BINGE DRINKING: A NEUROCOGNITIVE PROFILE

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Binge Drinking (BD) is a highlighted topic on current research, possibly due to its intrinsic integration of biological and social health concerning vulnerabilities. Especially prevalent during adolescence, a neurodevelopmental period marked by accentuated social relevance on decisions, BD has an underestimated financial, social and health cost. Described as the consumption of high quantity of alcohol in a short period of time, BD has shown to be related to differential brain activity and neuropsychological performance. Thus, there is growing scientific evidence reporting a wide range of neurocognitive impairments in adolescents and young people with a BD pattern, involving especially cognitive processes such as attention, executive functions, and learning and memory. However, the potential mid and long-term effects of BD remain unclear, so further studies should be conducted to elucidate the evolution of this neurocognitive profile, as well as to provide a more precise estimation of its reflection on the social functionality of binge drinkers. Therefore, the aim of the proposed chapter is to provide an updated scientific comprehension of BD neurocognitive profile, complemented by a discussion of some aspects related to it. Firstly, a definition and description of the binge drinking phenomena will be conducted. Secondly, it will be presented a review about neurodevelopment on adolescence and youth, period in which BD episodes are more common, followed by the principal outcomes about BD observed

in animal studies. Then, a comprehension of neurostructural impact of BD, as well as a description of neurocognitive profile associated to BD will be offered, mentioning neurofunctional and neuropsychological consequences of this alcohol consumption pattern. Finally, future perspectives will be proposed, considering the evolution of BD neurocognitive profile and its related aspects.

1. THE BINGE DRINKING PATTERN

Through the last decades, a specific pattern of intensive alcohol consumption became increasingly popular in the majority of western countries, with a high prevalence especially among young people and adolescents [1-3]. This pattern has been defined as "Binge Drinking" (BD) and it is characterized by the intake of large amounts of alcohol in a short period of time, which tends to lead to alcoholic intoxication, with periods of abstinence between these intensive alcohol consumption episodes [for a review, see 4,5]. This pattern has been associated with alcohol consumption at weekends, preference for alcoholic drinks with a higher amount of alcohol, peaks of prevalence among adolescents and college students, equalization of consumption between gender and also with low risk perception concerning alcohol use.

The establishment of a precise definition of binge drinking (frequency and amount, regularity, etc.) and its prevalence in population is important since this type of consumption has social and sanitary consequences that can be as serious (if not worse) as the costs resultant from regular alcohol consumption [6-9], including the possible development of alcohol abuse/dependence [10-12].

1.1. Conceptual definition

Generally, the term Binge Drinking has two distinct meanings. One refers to a pattern of intensive consumption of alcohol in a large period of time (at least two days in a row) that interferes significantly with the person's life, and is associated with clinical definitions of alcohol abuse or dependence [13,14]. The other one, which is also called *heavy drinking* [15-17] or *heavy episodic drinking* [18,19], refers to the intake of large amounts of alcohol in a single occasion, in a short period of time, which leads to intoxication or drunkenness. In this chapter we will refer to this second definition.

Ham and Hope [20] have noted that an adequate definition of BD pattern should integrate distinct variables, such as quantity, speed and frequency of consumption. They have also pointed out negative outcomes associated with alcohol consumption (such as academic failure, sexual assault, fights, problems with authority and reckless driving). However, although the numerous definitions proposed until now have included these variables, it has not been always done in an integrated way.

In the seventies, the epidemiologic study of 'Monitoring the Future Study' [21] introduced the term Binge Drinking to describe a prevalent pattern of alcohol consumption in the population between 18 and 24 years old (especially under 21). This pattern was characterized by the intake of large quantities of alcohol in a short period of time, which frequently leads to intoxication.

In the nineties, based on an investigation of *Harvard School of Public Health College Alcohol Study* [22] which arose the importance of gender differences in alcohol consumption among college students, the concept of BD was operationalized as the intake of 5 or more alcoholic drinks in men and 4 or more alcoholic drinks in women (5+/4+) in a single occasion, at least once in the last two weeks. Wechsler's group established these criteria based on data collected in a survey about alcohol consumption habits, which indicated that men show significant problems related to alcohol consumption with 5 drinks per occasion, and women with 4 drinks [23].

Despite the extent of Wechsler's proposal, a great controversy concerning some of its aspects still remains. Some critics have been pointed out to some elements, such as a) the establishment of a quantity of alcoholic drinks that are too small to be classified as disruptive alcohol consumption, b) the absence of specification regarding the period of time that constitutes "a single occasion", and c) the lack of a universal operational definition of an alcoholic drink (in grams of alcohol).

Regarding the quantity, or the cut-off of alcoholic beverages consumed in a single occasion in order to define the BD pattern, some authors have proposed hat if what is intended is to relate BD pattern with activities that undertake more risk, or which have grimmer consequences – traffic incidents, aggression or sexual assault –, it would be advisable to increase the number of alcoholics drinks consumed in a single occasion of reference [24,25]. However, although the rise in this number in the BD definition would certainly be useful to identify in a more accurate way the young who could fulfill the criteria for alcohol abuse and/or dependence according to Diagnostic and Statistical Manual of Mental Disorders – DSM-IV [26], it would not be accurate at all to the establishment of a breaking point of risk in general population [27]. For this, the criterion most employed and the one that gathers the most consent in the study of neurocognitive impairment of BD pattern in non-clinical population is still the one proposed by Wechsler and colleagues (5+/4+) [22,28].

Respect to the speed of consumption and the controversy of the meaning of "a single occasion", several studies have highlighted the need to register blood alcohol concentration (BAC) levels, in order to determine with more accuracy the limit starting from which a BD pattern is established [14,29,30]. For this, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) has redefined the term BD, taking in consideration the BAC: "Binge drinking means drinking so much within about 2 hours that blood alcohol concentration (BAC) levels reach 0.08g/dl. For women, this usually occurs after about 4 drinks, and for men, after about 5" [31].

With regard to the lack of a universal operational definition of alcoholic beverage, it is important to note that the quantity of alcohol grams in a regular alcoholic drink varies considerably between countries [32]. Considering these differences, the adaptation of the 5+/4+ criteria is required for the country in which the study takes

place. For instance, even though in Portugal it could be employed the same cuttoff as in the USA (since a drink contains the same quantity of grams of alcohol in both countries), in the UK the pattern of BD is usually defined by the consumption of 8 or more drinks for men and 6 or more for women in a single occasion [33,34].

Another relevant variable for a complete and precise definition of the BD pattern is the frequency with which the BD episodes take place [35]. As in the case of the quantity, also there is not a clear criteria concerning frequency and there is great variability between studies in the adoption of this criteria.

Even though the time frame mostly used to establish the presence of BD is two weeks, some studies have employed periods of 1 month, 3 months or 1 year. Results collected in these studies have demonstrated that, on the one hand, a too short timeframe (2 weeks) could underestimate the prevalence of BD pattern due to the variability that college students show in their frequency of consumption; on the other hand a too vast timeframe (3 months) could overestimate this prevalence. In this sense, a study with college students has demonstrated that, with a timeframe of two weeks, about 50% presented a BD pattern in alcohol consumption; however, if the timeframe was extended to 3 months, this percentage would raise up to 80% [36]. In line with these findings, a study conducted by Labrie *et al*. in 2007 [37] found that a third of the participants (college students) who had been classified as non-BD in the last 2 weeks of the month, were classified as BD in the first 2 weeks. Also, this group – named the 'inconsistent' group – presented a higher rank of negative consequences associated to alcohol consumption, similar to those classified as BD.

In the initial epidemiologic study conducted by Wechsler *et al*. [22], two distinct groups of BD were established according to the frequency of consumption: occasional BD (the subjects who consumed alcohol in an intensive way (5+/4+) 1 or 2 times in the

last two weeks) and frequent BD (the ones who consumed the same quantities considered before, but 3 or more times in the last two weeks). However, this classification has been questioned, since the description of frequent BD could cover who fulfill the criteria for alcohol abuse and/or dependence according to DSM-IV [38].

Therefore, despite the inexistence of an universal criteria to characterize the BD pattern, the most extended and accepted approach is to consider the presence of at least one episode of intensive consumption in 2 weeks or 1 month.

Ultimately, when we intend to study the binge drinking pattern, it turns out to be necessary the inclusion of several aspects such as quantity, speed of consumption and frequency. The combination of these variables, as well as the adaptation of them to the country where the study takes place, is what makes to the establishment of an operative and equanimous definition of the term BD more difficult.

1.2. Epidemiology

According to epidemiological reports of national and international institutions, higher prevalence of BD is observed in adolescents and youths aged until 25 years, especially between college students, among which binge drinking prevalence rate reaches 40-50% [1-3,13,28,39,40]. From this age, it is observed a gradual reduction, what some authors have associated with increased responsibilities that come with this age [20].

In United States, although among young adults aged 18 to 22 the rate of binge drinking appears to be declining somewhat, it remains very high. In 2002, the binge drinking rate within this age group was 41% compared to 36.9% in 2011. Among full-time college students, the rate decreased from 44.4% to 39.1%. Among part-time college students and others not in college, the rate decreased from 38.9% to 35.4% percent during the same time period [3].

Results from the 2011 National Survey on Drug Use and Health have shown that 22.6% of people over age 12 have a BD pattern, defined as consumption of five or more alcoholic drinks on the same occasion (in two hours) at least once in the past month. These results vary significantly depending on age. Thus, rates of binge alcohol use in 2011 were 1.1% among 12 or 13 year olds, 5.7% among 14 or 15 year olds, 15% among 16 or 17 year olds, 31.2% among persons aged 18 to 20, and peaked among those aged 21 to 25 at 45.4%. In older ages the percentage drops both progressively and significantly. Regarding gender, although recent reports have shown a trend to similar rates between genders, BD pattern still remains higher in men than in women. Thus, 17.5% of men between 12 and 20 years have this pattern, while only 14% of women in this age exhibit this habit of consumption [3].

Accordingly, the high prevalence of BD among adolescents and young people urges a thorough analysis of the consequences that may arise from this drinking pattern. In the following pages, we will address the neurocognitive implications that BD can have on a still-developing brain, as is the case of the adolescent brain.

2. ADOLESCENCE, BRAIN DEVELOPMENT AND VULNERABILITY TO ALCOHOL EFFECTS

Human adolescence is a period full of changes, characterized by a wide variety of behavioral, emotional, cognitive and psychosocial transitions from childhood to adulthood [41]. These transitions are subject to multiple maturational processes that can influence positively or negatively the life courses trajectories. Although the biggest proportion of brain development occurs before the age of five years [42,43], human neuromaturation is far from finishing in childhood. On the contrary, neurodevelopment is an intricate process that extends throughout adolescence and into young adulthood

[44,45]. Thus, significant exposure to alcohol or other drugs during this period may adversely affect a wide range of neuromaturational process and, consequently, determine the subsequent behavioral, cognitive and/or affective development of individuals.

2.1 Main maturational events during adolescence

Firstly through post-mortem studies [46-48] and later by means of magnetic resonance imaging (MRI) technique [49-51], it has been demonstrated that brain structure – specially the prefrontal cortex (PFC) – undergo considerable changes during adolescence. Among these changes, there are two major developmental processes that characterize the adolescent period. The first of these events is known as *myelination*. Myelin is an insulating layer that forms around axons. The formation of this layer entails an increase in the action potentials conduction speed and, consequently, in the neural information transmission speed. Myelinated axons are commonly known as white matter. While myelination in sensory and motor brain regions occurs relatively early during development, the prefrontal cortex (PFC), as well as other high-order association cortices, continue to be myelinated during adolescence and young adulthood [52,53]. Studies using MRI as well as diffusion tensor imaging (DTI), another non-invasive imaging technique more sensitive than conventional imaging to tissue microstructure measures [54], have showed that this myelination process follows a linear course, increasing throughout individual development, and that certain white matter connections, as the association fibers of the prefrontal cortex, show volume increased even after 30 years old [45,50].

In addition to the changes that take place in the white matter, grey matter experience, in turn, profound modifications during the adolescent period and, as in the

myelination process, these variations take place essentially in high-order association cortices, such as the PFC, the inferior temporal cortex and the posterior parietal cortex [51]. Nevertheless, while the increase in white matter seems to be linear, changes in grey matter volume show an inverted U-shape. Thus, a grey matter increment arises at the onset of puberty, which has been related with a wave of synaptic proliferation. Later, during adolescence, a gradual decrease in synaptic density and, therefore, in grey matter volume, takes place as result of *synaptic pruning*, i.e., the elimination of infrequently used connections. This synaptic reorganization has been linked to an improvement in neural networks functioning as well as to increased neuronal efficiency [55-57].

Given the relationship between cognitive development and brain maturation, synaptic pruning and myelination may directly influence developmental advances in maturation of cognitive processes such as attention, working memory or inhibitory control, which are partially supported by PFC and other high-order association cortices.

In this context of development of brain structure and functioning, alcohol consumption may have a severe negative impact on neuromaturation and, consequently, impair the normal functioning of cognitive processes that are essential for a correct adjustment to adult life.

2.2 Alcohol effects in the adolescent brain: evidence from animal studies

Given that alcohol use during adolescence may alter developmental processes ongoing in certain brain regions, it is not surprising that similar amounts of alcohol may entail different consequences in adolescents compared to adults. In the last decade, several animal studies have showed that, effectively, adolescence is a particularly sensitive period to the harmful effects of alcohol. Thus, it has been shown that adolescent rats

exhibit substantially more alcohol-induced damage than similarly treated adults, especially in developmental regions such as the PFC [58]. Also parts of the limbic system, such as the hippocampus, an essential structure for memory, are markedly impaired in adolescent rats exposed to alcohol [59]. Accordingly, it has been observed that young rats are more likely to exhibit cognitive impairments in learning and memory tasks as a result of excessive alcohol consumption [60,61], and that it may persist in the long-term [62-64]. Likewise, binge alcohol exposure markedly disrupted neurogenesis in hippocampus [65], to a greater extent in adolescents than in adult rats [66]. Finally, it has been demonstrated that BD episodes may be more harmful for the brain than an equivalent amount of alcohol without withdrawal episodes [67,68].

Ultimately, taking into account that 1) adolescence is a period marked by profound changes in the brain necessary for the proper functioning of cognitive abilities such as working memory or inhibitory control [55,69,70]; 2) alcohol is the most widely used drug among adolescents and young people [71,72]; 3) BD is the most common form of problematic drug consumption among these subjects [1-3]; 4) this intensive pattern of consumption turns out to be more harmful than the regular consumption of alcohol [73-75]; and 5) the adolescent brain appears to be more vulnerable to the effects of alcohol compared with the adult brain [58,59]; considering, therefore, all these factors, persistence of a BD pattern during these years of transition to adulthood is of particular concern. Human studies that we will see in the next chapters have confirmed and justified these concerns.

3. NEUROPSICHOLOGICAL PROFILE OF BINGE DRINKING

As a highly accepted and widespread social practice, binge drinking´s intellectual consequences among youth are commonly underestimated. Last decade literature has uncovered differences on neurocognitive functioning among healthy binge drinkers, not expected before. Next, it is presented a description of neuropsychological profile characteristic of binge drinking on youth.

3.1 Attention

Attention is a multifaceted process that represents the capacity to highlight relevant information from stimulus or situations [76]. It activates frontoparietal regions, as well as anterior cingulate cortex [77,78]. In a neuropsychological approach, it can be expressed as focalized, selective, divided or sustained attention. Focalized attention is the ability to guide someone´s own activation to a pre-defined aspect or stimulus. Binge drinkers show less focalized attention, both to orally and to visually presented information (Digit and Corsi forward tasks), compared to abstainers [79]. Another type of attention studied among binge drinkers is sustained attention, that is, the capacity to maintain response to attributes or stimuli for a prolonged period. It is inferior among this young subpopulation, as assessed by Paced Auditory Serial Addition Test (PASAT) [80].

3.2 Processing speed

Another neuropsychological index is processing speed, facilitated by a high integration (complexity and connection) of white matter [81]. Subjacent to many functions, it is characterized by the time duration of different neuropsychological processes, like attention, perception and visuoconstructive praxis.

Binge drinkers perform slower than abstainers or light drinkers on different tasks, such as planning, reading, and visual (color and abstract forms) discrimination and recognition [79,80,82-84].

3.3 Visuo-spatial Perception

Perception is a wide and non-automatic process of identifying different elements, accessed by visual, auditory, tactile or interoceptive sense. It orchestrates the activation of different and specialized brain regions in occipital, parietal and temporal areas [85,86]. As our quotidian activities are highly dependent on visual information, the most studied dimension is visual perception.

This function seems to be preserved from the impact of binge drinking pattern. There are no differences on visual pattern or spatial localization recognition in function of binge drinking pattern [79,80,84].

3.4 Memory

Memory is a crucial neuropsychological function, which expresses the capacity to retain information and use it for adaptive purposes [87]. It comprises encoding, consolidation and evocation of information. According to Ryle´s (1949) model, it can be declarative, when information can be stated, or non-declarative (procedural), when information refers to skills, habits and dispositions [88].

Verbal episodic declarative memory can be assessed through word-list learning tasks or story recall. Hippocampus and surrounding regions play a fundamental rol in consolidation process [89,90], especially in story recall tasks [91,92]. Prefrontal regions are more implicated in the recall of non-structured information. Patients with frontal lesions do not show difficulties in contextualized, structured information recall, given

they do not need to organize information. However, they do show difficulties in tasks like word-list learning tasks, in which the association of information must favor their performance [93,94].

Binge drinkers perform lower than light drinkers in immediate and delayed story recall [95]. Except for a study with female college students, that identified inferior immediate recall score [84], other works have not confirmed immediate or delayed recall differences in word-list learning tasks among binge drinkers [80,95]. Absence of differences in this task, mostly relying on executive processes, might inform about binge drinkers´ adoption of strategic alternatives of activation/processing (organizing information) in order to compensate possible retention limitations (observed on story recall).

Also in visual declarative episodic memory, binge drinkers differences are not global. Binge drinkers perform less well than abstainers when recalling line drawings of common objects [80], but not when recalling visually presented scenes, compared to light drinkers [95]. This differential profile might be attributed to the second task easiness, with fewer elements to be memorized.

Respect to non-declarative memory, BD do not present differences on procedimental learning performance, measured by Hanoi Tower [79,84].

3.5 Executive Functions

Executive functions are the primordial function of prefrontal cortex and comprehend different processes of managing and organizing information in order to reach an objective, say it a behavior, language or reasoning [96].

3.5.1 *Working memory*

Working memory is an ability highly used in everyday life. The most common example

is when we have to hold on a telephone number that we will next use. It can be defined as the capacity to briefly retain and manipulate information, that can be verbal or visuo-spatial [97].

Binge drinkers are not affected in visuo-spatial working memory [84,98,99]. About verbal working memory, evidence is still not consolidated [84,98].

3.5.2 *Prospective memory*

Prospective memory refers to the action based on recall about expected future events/actions, more related to frontosubcortical circuits [100]. Although binge drinkers do not notice lapses on their prospective memory, they perform less well on time-based prospective tasks (e. g., "Return a set of keys to the researcher when 7 min are remaining on the clock."), but no differences are observed on event-based prospective tasks (e.g., "When a cue word is encountered during the filler task, remember to return a book to the researcher.") [101]. Authors attribute this profile to differential implication of self-regulation in both kinds of tasks, suggesting more impact of binge drinking in the retrieval with higher degree of self-initiated control.

3.5.3 *Categorization*

Categorization is described as the ability to select different elements according to a specific criterion, like a phonetic cue (words that begin with the letter S). It has been associated to the activation of posterior regions of left frontal lobe [102,103]. Phonetic fluency among binge drinkers is similar to light drinkers, without significant differences [98].

3.5.4 *Concept Formation*

The capacity to form a concept from a pattern of stimuli is commonly studied through rule learning tasks, like Wisconsin Card Sorting Test (WCST) or subtest Intra-Extra Dimensional Set Shift, from CANTAB. Its functioning has been related to dorsolateral

prefrontal functioning [104] and seems not to suffer effect from binge drinking, due to similar scores presented by binge drinkers and light drinkers [98] or abstainers [80].

3.5.5 *Cognitive Flexibility*

Cognitive flexibility is a frontostriatal function [105] that can be described as the capacity to change a class of response according to changes in the situation. Binge drinkers present less cognitive flexibility in a complex task (perseverative errors in WCST-3) [98].

3.5.6 *Planning*

Planning is the capacity to previously organize multiple actions, in order to reach a specific objective, commonly associated to dorsolateral prefrontal activation [106]. Binge drinkers have no difficulties on planning accuracy [80,98].

3.5.7 *Self-monitoring*

Self-monitoring is the ability to supervise own response in order to guarantee a successful performance, related to medial frontal regions [107]. Perseveration, intromission and susceptibility to interference while performing a task might be a signal of difficulties on self-monitoring. Binge drinkers have showed these influences in a verbal learning task [79,84,95], in an inhibiton task (Stroop) [84], as well as in a self-ordering task [98].

3.5.8 *Decision Making*

Decision-making is the ability to select an advantageous choice out of different options, primordially attributed to ventromedial prefrontal activation [108]. Binge drinkers are less effective making decisions than abstainers. Those attend more to immediate positive consequences than to long-term consequences [109]. Among binge drinkers, intensive binge drinkers select less advantageous options than light binge drinkers

[110]. Interestingly, less effective decision making has been associated to establishment or maintenance of binge drinking pattern one year later [111].

In conclusion, initial findings suggest that binge drinkers neuropsychological profile at late adolescence or early adulthood is marked by inferior: 1) focalized and sustained attention, as well as processing speed, respectively related to frontoparietal circuits and white matter integrity; 2) verbal and visual declarative episodic memory (with variations in function of task nature), associated mainly to medial temporal activation; 3) executive functioning that expresses self-regulation (cognitive flexibility, self-monitoring, time-based prospective memory) and engages medial frontal activation, but not the executive functions characterized by organization of information/objectives (planning, concept formation, categorization), associated to dorsolateral prefrontal activation; 4) decision making, dependent on ventromedial prefrontal regions.

4. BINGE DRINKING EFFECTS ON BRAIN STRUCTURE AND FUNCTIONING

4.1 Neurostructural impact of Binge Drinking

Despite the multitude of studies along the last few decades indicating that adult alcoholic patients present serious changes at a neurostructural and neurofunctional level, the number of human studies on the impact of alcohol consumption on the adolescent brain is still relatively scarce. Most of the studies conducted with human samples have had adolescents and young adults with Alcohol Use Disorder (AUD) as participants; the studies that have used a non clinical sample – adolescents and young adults from general population who exhibit a BD pattern of alcohol consumption – are fewer and much more recent.

Studies with adolescents and young people with AUD using MRI technique are yet very scarce and inconclusive. Such studies seem to corroborate results from animal studies and have shown that these youngsters present significant reductions – up to 10% – of hippocampus volume [112], more characteristically in the left hemisphere [113,114], and of the prefrontal cortex volume [115,116]; brain regions which, as we have seen above, undergo a marked development in adolescence and early adulthood.

Regarding BD pattern of alcohol consumption, to our knowledge, there are few studies using neuroimaging techniques in the study of alterations in brain structure resulting from BD in adolescents and young people, and all of these correspond to Susan Tapert's group, from San Diego University (USA). Two of these studies have used DTI in order to evaluate the integrity of white matter, and the third one has used MRI to estimate the density of cortical grey matter.

The first two studies [117,118] compared the integrity of white matter of a group of adolescents (from 16 to 19 years old) that showed a BD pattern with an age-matched control group. Results indicated that adolescents with a BD pattern showed less fractional anisotropy (index of structural complexity of myelinated axons) in several connection fibers, such as the superior and inferior longitudinal fasciculus, the fronto-occipital inferior fasciculus, or the pathways of limbic projection. Results from the first study [118] have also demonstrated a relationship between abstinence and withdrawal experiences and lower fractional anisotropy in the corpus callosum.

In the third, a very recent study conducted by Squeglia *et al*. in 2012 [119], MRI was used to compare cortical volume of a group of adolescents that showed a BD pattern of alcohol consumption with a control group also formed by adolescents. Besides the MRI, it has also been used a battery of neuropsychological evaluation tests, in order to estimate the executive functioning, attention and spatial planning ability, and

also to estimate if the results in these trials were correlated to possible changes in the volume of the frontal cortex.

Results have only shown structural modifications in the frontal cortex density associated to the BD pattern when gender was considered. These modifications were selectively distinct for men and women: adolescent female binge drinkers showed larger cortical density in left frontal regions than demographically similar female non-drinkers, which was linked to worse visuospatial, inhibition, and attention performances. In contrast, adolescent binge drinking males showed lower cortical density in these areas than non-drinking males. Furthermore, thicker left frontal cortices correlated with poorer visuospatial planning, inhibition and attention performances in women and with worse attention in men with a BD pattern [119].

In summary, the few available structural neuroimaging studies definitely suggest that the BD pattern of alcohol consumption in adolescence is associated with structural differences in white matter (as indicated by the lower fractional anisotropy in fiber tracts that connect sensorial regions with the frontal lobe), as well as in grey matter (with changes in the frontal lobe structures, that correlate with cognitive deficits modulated by gender in attention and executive functioning tasks, such as planning and inhibition). Also, the involvement of grey matter seems to entail an inverse pattern between women and men, which would imply greater deficits in the former than in the latter. Nevertheless, more research is needed, especially longitudinal studies, in order to confirm these results and attain a precise knowledge of the neurostructural alterations associated to the BD pattern of alcohol consumption during adolescence and its possible implications.

4. 2 Neurofunctional changes in adolescent binge drinkers

In addition to structural imaging studies, in the last years, functional magnetic resonance imaging (fMRI) technique has begun to be used to explore the effects of BD on the brain activity. Although scarce, these studies show that, even in absence of behavioral performance differences, intensive alcohol consumption has a significant impact on neural signaling in adolescents and young people.

The fMRI technique provides measures of brain activity by detecting changes in cerebral blood flow [120]. Through observation of changes in blood oxygen level-dependent (BOLD) signal, different estimations or inferences about neural activity can be made. As in the structural studies, major findings about the harmful effects of alcohol on young people and adolescents come from studies in subjects with AUD. In these studies, an abnormal pattern of brain activity has been recurrently observed in adolescents and young people with a history of alcohol abuse. Studies from Tapert and colleagues have shown that both adolescents (aged 14 to 17 years) and young people (aged 18 to 25 years) with AUD present differential neural activity compared to age-matched controls [121-123]. In particular, young women with alcohol dependence showed reduced BOLD response (i.e., reduced neural activity) during a spatial working memory task in parietal and frontal cortices [121]. Adolescents, meanwhile, had also decreased activity in certain regions of frontal and parietal cortices but it was accompanied by increased activation in posterior parietal, middle/inferior frontal and cerebellar cortices [122,123]. According to the authors, these differences may be related to the greater cumulative lifetime of alcohol use in young people compared to adolescents. Initially, subtle neuronal disruptions can be compensated by reorganization (or additional neural recruitment) of some of the circuitries involving in task performance. However, if heavy drinking continues, the brain may not be able to

compensate the damage and, consequently, it leads to reduced capacity in neural functioning.

Similar disruptions in neural activity appear to arise in the subclinical population of young binge drinkers. Thus, differences in brain activity during encoding of verbal items have been observed in bingers regard to controls [124,125]. In particular, binge drinkers presented increased activation of frontoparietal systems along with hypoactivation of occipital cortex. The authors proposed that these findings were suggestive of the use by binge drinkers of alternative memory systems during verbal learning and also indicated greater "neural effort" performed by these subjects to resolve efficiently the task.

The other two studies that have used functional neuroimaging to explore BD effects in adolescents have also observed abnormal patterns of neural activity. Thus, adolescent binge drinkers showed enhanced activity in limbic brain regions while they performed an affective decision making task [126], as well as in frontal and anterior cingulate regions during a spatial working memory task [99].

Although the functional reason for these differences in brain activity is still unknown, the greater neural activity observed in binge drinkers compared to light or non-binge drinkers may reflect the employment of additional neural resources that would allow them to compensate emerging functional alterations in those regions involved in task performance. Likewise, the reduced activity of binge drinkers in some regions may suggest a limited capacity in neural functioning of these regions, which might no longer be able to counteract the harmful effects derived from this type of drinking.

Finally, these results appear to show that, in order to perform adequately on the task, a greater neural response and/or a greater neural recruitment from certain regions is used by binge drinkers to compensate the damage in these or in other regions.

4.3 Electrophysiological correlates of binge drinking pattern

In line with results from neuroimaging studies, anomalies in brain functioning in adolescents and young binge drinkers have been also observed by means of electrophysiological studies. Through this technique we can indirectly measure the neural (electrical) activity generated by the brain during resting states – electroencephalographic (EEG) recording- or during stimulus/events presentation – event-related potentials (ERP) recording.

Regarding ERPs, this technique has been commonly used in the study of brain functioning. Numerous studies have employed it to assess the neurofunctional effects of alcoholism, paying particular attention to the P3 component [for a review, see 127]. This positive wave, which peaks at around 300-600 ms after the stimulus onset and reaches its maximum amplitude at centroparietal sites, is elicited by visual or auditory "task-relevant" events and, although it can be related to different cognitive processes according to the task to perform, it has been functionally associated with attention and memory access [128]. In particular, while P3 latency is usually related to the time required to detect and evaluate a target stimulus/event (i.e., an index of classification speed), P3 amplitude has been linked to the amount of attentional resources involved in the processing of target stimuli/events, phenomena that appears to be related to memory processing [129].

Besides in chronic alcoholics, anomalies in latency and amplitude of this component have been also observed in binge drinkers. Adolescents with this pattern of

consumption have showed delayed P3 latency in several studies [130-132], which has been interpreted as a slowed cerebral activity in these subjects. Similarly, differences between controls and binge drinkers in the P3 amplitude have been repeatedly observed in different paradigms such as emotional [130,131], oddball [132,133], working memory [134] or Go/NoGo tasks [135].

Although in some of these works lower P3 amplitude was observed in BDs than in non-BDs [130,132], increased amplitude of this component in adolescents and young with a BD pattern was recorded in other studies [133,135]. These discrepant findings probably reflect differences in the samples used (some of them with relevant factors such as family history of alcoholism or personal history of externalizing disorders), as well as differences in task demands resulting from the different paradigms used.

Special mention might be attributed to studies with the Go/NoGo paradigm given that it involves inhibitory control processes, a cognitive function widely related to addictive behaviors. In a recent study, a greater NoGo-P3 (a component that reflects inhibition-related activity [136,137]) linked to a hyperactivation of right inferior frontal cortex (a region involved in inhibitory control process [138,139]) was observed in young binge drinkers [135]. These results were interpreted as the activation of additional neural mechanisms needed to compensate emerging functional alterations in the regions engaged in inhibitory control, which would allow binge drinkers to perform efficient inhibitory control. In the same way, another recent study with heavy social drinkers showed a delayed NoGo-P3 component in these subjects compared to light drinkers, which was considered as an index of decreased neural processing speed related to inhibition [140].

All these anomalies might represent a neural antecedent of posterior difficulties in impulse control (and, therefore, in control of alcohol consumption) and might be considered as important vulnerability factors in developing alcohol misuse [135,140].

Lastly, all the cerebral abnormalities observed in adolescents and young binge drinkers by both electrophysiological and blood flow measures appeared in the absence of behavioral impairments. In other words, they retained the ability to perform the tasks normally but responded abnormally at the neuronal level. This appears to be in contrast with the results observed in the neuropsychological tasks, where a poorer performance in several neurocognitive tests was showed in BD subjects. However, on the basis of the differences between both neurofunctional and neuropsychological studies, an explanation can be proposed. Probably, in the type of tasks used in neuroimaging and electrophysiological studies (in which a "ceiling effect" is common) less robust neural activation – as what is observed in BDs – may be enough to support the cognitive demands, leading to an absence of behavioral response differences. Neuropsychological paradigms, for their part, typically use more demanding tasks and, consequently, they are more sensitive to assess behavioral impairments.

Together, it suggests that adolescents and young binge drinkers could have non-observable "latent" lesions which might be heralding future performance problems if BD continues and underlines the usefulness of neuroimaging as well as of electrophysiological studies to evaluate this kind of alterations that are still undetectable at the behavioral level.

5. FUTURE PERSPECTIVES

Although these findings are clarifying and highlight priority questions in youth health, diversified and replicated studies become necessary in order to reach consistence in the field. So, methodological differences might be overcome by the adoption of equivalent: criteria of BD and comparison drinking pattern (considering differences between countries on alcohol concentration and social habits), age range studied, and theoretically based tasks. Despite the initiative of some studies [80,82,83,95,98,110], sex differences on neurocognitive impact of binge drinking are not sufficiently explored and might be more deeply investigated.

Likewise, it is still unclear whether these differences on neurocognitive functioning express a persistent profile or a malleable condition related to BD. Longitudinal studies are crucial for understanding the interaction between neurotoxic effects of BD and neurodevelopmental mechanisms.

As well as some questions have been answered, others have invariably emerged. What about emotional control? Analysis of the impact of BD on emotional processing and its regulation, controlling for premorbid emotional conditions, should clarify mechanisms engaged on BD maintenance and could enrich prevention polices. How is this neurocognitive profile expressed on social functioning? Ecological studies could relate laboratory performance to fulfillment of social demands, like college, work or home responsibilities.

Fortunately, BD phenomena is now better understood on its different dimensions, like epidemiologic, psychosocial, neurologic and neurocognitive domains. Nonetheless, what is unquestionable is the contribution of this field to the awakening about the complex and ongoing neurodevelopmental process during second and third decade of life, which demands more investment in youth health.

6. CONCLUSION

Alcohol is the most widely used drug among adolescents and young people. A singular form of alcohol consumption especially prevalent in this population is the binge drinking. This type of intensive and intermittent alcohol consumption turns out to be substantially detrimental to the adolescent brain, where cerebral and cognitive maturational processes are still ongoing.

The knowledge about the extent to which this form of alcohol consumption impacts on health of adolescents and young people is still an outstanding question. Even so, there is already a growing scientific evidence that shows that the BD pattern can have important consequences at neuropsychological, neurostructural and neurofunctional level in this population. However, the potential mid and long-term effects of BD remain unclear, so further studies should be conducted to elucidate the evolution of this neurocognitive profile, as well as to provide a more precise estimation of its reflection on the social functionality of binge drinkers. In that sense, although more research (especially of longitudinal type) is required to clarify the scope of the BD consequences, early prevention and treatment programs that attempt 1) to delay the onset of alcohol use, 2) to reduce BD habits in adolescents and young people, and 3) to help to identify any signs of BD-induced brain damage might be useful for a better and more efficient development of intervention strategies.

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