorder treatments.* ***Results:*** *Evidence about this topic suggests a preventive role of CR and BR on drug use onset and when drug addiction is established, these factors led to less severe addiction-related problems, as well as better treatment outcomes.* ***Conclusion:*** *CR and BR are variables not taken yet into account in drug addiction. However, they could give us a valuable information about people at risk, as well as patient's prognosis.*

Keywords: Drug; addiction; cognition; cognitive reserve; brain reserve; neuroplasticity.

1. INTRODUCTION

The construct of "reserve" has been raised in clinical studies to elucidate the deficient correlation between brain pathology and clinical outcomes in numerous brain disorders [1]. In fact, the severity of cognitive outcomes can vary considerably in patients with amounts of brain damage similar in nature and extent. Thus, the reserve concept has a great heuristic value since it explains individual differences in facing neuropathology and indicates that some aspects of cerebral function and neural substrate can buffer the effects of brain disease. In particular, the individual variability in the functional use or structural integrity of the nervous system may alter a person's cognitive and behavioral skills following the onset of brain pathology.

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It seems that higher levels of reserve may lead to better functional outcomes by moderating the effects of normal ageing or neurodegenerative brain pathologies [2].

Reserve differences may address both the extent of the initial impairment and the extent of recovery over time [3]. Furthermore, reserve may result from innate intelligence, brain size, or aspects of life experiences (e.g., educational levels, occupational attainment, social relationships, or leisure activities) which allow some people to cope with pathology better than others. In any case, the brain networks that are more efficient or plastic could be less susceptible to damage. The concept of reserve has been widely applied in the context of dementia and neurodegenerative diseases, such as Parkinson's disease, Huntington's disease, and multiple sclerosis [4, 5, 6, 7, 8], and more recently in context of brain injury [9], and it is frequently used to explain the mechanisms of "resilience" to brain aging, disease, or insult.

In the present review article, we analyzed two commonly studied types of reserve: "cognitive reserve" (CR), which refers to "active" mechanisms for coping with neuropathology, and "brain reserve" (BR), which refers to a

"passive" protective potential that depends on the anatomic substrate of the brain [1, 10]. Hence, although BR and CR began as very distinct concepts, recent studies have revealed that our brain undergoes plastic changes (e.g. molecular, cellular, and synaptic) in response to our experience and for this reason, the boundaries between these two concepts should be shortened [1, 2, 6]. For instance, a recent study carried out with middle-aged adults at risk of dementia showed that people with higher occupational attainment are able to better tolerate Alzheimer's disease-like pathology (reduced hippocampal volume and brain atrophy) and maintain a similar level of cognitive performance compared with those with less pathology [11]. Furthermore, physical activity and cognitive training have shown important benefits, both in humans and animal models, due to their effect on neuroplasticity, hippocampal-dependent neurogenesis, as well as on several growth factors [12]. Finally, in humans, years of education is usually considered the most relevant factor impacting on brain plasticity [13]. Indeed, schooling may induce an increase of synaptic density in the neocortex promoting neural connectivity [14, 15].

Taking this into account, and given the importance of CR and BR in facing neuropathology, here we focused on the role of CR and BR constructs in modulating or even preventing drug addiction. For this purpose, a comprehensive review was carried out in the PubMed, ScienceDirect and Scielo databases (Scientific Online electronic library). The search was limited to those articles that contain the following descriptors: drug; addiction; substance use disorder; cognition; cognitive reserve; educative level; occupational attainment; socioeconomic status; leisure activities; social support; treatment; brain reserve; neuroplasticity. We excluded those works in which the subjects with substance abuse also had comorbid pathology (depression, borderline personality disorder, anxiety disorder, among others). Besides, we used the Boolean operators Y and O to combine or exclude keywords in a search resulting in more focused and productive results. The search was not restricted for years, although mainly works published after the year 2000.

2. COGNITIVE AND BRAIN RESERVE

2.1 Cognitive reserve (CR)

The concept of CR has been proposed to account for the disjunction between the extent of brain pathology and the severity of clinical outcomes observed in patients with Alzheimer's disease (AD) [16, 17]. CR is considered as a protective factor able to postpone the onset of cerebral pathology and/or cognitive decline in old age by modifying cognitive or neural networks and cognitive abilities [1, 2, 10, 18, 19]. Therefore, CR is conceived as the active model of reserve.

CR is a latent variable that is commonly assessed using indirect measures of cognitive efficiency and flexibility that are less affected by ageing or acquired neuropathology and reflect how a person uses one's own cognitive resources, like educational level, occupational complexity, or premorbid intelligence quotient (IQ) [1, 2, 20]. The concept of CR posits that individual differences in optimizing cognitive performances can be achieved through differential recruitment of cerebral areas and circuits [1, 19]. Neural reserve and neural compensation are the mechanisms underlying the CR [21, 22, 23]. Neural reserve corresponds to preexisting brain networks that are more efficient and flexible, and thus less vulnerable to disruption. Neural compensation indicates an increased neural activity in task-related networks or the recruitment of additional brain regions or compensatory networks when neuropathology disrupts the preexisting task-specific networks.

CR has been primarily implicated in the clinical expression of AD pathology [19]. Epidemiological and clinical studies have identified a number of CR proxies, including years of education [24, 25, 26, 27], occupation status/attainment [28, 29], and leisure activities [30, 31]. The consideration of these CR proxies is important in studies of "preclinical" AD and in clinical trials, since they could play a role in delaying the onset of cognitive impairment or even forestalling the diagnosis of AD.

Neuroimaging techniques have allowed to study many CR correlates in AD patients. In particular, high-educated patients showed lower perfusion [17], hypometabolism [32, 33], and smaller cortical thickness [34] in temporoparietal regions, as well as increased accumulation of Aβ plaques and tau tangles [33, 35] in comparison to low-educated patients with the same level of cognitive deterioration. These data indicate that patients with greater CR can withstand a greater degree of AD pathology for a longer time before cognitive decline becomes clinically evident. It is noteworthy that years of education and occupational attainment are the most studied CR proxies not only in AD and neurodegenerative diseases, but also in many other pathologies such as human immunodeficiency virus (HIV) infection [36], schizophrenia [37], bipolar disorder [38], depression [39], stroke, and traumatic brain injury [40]. However, CR proxies such as education, occupation, or leisure activities have limitations. In fact, they can be highly correlated among themselves and not totally accurate since the same value may be associated to different degree of experience across individuals, and they are not dynamic as they do not reflect the current state of CR.

Lastly, many other psychosocial factors have shown to be similarly able to provide CR in either disease and health, including exercise and physical activity [41, 42, 43, 44, 45], diet [41, 44, 46], good sleep [47, 48], socioeconomic status [49], and social stimulation and support [37, 50].

2.2 Brain reserve (BR)

BR refers to individual differences in the structural properties of the brain that are available to a person [10]. BR is conceived as the passive model of reserve. The concept of BR suggests that each person has a certain amount of biological resources, which determines the degree to which neuropathological damage can be tolerated before people reach their maximum resource capacity and the consequent cognitive decline [1, 6]. This "threshold model" has been developed to explain discrepancies observed in demented

patients, especially affected by AD [1, 51]. Patients with more BR are considered to have a higher threshold for the expression of cognitive symptoms after the onset of neuropathology. Thus, it can be hypothesized that as brain volume or synaptic density diminishes, those with higher premorbid BR (e.g., larger brains or more neurons) will manifest AD symptoms less quickly and severely in comparison to those with lower premorbid BR.

BR is commonly assessed by using anatomical measures of brain size, neuronal count, and synaptic density. For example, premorbid brain size can be indirectly estimated by head circumference or total intracranial volume [52, 53, 54]. Both head circumference and intracranial volume resulted to be inversely associated with risk of dementia and AD in early studies [55, 56, 57]. In subsequent studies, BR capacity has been further characterized as the overall and regional size of the brain [58, 59], the number and size of neurons [60], synaptogenesis [61], cortical thickness [62, 63], white matter integrity [64, 65], and dendritic length and density [21]. Notably, in the long run these BR proxies are modifiable and susceptible to neuropathological processes, brain insult, psychiatric disease, life experiences, and/or environmental factors [44, 66, 67].

Passive BR model is essentially a quantitative model since when brain capacity (e.g., synaptic density) falls beyond a critical point ("threshold"), clinical deficits emerge. Therefore, the depletion of neurons and synapses must be very severe in individuals with more BR for the symptoms to become clinically relevant. This model underlines the important role of environmental factors during prenatal and early life in affecting the brain capacity and thus determining the expression of neuropathology in vulnerable individuals in late life. BR model can be applied to normal ageing, injury, or disease-related brain pathology. Anyway, the studies on passive BR model have reported conflicting results. The weak relationships between the traditional BR variables (e.g., morphological measures of the brain) and clinical status are potentially due to the coarse nature of these variables [68]. To date, in fact, the largest neuroimaging studies [69, 70, 71] did not find any predictive relationship between total intracranial volume and AD, except for a subgroup of male patients with presence of ε4 APOE allele and low intracranial volume (Jenkins et al., 2000). Conversely, new studies on the structural connectivity patterns between brain regions using advanced network analysis techniques could provide more sensitive measures to predict individual variations in cognitive ability [68, 72]. Since brain structural and functional components are strictly codependent, one proposed mechanism of reserve consist in brain plasticity [42] comprising functional network plasticity, neurogenesis, as well as morphological, synaptic, and vascular changes, which may contribute to both BR and CR. Better understanding of the neuroplasticity properties underlying reserve may help clinical neuroscience to develop innovative treatment strategies for different neuropathologies, such as addiction disorders.

3. COGNITIVE RESERVE: A PROTECTIVE EMERGING FACTOR IN SUD FIELD.

CR construct has begun to emerge in the field of addiction showing that there are patients whose neurological disorders caused by chronic drug consumption are not related to their clinical manifestations. Thus, factors such as the educational level, the occupational attainment and the practice of healthy leisure activities seem to be protective elements, even when an addictive process is established. These variables have shown to be able to attenuate the impact of the drug on cognitive performance and, consequently, favoring the treatment outcome. For instance, lower CR, as reflected by childhood IQ, mediates the onset, maintenance and comorbidity of several psychiatric disorders [73]. Hence, cognitive ability is an important element which must be considered in many subjects who seek mental health treatment [74, 75]. A recent study about this issue revealed that a high CR in individuals with SUD led to lesser severe drug addiction-related problems, longer periods of abstinence, better cognitive performance, as well as better daily functioning in their lives compared with patients with low score in this construct [76].

Taking this into account, in this section, we will summarize some evidence about the impact of CR-related measures on drug use disease and the possibility to improve these variables when SUD is diagnosed. Furthermore, due to the relationship between CR and BR, we will also focus on describing some brain characteristics which could reduce substance consumption effects.

3.1. Role of factors involved in the cognitive reserve on the SUD

3.1.1. Educational level

CR operationalized as years of education is one of the most employed measures within the tests used to assess this cognitive construct [77, 78, 79, 80]. It is probably due to this variable could allow us to infer the rest of factors involved in CR because a person with high level of education may have a higher employment position, socioeconomic status, incomes, as well as social support. Concerning this issue, early school failure and low attachment to school have been recognized to be key risk factors for substance use onset [81, 82]. Besides, young people who drops out of high school or college have shown to be at higher risk of develop alcohol abuse in adulthood compared with persons with a completed college degree or postgraduate education [82]. Longitudinal studies, such as the longitudinal GLOBE study, found that lower educated people were almost three times more likely to start excessive alcohol consumption compared with people with higher educational level [83]. On the other hand, educational expectations seem to be another protective factor regarding drug use [83]. Hence, adolescents anticipating university attendance exhibited higher levels of engagement in health-protective behaviors and were more likely to avoid unhealthy behaviors such as alcohol, tobacco and cannabis use [84].

An interesting research focused on the relationship between gender discrimination, drug abuse and educational

level found that women with only primary education were at significantly higher risk for drug use associated with discrimination compared with women with higher education level [85]. Finally, when alcohol dependence occurs, alcohol-related medical problems are frequently found among those with low compared with high education [85].

Nevertheless, the relationship between substance use and academic achievement is complex because it is difficult to distinguish if SUD is a cause or consequence of few years of education. Besides, when this variable appears to be cause of drug use onset, we must consider other factors such as psychiatric disturbances, which could impact not only on the development of substance consumption, but also on the ability to complete educative grades [86, 87, 88, 89].

3.1.2 Occupational attainment and socioeconomic status

There are conflicting data which reflects the complexity between drug abuse and employment characteristics. Hence, parameters as age range, gender and ethnicity must be considered when we analyze the impact of this variable on SUD. Thus, it has been found that unemployment was associated with increased cannabis and sedative use in both women and men [90, 91]. In general, marijuana use was associated with less prestigious occupations and lower family income, whereas nicotine use was unrelated and moderate daily drinking was positively associated [90]. Furthermore, a comprehensive review carried out by Henkel (2011) [91] showed that risky alcohol consumption is more prevalent among unemployed which are also more likely to be smokers, use illicit and prescription drugs and develop SUD.

A recent review about the impact of economic recessions and unemployment on illegal drug use suggests that psychological distress related to unemployment led to an increase of substance consumption [92]. On the other hand, and as expected, our employments status is related to our incomes, so it has been found that the volume of alcohol consumption and the number of drinks decreased during economic recessions due to lower individual incomes [93]. Therefore, future research efforts should focus on identifying specific risk groups, such as unemployed people, to help and develop preventive measures. For instance, several studies have found that improving employability and achieving paid employment through educational programs and vocational training enhanced health and social functioning, as well as the success of SUD treatments [94, 95].

A closely related aspect to the occupational attainment is the socioeconomic status (SES). In general, a lower SES is related to an impaired health status, more health problems and a shorter life expectancy which is probably mediated by unhealthy lifestyle factors such as drug abuse [96]. Regarding alcohol and tobacco smoking, there is a clear evidence of a relationship between smoking rates and low SES, while in alcohol use, the evidence is mixed, with some studies pointing to a link between harmful alcohol use and lower SES [97] and other studies suggesting opposite results [98]. Interestingly, in the study performed by Sabia et al.'s [99] with middle-aged male population, heavy alcohol consumption in low socioeconomic group is associated with poorer cognitive performance, whereas this negative effect was attenuated in the high SES group.

Furthermore, a strong positive relationship was found between incomes and cocaine use [100], whereas crack users tend to be more marginalized from employment and less likely to have a work [101]. Nevertheless, there is also a growing evidence that individuals with high SES are also at elevated risk for substance abuse due to the fact that drug use also depends on its cost [102]. For instance, for adolescents with higher SES, the cost of substance use may be lower than for adolescents with lower SES increasing the likelihood of consumption [103]. Even, it has been described a different pattern of alcohol intake depending on SES. Thus, people with a higher SES tend to drink smaller amounts more frequently, whereas in the case of people with low SES who drink, binge-drink pattern is more often observed. Nevertheless, a higher proportion of abstainers is also found among people with low SES [104, 105].

3.1.3. Leisure activities

Healthy leisure activities are enriching experiences also involved in increasing our CR [106]. It refers as free-time used in a positive and meaningful way beyond school and work. One of the main studies about this topic, carried out by Sharp et al.'s group (2011) [107], found that a higher level of healthy leisure led to a decrease likelihood of using alcohol and marijuana, and as healthy leisure increased over time, the probability of using alcohol, tobacco, and marijuana kept decreasing. Following with this finding, Weybright et al.'s [108] revealed that higher levels of healthy leisure were associated with a tendency to use fewer substances among adolescences. Owing to this beneficious impact, some school-based prevention programs have been developed targeting youth's leisure and showing a reduction in the likelihood of initiating drug use mainly among girls [109]. Besides, taking part in after-school recreational activities has been found to be a protective factor against substance use [110].

Additionally, habitual practice of aerobic exercise has also shown to be a protective factor against SUD [111]. As is well-known, a risk factor of drug addiction is the lack of healthy leisure opportunities in the adulthood and, for this reason, programs of healthy education in which physical activity is taken into account could be a valuable strategy to reduce the negative impact of drug abuse [111, 112]. On the other hand, findings indicate that moderate aerobic exercise interventions are efficacious adjunct to SUD treatment by improving adherence and avoiding relapses [113]. In contrast, sedentary behavior, reflected by the number of hours of TV and video games, was positively related to drug use among adolescents [114]. These types of leisure activities along with doing nothing in particular led to poorer scores in a wide range of well-being variables such as negative mood, social alienation, self-esteem and life satisfaction [115] which are known to be involved in substance use onset [116]. As consequence, it has been found that young people which do leisure activities such as

exercise, going to the cinema or reading books are less vulnerable to suffer from a SUD, whereas leisure activities requiring going out with friends to have a drink increased the probability of drug use [117].

3.1.4. Social support

In general, humans have the basic need to be accepted by social groups which are considered relevant for them [118]. Thus, exclusion and social rejection can lead to lower self-esteem, self-efficacy and individual´s overall health, as well as mental diseases, such as depression and anxiety [119, 120]. Regarding SUD, a positive social network has been shown to be beneficial for abstinence and recovery, whereas people with poor family relationships and low social support have been proved to be more prone to use drugs [121, 122, 123, 124]. In particular, it is the quality of relationships with family, friends and significant others and not the quantity which can buffer SUD behaviors [121].

For instance, it is well known that during the young adulthood, a critical period for starting substance use, peer networks have shown to exert important effects on substance use onset [125, 126]. Peer support has not been always related to a protective effect, whereas parents and other adults have consistently been found to be a beneficious factor which suggests that the positive effect of social support depends on the source of the support [127, 128]. Within the familiar context, a pattern of warm relationships, good communicative abilities, cohesion and clear rules have shown to play a preventive role on drug use beginning [129, 130]. Thus, it is common that people with SUD frequently experience severe impairments in their family environments, which could be even worse if they also present psychiatric disorders [131, 132]. In addition to peer and parent contexts, other studies have taken into account the variable "liking school" (taste for attending to school and taking part in school activities) which has shown to have an inverse association with alcohol consumption [133, 134].

On the other hand, religiosity could be considered as other type of social support that may help to protect against SUD in adults [135, 136, 137]. Concerning this aspect, it has been found that more frequent church attendance is associated with lower odds of developing an alcohol use disorder over a three-year period [138]. Among adults, other important social factor is the marital status [139, 140, 141]. Hence, the frequency and quantity of alcohol consumption is lower among married individuals than among singles [140]. In contrast, heterogeneity and instability in romantic relationships, as well as divorce have been associated with increases in substance use, particularly alcohol [139, 142].

In summary, the different variables involved in the CR construct seem to have a relevant role on drug addiction constituting a potential target within SUD treatments. Training these variables could promote resistance against cognitive deficits induced by drug abuse, as well as reduction of the rewarding value of drug-related behaviors. On the other hand, it is very difficult to analyze the contribution of each of these variables due to the high relationship between them. For instance, it has been found that approximately 45% of adults with HIV are unemployed [143] and the lack of a job position reduces economic resources and at the same time, the possibility of travelling, taking classes or seeking mentally stimulating leisure activities [144]. Going further, CR has also shown to impact on our behaviors when we are under drug effects. Thus, Abbey et al's study [145] has revealed that participants with less CR made riskier decisions (e.g. have unprotected sex) when they were alcohol intoxicated. This evidence suggests that individuals with high levels of CR may be particularly vigilant when they are under drug effects being able to attenuate or compensate them.

3.2. Cognitive reserve as a new therapeutic target within SUD treatment.

Evidence suggests that a low CR increases the vulnerability to drug use onset. Thus, the different measures associated with this construct can be included and trained as a complement of conventional SUD therapies. For instance, physical activity has been suggested as a potential treatment for drug addiction and individuals with SUD are usually interested in exercise to reduce drug craving and boredom [146, 147, 148, 148, 149]. For many individuals, exercise training has shown a positive effect reducing drug consumption [150, 151, 152, 153, 154, 155, 156], craving [154, 155, 156, 157], as well as increasing both treatment adherence [158] and abstinence period [159, 160, 161]. Interestingly, the beneficious effect of exercise was also found on comorbid psychiatric disorders related to SUD. Thus, a four-week exercise training program led to reductions in depression symptomatology in an inpatient SUD sample [162], while in a methadone maintenance sample, significant reductions in stress were found during an intervention through Wi-Fit program [163]. Besides, individuals participating in exercise training programs have shown greater decreases in anxiety compared with common forms of treatment, such as psychotherapy, and also regular exercise can be as effective as pharmacotherapy [164]. In spite of this apparent positive impact of exercise, it is unknown how long this effect maintains and which conditions are necessary to induce a long-term beneficial response. According to this, the recent study of Wang et al.'s [165] described that moderate and high-intensity aerobic exercises, designed according to the Guidelines of American College of Sports Medicine, can be an effective and persistent treatment for those individuals with SUD. Similarly, enrolling in leisure activities such as mindfulness, play music and art have shown to induce benefits not only on drug related measures (craving: [166, 167, 168], psychological well-being: [169, 170, 171], treatment adherence and reduction of drug use: [166, 170, 172], relapse prevention: [166, 172], but also in cognitive performance: [173].

On the other hand, standard SUD treatments appear to have little effect on patients' employment outcomes [174, 175]. Hence, job-related activities may be a useful approach to improve employment outcomes, as well as enhance quality of life and decrease drug abuse. Specifically, these activities include developing resumes, searching job want ads, completing job applications and attending vocational

rehabilitation programs [176]. Besides, rehabilitation programs focused on these job skills should also include training in computer knowledge and managing interpersonal relationships at work due to the fact that drug users usually have problems in these skills compared with job seekers in the general population [177]. Hence, in a study performed by Silverman et al. [178], subjects who received therapy focused on job skills showed higher abstinence rates from opiated and cocaine relative to the control group specially during the first 6 months. In addition, intensive vocational training programs has shown not only to improve employment outcomes [179], but also abstinence [180] and psychological functioning [179]. Furthermore, a positive relationship with the supervisor and a strong feeling of belonging to a work community has shown to be a positive aspect of preventing relapse [181]. Nevertheless, based on Magura et al.'s review [182], effects produced by these interventions focused on promoting employment had modest or non-significant results and the most of them did not analyze their impact on drug-related measure (e.g. craving, abstinence, relapse…).

Interventions designed to strengthen social networks have shown to improve drug recovery outcomes [183, 184]. Specially, women expressed the need to include family and friends in treatment programs [185, 186]. Besides, having fewer drug users in one's social network, as well as social support available, predicted cocaine abstinence in a group of individuals receiving treatment [187]. Interestingly, the study of Cavaiola et al.'s group [188] revealed that not all members of a social network have the same impact on drug addiction recovery. Thus, in this study, most of the sample of opioid-dependent individuals indicated that immediate family (e.g. mothers and siblings) were part of their support network, whereas extended family, such as friends, boyfriends/girlfriends, were less involved as support. This result coincides with Falkin and Strauss [189] who found that immediate family, especially mothers, had an important role as sources of recovery support. Owing to the key involvement of parents as social support, parenting skills interventions promoting adequate levels of monitoring and supervision, parent disapproval of underage drinking, high-quality parent-child interactions, low family conflict, and general communication could have a positive impact on reducing or mitigate adolescence substance consumption [190]. Concerning this issue, it was found that a group therapy program for opioid-dependent adolescents and their parents had successful completion rates [191].

Finally, neuropsychological research has consistently found that individuals with drug dependence often present impairments in different cognitive functions [192, 193, 194, 195]. Hence, cognitive training programs, in which several organized exercises are used to improve different cognitive domains, could be employed as a valuable adjuvant intervention in drug addiction [196]. In our recent review, we have summarized the promising impact of cognitive therapy, focused on either one or several cognitive areas, on drug-related measures such as craving, mood, self-regulation, treatment adherence, reduction of substance use and relapse prevention [75].

Fortunately, evidence suggests that although subjects with drug use problems usually have a low CR which makes them more vulnerable to initiate substance consumption, protective factors-involved in this construct, such as work engagement, social support, exercise and cognitive activities can be included and improved within SUD treatment programs.

4. BRAIN RESERVE IN SUD

The concept of CR is linked to the existence of a BR which allows to cope brain damage improving the prognosis of the patients [1, 31, 197, 198]. Traditional approaches have focused on CR-related measures, but neurobiological mechanisms remain poorly understood. To date, BR is understood as an "extra" capacity provided by a larger premorbid brain size which contains a greater number of neurons and synapses [23, 199].

Regarding SUD, a recent study of Ahluwalia et al.'s [200] revealed that a poor BR (indicated by neuro-metabolic and neuro-structural brain characteristics) in alcoholic cirrhosis worsened disease severity and increased the patients' vulnerability towards further deterioration. Reduced brain size may also reflect the effects of a poor prenatal or early childhood environment on brain development. Thus, substance abuse during pregnancy can inhibit brain growth, resulting in reduced brain size and a lower reserve capacity which could exacerbate the effects of drug abuse [201]. Interestingly, a dose-response effect of maternal cocaine use on newborn head circumference has been documented [202]. For instance, maternal addiction to alcohol or heroin during pregnancy has a persistent, deleterious effect on brain-head size [203, 204, 205]. Interestingly, head size has shown to account for more than 20% of the variance of the global cognitive impairment score in a cocaine-dependent sample. Specifically, performance in cognitive domains such as attention, spatial abilities and abstract reasoning were related to head size [206]. Likewise, prenatal cocaine exposure predicted poorer perceptual reasoning IQ mediated through birth head circumference indicating a relationship with fetal brain growth [207].

Furthermore, better cognitive performance was found more frequently in detoxified alcoholic Korsakoff men than women. This evidence was associated with higher premorbid education and fewer detoxifications in this group over two years of follow-up [208]. Authors suggest that similar to previous findings in other pathologies and normal aging, higher education may promote an increased level of neural connections, or raises the threshold of neural damage to be exceed.

One aspect associated with CR and BR is the recruitment of compensatory brain networks to maintain an acceptable performance in demanding cognitive tasks [21, 209]. The first studies about this issue focused on working memory tasks revealing that patients with alcoholic SUD activated not only the same brain regions than the control group (occipital-parietal networks), but also additional areas such as the inferior occipital-temporal and limbic systems during the execution of the task [210]. Similar results were found

during verbal working memory tasks, where both groups differed in their pattern of brain activation, but not in their task performance [211]. In a recent study, reduced working memory performance in an N-Back task was found in individuals with alcoholic SUD [212]. This impaired performance was related to an inability to suppress brain regions involved in the default-mode network, as well as a compensatory increase of activity in the dorsolateral prefrontal cortex. Regarding motor activities, such as finger tapping tasks, detoxified alcoholic patients performed more slowly than the control group reducing the brain activation in key areas involved in this task (cerebral cortex and cerebellum) along with an enhanced activity in cortical brain regions on the same side as the active hand during the task [213].

Additionally, it has been well established that the HIV directly affects the central nervous system and it appears to occur shortly after infection [214, 215, 216]. Hence, low educative level, as an indirect index of lower BR, might act as mediator in the appearance of neuropsychological deficits in cases of early HIV infection [217]. Ernst et al. [218] studied cognitively normal individuals seropositive for HIV versus cognitively normal individuals seronegative for HIV using functional MRI to analyze the brain activity during a working memory task. The sample seropositive for HIV showed a greater magnitude of brain activation in the lateral prefrontal cortex than observed for the sample seronegative for HIV. This greater use was not present in other areas activated during the task. Authors suggested that the delayed appearance of the clinical manifestations of early injury to the prefrontal cortex neural substrate in the patients who were seropositive for HIV was due to recruitment of prefrontal reserve capacity. Recently, evidence has shown that a high CR has a protective effect in the presence of neuropsychological impairment associated with HIV [219]. Similar results were found respect to Hepatitis C virus (HCV) showing that HCV-infected individuals with low CR might be more susceptible to cognitive impairment, particularly on tests of memory, attention, motor speed, and executive function [220, 221].

On the other hand, it is well known that cannabis use is associated with increased risk of psychosis [222, 223, 224, 225]. In a recent study of Cunha et al. [226], the relationship between cognitive functioning and brain structure after the first psychotic episode was analyzed. Surprisingly, results revealed that cannabis-using patients who develop psychosis had lesser brain impairment and better CR than other psychotic patients. This evidence is consistent with other studies showing an association between high premorbid IQ and cannabis use [227]. Hence, it is possible that a high premorbid CR in these subjects makes them more resilient to drug-induced damage, but when symptoms appear (e.g. psychotic episode), it is probably that brain impairment is highly advanced.

Finally, substance use onset may be also related to alterations in reward circuitry development, such as reduced ventral striatal function [228], delay in the maturation of prefrontal brain regions or an increased dopaminergic activity in subcortical regions during youthhood [229]. Regarding this, the recent study of Bertocci et al's group (2017) [230] had the aim of identifying some brain parameters through neuroimaging measures that predicted drug use in a large group of young people. They found that future substance use was associated with higher left middle prefrontal cortex activity, lower left ventral anterior insula activity and thicker caudal anterior cingulate cortex. Related to the latter, a reduced volume in frontal and insular regions was also found in marijuana adolescent users compared with non-users [231]. However, it is yet unknown if these brain changes are consequence of drug consumption or a premorbid characteristic of gray matter development which could promote substance use.

CONCLUSION

In summary, evidence shown in this review points to the necessity to consider CR and BR in patients with SUD due to the important role of these variables in the treatment, prognosis and the severity of the drug addiction (probability of relapses, abstinence, adherence measures, as well as treatment drop outs). Due to the relevance of CR as a protective factor, some questionnaires have been developed to estimate it using proxy variables such as years of education, number of intellectually stimulating leisure activities, degree of occupational complexity, and socioeconomic status, among others. The most used is *The Lifetime of Experiences Questionnaire* (LEQ) [232] which assesses the CR through the practice of diferent intellectual and non-intellectual activities throughout life (years of education, formal courses, physical activity, musical training, travelling, reading…). Another validated test for the estimation of the CR is the *Cognitive Activities Scale* which evaluates the frequency with which subjects have performed activities related to cognitive function such as reading, games, visits to libraries, among others, at different stages of life (6 years, 12 years, 18 years, 40 years and current age) [233]. Finally, and standardized for the Spanish population, the *Cognitive Reserve Questionnaire* [234] has been developed by the group of Rami et al. (2011) showing to be useful to test the CR of cognitive healthy patients, as well as patients in the early stages of dementia.

Moreover, more longitudinal studies should be done to know the impact of a high CR on ecological and meaningful measures, such as social and occupational functioning. On the other hand, training CR-related variables as complement of conventional SUD therapy could provide promising results as it has been described in other pathologies, such as neurodegenerative disorders.

CONFLICT OF INTEREST

Authors do not have conflict of interest.

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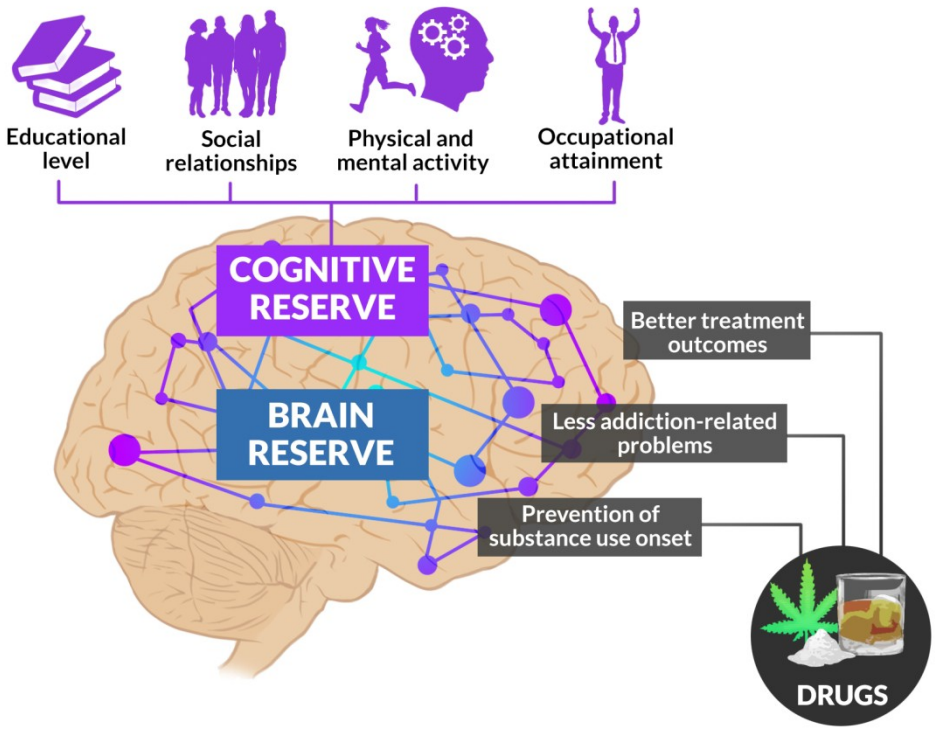

Graphical abstract