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Adolescent Alcohol Consumption: Brain Health Outcomes

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Abstract

Adolescents consume alcohol in moderation mainly to enjoy and enhance mood but adolescents also drink hazardously, e.g. to cope with stressful life events. Drinking hazardously may be related to the developing adolescent brain going through a number of structural and physiological changes. These structural and physiological changes affect adolescent behavior aimed at gaining experience in life. Adolescent drinking patterns vary and may include risky behaviors such as binge drinking. Motivations to drink and risk factors for binge drinking and alcohol abuse are both internal and external. Internal risk factors include amongst others genetic predisposition to have less self-control, whereas external risk factors includes early life stress. Integrative approaches underline the value of multi-domain analysis for prediction; any one feature in isolation only modestly predicts drinking behavior.

Health consequences of drinking vary widely depending on dose and drinking pattern. Moderate alcohol drinking may be associated with a lower incidence of chronic disease and mental health, whereas alcohol binging and abuse appear to negatively affect social functioning mainly in the short term and mental and physical health in the long term. Resilience towards behaving non responsibly may best prevent alcohol abuse and stimulate enjoyment of moderate alcohol consumption.

Limitations in current knowledge concern the interpretation of alcohol drinking being the cause for adolescent risky behavior, generalizability of findings on abusing adolescents to the general population and insufficient knowledge of relevant covariates and mediators.

Keywords: Alcohol; Adolescent; Brain; Health; Moderate

Introduction

Adolescence is the transition from childhood or puberty to adulthood [1]. The period may start between the ages 10 and 15 and may end between the ages 19 and 24. Age ranges defining adolescence vary over countries and institutions, because adolescence is a legal phenomenon defined by culture and society [2]. Also, the average age of onset of puberty has decreased over the past century [3].

Adolescence is a transition period characterized by many physical and psychological changes in which the individual needs to learn from experience. One of the most prominent changes that occurs at this stage of life is the maturation in cognitive functioning [4]. An important concern is that these learning experiences may be accompanied by hazardous situations and problematic behavior, for instance when adolescents start drinking alcohol.

These hazardous situations and problematic behaviors form the basis for an increasing scientific interest and discussion on the topic of drinking at younger age. Since the early sixties more than 55,000 papers have been published on 'alcohol' and 'adolescents' (Figure 1). Main topics include: reasons to drink and more specifically to binge drink; immediate consequences for behavior, and health consequences later in life. Scientific interest in the effects of alcohol and other drugs of abuse was further increased when studies showed that the brain continues to develop until puberty has ended [5,6].

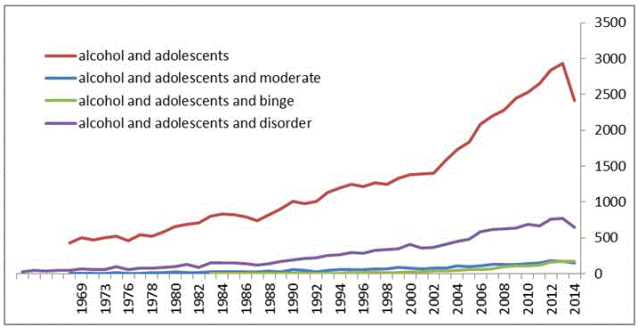

Figure 1: Number of papers published in PubMed on the topic 'alcohol' in combination with 'adolescent', 'moderate', 'binge' and 'disorder'. Note a further increase since 2002.

Drinking alcohol in large quantities is undesirable in all ages, since alcohol is a toxic substance. Humans have developed the metabolic ability to metabolize this toxic substance, but the system needs to be overloaded to some extent for the alcohol to reach the brain and to obtain the psychological effects. The aim of this narrative overview is to summarize the data obtained so far on the reasons why adolescents

drink and how drinking may affect their brain and behavior, both when drinking hazardously but also when drinking in moderation. This review also describes the limitations that need to be considered before general conclusions can be drawn and public health advice can be given. This review will not summarize the effects of prenatal alcohol exposure and its consequences, this topic has recently been covered by others [7,8].

The adolescent brain development

It is well established that the brain undergoes a rewiring process that is not complete until approximately 25 years of age [5,6]. This rewiring takes place during puberty and mainly involves an increase in its complexity rather than the growth of the brain.

Structural changes

Brain structural changes start in early adolescence and are characterized by (a slightly) expanding cerebral cortex, as well as an increase in the complexity of subcortical structures within the medial temporal lobe. Complexity growth involves gradual decreases in grey matter volume, due to processes such as reductions in synaptic connections among neurons (dendritic pruning) and increases in myelin (the white sheath surrounding axons). Increases in myelin not only increase the speed of information transmission but also contribute to the timing and synchronicity of the neuronal firing patterns that create functional brain networks. Such changes in connectivity most likely contribute to maturation of neurocognitive processes. So, changes in structural connectivity allow for a better flow of information and a larger engagement of specific brain regions during cognitive tasks [9].

Maturation of the adolescent brain, studied in a longitudinal design, takes place from early to late adolescence. In general the maturation of brain regions is not synchronous but seems to follow a specific trajectory, i.e. from the back to the front of the brain [10]. While children have equally immature limbic and prefrontal regions and adults have acquired both fully developed systems, the adolescent phase is characterised by an asynchrony in the maturation of the two regions [11]. Maturation differs not only in the various regions but also in the rate of maturation of the various subcomponents of cognitive functioning [12]. For instance, attentional control develops more rapid and earlier than information processing, cognitive flexibility and goal setting.

Physiological changes

At a physiological level various dramatic changes occur as well, including profound changes leading into sexual ripening and a changing sleeping pattern. Although sexual maturation is considered to occur at the level of the sex organs, the brain is also heavily involved. The brain governs reproductive functioning specifically by producing the gonadotropin releasing hormone from regions within the hypothalamus [13].

Additional major physiological changes include changes in sleeping patterns and arousal regulation. The 10- to 15-year-old period also involves profound changes in sleep, including maturational changes in aspects of circadian regulation accompanied by a decrease in slow brain wave activity, which may reflect cortical pruning. These maturational changes result in perhaps the best known characteristic of teenage sleep patterns, namely the tendency to stay up late [14]. Sleep and circadian rhythms modulate reward function, suggesting that adolescent sleep and circadian disturbance may contribute to altered reward function [15]. Furthermore, the balance of sleep and arousal regulation tends to shift toward high arousal [16].

Sexuality and sexual arousal regulation also shows robust changes. While elements of sexuality and sexual interest are present in children, the reorganization of the hormonal, anatomic, and neuropsychological substrates of sex during early adolescence is profound. Also, adolescence is associated with complex issues on sexual display, sexual interaction and mating [17].

Behavioral changes

In adolescence, brain networks that are sensitive for social and emotional stimuli and reward-processing mature quickly, while the cognitive control functions lag behind. These processes form the basis for the three most commonly observed behavioral changes associated with adolescence, which are: (i) increased novelty seeking, (ii) increased risk taking and (iii) a social affiliation shift towards peer-based interactions. These behaviors may be a cause for an increased risk and vulnerability during the adolescent time period [18]. However, these behaviors may also be essential in obtaining experience and in developing an independent life style. Experience helps to develop the neuro-circuits needed for increased cognitive control of emotions and impulses [19]. Adolescents therefore tend to engage in experimental behaviours not only in relatively safe environments, but also in more dangerous situations [20]. Such experimental behaviors may include initiation or escalation of substance use.

Adolescents and alcohol

A large number of studies have been published on alcohol drinking by adolescents, specifically adolescent students at school and university campuses. This section describes adolescent drinking patterns, the reasons why adolescents drink and why adolescents may binge drink and what is known on the consequences of such drinking patterns later in life.

Drinking patterns

In Europe, contact with alcohol already starts early in life. A lot of information is available through the ESPAD (The European School Survey Project on Alcohol and Other Drugs), which aims to collect data on substance use among 15–16 year old students in as many European countries as possible [21].

This survey project shows that on average, nearly 60% of the students had consumed at least one glass of alcohol at the age of 13 or younger and 12% had been drunk at that age. This reply was given by more boys than girls, and that tendency was the same in almost all countries [21]. In most European countries first contact with alcohol may be as early as the age of 10. Percentage of adolescents having been in contact with alcohol by the age of 15 increases rapidly and may rise up to about 80% of all adolescents.

In the US, national surveys have shown that almost 40% of the high school students (14 to 18 years of age) reported to have been drinking some alcohol and 22% have been binge drinking [22]. Also, 33% of youngsters aged 14 and 70% of those aged 18 have been drinking during the last month [23,24].

A study from a prospective UK birth cohort reported on alcohol use at 10, 13 and 15 years and found that by the age of 15 over half of the

boys and girls had consumed alcohol and one-fifth reported drinking in a binge fashion [25].

A study comparing data from the US [23] with those of ESPAD [21] revealed much higher intoxication rates for the UK as compared to the USA and higher as compared to the European average. In the UK, 33% of students reported intoxication in the last 30-days compared to 18% in the USA and 24% reported intoxication before the age of 13-years compared to 8% for the USA [26,27].

In other words, experimenting with alcohol starts during adolescence with a high prevalence of binge-drinking in most countries of the world.

Motivations to drink or binge drink

Adolescents may drink for very similar reasons as adults do, mainly for the rewarding value of alcohol. Part of the motives to drink may be hereditary [28]. Rewarding value of alcohol may translate into three broad categories of reasons to drink: first to cope, viz. to cope or escape unpleasant emotions, second to socialize, viz. to be sociable, to celebrate and third to enhance mood and to enjoy [29]. In general, most adolescents drink for social reasons or for enhancement reasons in the sense of enjoyment. Various studies have reported that 80 to 90% of adolescents drink for these reasons, which are usually associated with moderate drinking levels [30-32]. Drinking to cope or escape unpleasant emotions or drinking to reduce tension, however, are more frequently associated with heavy drinking and binge drinking. Social anxiety appears to be negatively associated with quantity and frequency of alcohol use and frequency of binge drinking. Social anxiety was, however, positively associated with alcohol related problems as well as coping, conformity, and social motives for alcohol use [33].

Why adolescents may drink in binges has been investigated in animal studies. These studies indicate that adolescent animals are consistently less sensitive to the aversive sedative effects of ethanol than their adult counterparts [34-36], whereas they are more sensitive to the rewarding, stimulant effects of alcohol [37]. Such a decreased sensitivity in combination with the rewarding effects of alcohol may lead into loss of control for drinking, in which the negative consequences of alcohol abuse are ignored and lead into binge drinking. In case the binge drinking becomes a pattern, this may ultimately lead into an increased risk of alcohol dependence in adulthood. How the adolescent brain is involved in the development of this disorder is largely unknown.

Risk factors for binge drinking

Brain and drinking behavior are shaped during development by the combined effects of internal factors as well as external factors. Epigenetics seem to play a role in linking the internal changes with external experiences during brain maturation and development [38]. Evidence on the interaction between 'internal factors' and 'external factors' illustrates that, in adolescence, external factors play a more important role than genetic factors on the risk of developing alcohol related problems later in life [38].

Internal risk factors

It is well-established that those with a positive family history of alcoholism are at increased risk for developing alcohol use disorders [39]. The identification of specific genetic variations associated with increased risk for problem drinking is, however, progressing slowly [40]. It is now recognized that genetic risk for alcoholism is likely to be due to common variants in many genes, each of small effect, although rare variants with large effects might also play a role. This has resulted in a paradigm shift away from gene centric studies toward analyses of gene interactions and gene networks within biologically relevant pathways [41].

Genetic differences in reward sensitivity may mediate such a predisposition [42,43]. The underlying mechanisms for this hypersensitivity to rewarding, however, are not yet clear [44]. Two primary theories of reward processing in adolescence appear to be relevant. The first postulates that hypo-activation of the striatal system leads into reward seeking as a compensatory response [45,46] whereas the second suggests that the striatum's hyperactivity leads to greater reward-seeking behaviour [47,48]. Both activation states of the striatal system have been observed using fMRI (functional Magnetic Resonance Imaging) analysis after a reward anticipation task.

Whatever the mechanism, a study reported no differences between children with alcohol-dependent parents and controls at young age on reward anticipation or feedback of win [45], but this outcome contrasts with studies of older individuals [49]. Possibly, the effect of family history has not yet exerted its influence on the still developing reward circuit at a younger age [50].

There is also evidence for a link with self-control difficulties [51]. One set of factors appears to reflect predisposition towards dependencies on a range of substances. These factors include a constellation of personality characteristics such as impulsivity [52], sensation seeking [53], neuronal disinhibition and an impaired ability to easily learn from mistakes [54]. Additionally, several genetically influenced syndromes, primarily schizophrenia and manic depressive disease, are associated with an enhanced risk for alcohol dependence and additional substance use disorders [55,56].

Thus far, findings relating family history for alcoholism to impaired control have been limited. Self-reported impaired control, however, is still considered as an important contributing factor to problem drinking in young adults [57].

External risk factors

External factors contributing to binge drinking include stress [58], childhood experiences, and environment. Stress at an early age has been described as an important factor contributing to substance abuse in general and problem drinking at later age [59]. A recent narrative review concluded that experiencing maltreatment and cumulative stressful life events prior to puberty and particularly in the first few years of life is associated with early onset of problem drinking in adolescence and alcohol and drug dependence in early adulthood [60].

Stressful changes also include common events like the transition from high school to college or sexual development. Such stressful experiences may in part explain the high prevalence of problematic drinking in college. Early onset long-term stress can result in permanent neuro-hormonal and hypothalamic-pituitary-adrenal axis changes, morphological changes in the brain, and gene expression changes in the mesolimbic dopamine reward pathway, all of which are implicated in the development of addiction. However, a large proportion of children and adolescents who have experienced severe stress do not develop psychopathology indicating that mediating factors such as gene-environment interactions and family and peer relationships are important for resilience. This may be less true for

vulnerable groups such as sons of alcoholics of whom it has been shown that stress responses are attenuated [61]. It has been suggested that epigenetic processes play a role in linking the expression of genes with external experiences during brain maturation and development [38].

Integration

Altogether, adolescents are in a developing stage of their learning from many, sometimes stressful, experiences. Most individuals use alcohol, mainly to socialize and enjoy. However, in some cases the combination of reward-related personality traits, behavior, and neural response patterns may convey risk for later alcohol abuse [62]. These factors, that could be applied as a vulnerability factor for the development of substance use disorders explained up to 26% of the variance only [62].

In a new integrative approach, machine learning was applied to construct neuropsychological profiles of current and future adolescent alcohol abusers [63]. To identify the vulnerability factors underlying individual differences in alcohol misuse, the models incorporated brain structure and function, individual personality and cognitive differences, environmental factors (including gestational cigarette and alcohol exposure), life experiences, and candidate genes. A generalizable risk profile for alcohol misuse initiation was generated, which relied on a combination of three domains, namely 'History', 'Personality' and 'Brain', which included both internal and external risk factors. These models were accurate and classified non-drinkers and binge drinkers with high (about 90%) accuracy. The models point to life experiences, neurobiological differences and personality as important antecedents of binge drinking [63]. Thus, these results underline the value of a multi-domain analysis for predicting adolescent alcohol misuse and speak to the multiple causal factors for alcohol misuse. Further, it was noted that the influence of any one feature in isolation was modest.

Health consequences of drinking alcohol in adolescence

Alcohol appears to be the drug for pleasure and enjoyment by far for adolescents and adults. Smoking tobacco is less common both in adolescence as well as in adulthood. Use of both alcohol and cigarette smoking is decreasing in the US [64] and the UK [65], with mixed trends in Europe [21]. Health consequences of drinking alcohol depend heavily on the dosage and pattern of drinking (Table 1).

Short-term		
	Moderate drinking [66]	**Alcohol abuse / binge drinking [98]**
Stress response	↓ [69-73]	↑ [135]
Subjective well-being / QoL	↑ [84-90]	↓
Accidents / Trauma	↑ [136]	↑ [104,137]
Trauma recovery	?	↓ [105]
Social interaction	↑ [89,68]	↓ [21]
Long-term		
	Moderate drinking [66]	Alcohol abuse / binge drinking [98]
Cognitive performance	↑ [74,75]	↓ [76]
Depression	↓ [92-97]	↑ [97]
Metabolic diseases including coronary heart disease and diabetes mellitus II	↓ [81-83]	↑ [82,138]
Alcohol dependence	↔	↑ [108,109]
Disability	↔	↑ [114]

Table 1: Possible short-term and long-term consequences of alcohol drinking in adolescents.

Drinking in moderation

Many but not all countries have formulated guidelines for drinking and health. Most countries have defined drinking in moderation as 1-2 glasses on average per day. There usually is a gender differentiation indicating men to drink about twice as much as women, but there is usually no age-differentiation, except for young adults not to drink up to the age of 16 or 18.

Literature on adolescents drinking in moderation is limited. Literature on moderate drinking focuses primarily on physical health of adults, namely the epidemiological associations of moderate drinking with a lower risk for overall mortality, coronary heart disease and other metabolic disorders in middle-aged adults. Mechanistic studies have been performed and indicate physiological changes that would explain most of the cardiovascular benefit. The relation between drinking in moderation and mental health has received little attention even in adults, so far.

Adolescent drinking may usually be heavier and may more often be binge drinking, but research shows a rapid decline in heavy and binge drinking after high school and college. By the age of 24 more than 80% of young adults were not regular binge drinkers, whereas nearly two-thirds of those who had frequently engaged in such drinking as high

school seniors [66,67]. Several areas of potential benefit have been identified for drinking in moderation, which are relevant for adolescents as well. These areas are stress response reduction, mood enhancement, cognitive performance, reduced clinical symptoms, primarily of depression and improved physical functioning [68].

Several studies have shown that alcohol consumption before a mental stressor blunts the stress response [69-71]. Similarly, a reduced HPA-axis activity, evaluated as ACTH and cortisol hormones has been reported [69,70]. However, data on the effect of alcohol during stress response recovery is scarce. This is surprising, because alcohol is frequently used to take away the tension of a working day or learning period.

Two studies [72,73] compared the influence of both intravenous alcohol infusion or alcohol consumption with a meal after a mental stressor on the stress response. These studies showed that alcohol exposure after the stressor blocked or reduced the cortisol response.

Positive relationships between drinking and a variety of cognitive measures were described in young adults [74]. These cross-sectional observations correspond well with those reported for elderly woman obtained in a longitudinal study. Women drinking in moderation were less likely to have a decline in their cognitive performance several years later as compared to non-drinking women [75], whereas men drinking excessively would have experience cognitive impairment [76]. The beneficial effects of moderate drinking on the brain may partly be mediated by the stimulation of brain blood flow. A study in adolescents showed that moderate alcohol consumption stimulated global brain perfusion by 7% on average which started immediately after alcohol consumption and lasted for about 2 hours [77]. Alternatively, moderate alcohol drinking may lead into decreased low grade inflammation [78,79].

It is widely known that light and moderate drinking is associated with a decreased risk for overall mortality [80], cardiovascular mortality [81] and other metabolic diseases [82,83]. Several epidemiological studies have indicated that people with higher self-rated health or good health practices are at low risk of mortality and cardiovascular disease. Also, a limited number of studies indicated that light to moderate drinkers rate their health as good [84]. Most of these studies are cross-sectional, however. These few studies indicate that light and moderate drinking are positively associated with mental health, vitality and social functioning [84-86]. A similar positive association between moderate alcohol consumption and quality of life [87,88], subjective wellbeing [89], subjective health [90] and life satisfaction [88] has been reported. Positive associations with drinking were demonstrated with 18–19 year-old Swedish conscripts in regards to sociability, and also mental health when considering abstainers whose fathers had been drinkers [91].

Some studies have indicated that moderate alcohol consumption is one of the lifestyle factors that may be associated with a lower incidence of depression [92-95]. Also, a cross-cultural study conducted in 5438 primary care attenders from 14 countries who participated in the WHO Collaborative Study of Psychological Problems in General Health Care, showed that excessive drinking is associated with an increased prevalence of depression, but also suggested that light to moderate drinking may be associated with a reduced prevalence of both depression and anxiety [96]. In another cross-sectional study the age of drinking onset was related to major depressive symptoms: an adolescent age of onset for alcohol drinking was associated with a lower risk of major depressive symptoms [97].

Binge drinking

Regular binge drinking has adverse health and social effects, both in the short-term and in the long-term. Many reviews have been published on the deleterious effects of binge drinking in adolescence [98]. Here we will highlight the main findings.

Definitions of binge drinking vary, but most used is the definition formulated as the consumption of five or more consecutive drinks by men or four or more consecutive drinks by women during a drinking episode [99]. This formal definition may be different from the informal definitions used by some college students [100,101].

Adolescent binge drinking may be combined with several additional risk factors enlarging the detrimental effects of binge drinking. These factors are indicated above: internal and external factors may all contribute to a risk of alcohol abuse and its related negative health effects later in life. One well-studied risk factor is early onset of drinking, which would be related to alcohol problems in adulthood [102]. This information formed the basis to justify efforts to prevent drinking among children and young people. However, a recent systematic review of prospective cohort studies, in which age of first drink was separated by at least three years from adult alcohol outcomes, showed the existence of effects of age of first drink on adult drinking, but not at all strongly, and not in all studies. Rigorous control for confounding markedly attenuated or eliminated any observed effects [103].

However, binge drinking may have serious consequences, both in the short-term as well as in the long-term. Short-term adverse effects consist, amongst others, of physical, mental and social danger by loss of control. Physical danger occurs as being involved in accidents and trauma [104]. Possibly, recovery from such trauma may be impaired [105]. The reduction in alcohol prices and the concomitant increase in alcohol consumption, however, did not increase the incidence of alcohol-related trauma [106], nor of fatal trauma [107].

Adolescence represents a critical period in brain development that is particularly vulnerable to alcohol misuse which may be dangerous for their mental state and development. However, the extent to which there are pre-existing versus alcohol-induced neurobiological changes remains unclear [108] and vulnerability markers may be mediated by mental health and substance use comorbidities [109]. Social danger occurs; the problem most commonly reported was having serious problems with friends (12% each) [21].

There are, however, few surveillance studies of alcohol use and alcohol-related problems among children and preadolescents, a situation that makes estimation of alcohol burden problematic [110]. We also know relatively little about the consequences in adulthood of late adolescent hazardous drinking. A small number of systematic reviews were carried out using general population cohort studies where data on baseline alcohol consumption had been obtained from adolescents and follow-up data had been obtained from the same cohort [111]. The main conclusion was that late adolescent alcohol consumption persisted into adulthood and was associated with alcohol problems, including dependence [112,113]. Non-alcohol outcomes such as mental health and social consequences of adolescent drinking could not be fully explored due to lack of evidence. Higher alcohol consumption at 15 was associated with a significantly higher prevalence of engagement in other risk behaviors at 16 years of age, in particular substance use and sexual risk behaviors. Those who met criteria for hazardous drinking at 16 were six times more likely to engage in substance use behaviors than those who did not meet these

criteria [25]. One of the topics investigated is the association between adolescent drinking with future disability pension. Alcohol "risk use" in adolescence (aged 18-21), defined as, e.g. drinking more than 250 g alcohol per week, was associated with increased risk of future disability pension [114]. Similar patterns were seen for moderate and high consumption, though that risk disappeared when fully adjusted. These outcomes are supported by other studies in adults, but not all [115,116].

The current literature suggests that binge drinking during adolescence does have a subtle, but significant, deleterious effects on adolescent neurocognitive functioning, such as decrements in memory, attention and speeded information processing and in executive functioning [117-119]. These population studies have, however, only shown small differences between excessive drinkers and controls in neurocognitive functioning [120,121]. It is also important to realize that these studies have a cross-sectional design. Only a limited number of studies [117,118] have investigated the effects of alcohol use on neurocognitive functioning using a longitudinal design. These studies showed that adolescents who initiated heavy drinking showed less frontal and parietal response to working memory before the onset of drinking and had less efficient information processing after high-dose alcohol use.

Prevention of detrimental alcohol drinking patterns

Binge drinking and alcohol abuse are detrimental for health and society. Therefore, binge drinking and alcohol abuse need to be prevented to reduce its negative impact. Effective ways to reach these goals, however, are hardly available. Several options have been presented in literature, like motivational interviewing, brief interventions and increasing resilience.

The results of a recent Cochrane review [122] indicate no substantive, meaningful benefits of motivational interview interventions for the prevention of alcohol misuse. Although some significant effects were found, effect sizes were too small to be of relevance to policy or practice. Also, various misuse measures were not consistently affected and bias may be a potential cause of the findings [122].

Another review summarized the effectiveness of alcohol screening and brief interventions. Only a limited number of randomized controlled trials in non-medical settings were identified but with an equivocal evidence of effectiveness of alcohol screening and brief intervention. However, the heterogeneity of non-medical settings makes it challenging to draw overarching conclusions [123]. It appears that face-to-face interventions are more effective than computer delivered interventions [124].

The most promising program approaches appear to be those aiming at reducing multiple risk behavior simultaneously [125]. These programs seek to increase resilience and promote positive environments supportive of positive social and emotional development. In a pilot study the potential efficacy of a resilience-based intervention was examined. The outcomes suggested that the intervention has the potential to increase resilience and protective factors, and to decrease the use of tobacco, alcohol and marijuana by adolescents [126].

Limitations

In our opinion three major limitations exist in the knowledge on neurocognitive functioning and adolescent alcohol use, these concern the interpretation of causality, generalizability of findings from adolescents abusing alcohol to the general population, and assessment of confounders.

The first limitation concerns the causality. Not only is alcohol abuse presumed to have an effect on cognitive and behavioural control functions, but also the reverse may be important: weaknesses in cognitive and behavioural control could be a risk factor for engaging in alcohol abuse. Evidence suggests that cognitive control functions, such as inhibition, attention, and working memory [127,128] and indices of behavioural control, such as high-intensity pleasure and effortful control, are prospectively related to substance abuse [129-131]. Therefore, the extent to which differences between alcohol abusers and controls found in cross-sectional studies preceded alcohol abuse is unclear, and the results should therefore be interpreted with caution. This calls for longitudinal studies with measures of cognitive and behavioural control before and after the onset of drinking. Such a design facilitates disentangling the reciprocal relation of cognitive and behavioural control with alcohol use.

Secondly, the results from research conducted among alcohol abusing adolescents are often generalised to the general population, assuming that findings in this at-risk group apply to moderate and heavy drinkers in general. Alcohol abusing subjects, however, represent a group at high risk for aversive outcomes and are identified using clinical diagnostic criteria. However, comparing alcohol abusing adolescents and moderately or heavily drinking adolescents may be problematic. Alcohol abusing adolescents form a considerable group, but they only form a smaller part of all drinking adolescents and may therefore not be representative.

Thirdly, there is insufficient knowledge on relevant covariates and mediators that play a role in alcohol use. Sample sizes of the available longitudinal research are relatively small. A relevant covariate, psychiatric comorbidity, is highly prevalent in alcohol abusing adolescents. Also, external risk factors, which are considered important in determining alcohol abuse, are usually not controlled for and therefore it is not clear whether differences between alcohol abusing adolescents and controls are the result of the alcohol intake or of other confounders.

In addition, a lot of knowledge is based on animal models [132] and a lot of human research is based on fMRI analyses. The relevance of these types of research may be questioned since animal models do not represent the complex psychobiological and social interactions that occur in human behavior. Also fMRI analyses have their draw-backs. Imaging pitfalls include the overall uncertainty of structure – function relation, the technical limitations such as the relatively low resolution and on the other hand, zooming in on very specific relatively small areas without understanding the overall connectivity in the brain [133-138].

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