Effects of adolescent alcohol consumption on the brain and behaviour

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Abstract | Per occasion, alcohol consumption is higher in adolescents than in adults in both humans and laboratory animals, with changes in the adolescent brain probably contributing to this elevated drinking. This Review examines the contributors to and consequences of the use of alcohol in adolescents. Human adolescents with a history of alcohol use differ neurally and cognitively from other adolescents; some of these differences predate the commencement of alcohol consumption and serve as potential risk factors for later alcohol use, whereas others emerge from its use. The consequences of alcohol use in human adolescents include alterations in attention, verbal learning, visuospatial processing and memory, along with altered development of grey and white matter volumes and disrupted white matter integrity. The functional consequences of adolescent alcohol use emerging from studies of rodent models of adolescence include decreased cognitive flexibility, behavioural inefficiencies and elevations in anxiety, disinhibition, impulsivity and risk-taking. Rodent studies have also showed that adolescent alcohol use can impair neurogenesis, induce neuroinflammation and epigenetic alterations, and lead to the persistence of adolescent-like neurobehavioural phenotypes into adulthood. Although only a limited number of studies have examined comparable measures in humans and laboratory animals, the available data provide evidence for notable across-species similarities in the neural consequences of adolescent alcohol exposure, providing support for further translational efforts in this context.

Adolescence is the gradual period of transition from the dependence on others that is characteristic of the juvenile period to the relative independence of adulthood. This developmental period has been highly conserved across mammalian species and is associated with various age-specific neural, physiological, cognitive and behavioural transitions, including the temporally restricted hormonal and physiological changes associated with puberty[1]. In terms of behavioural alterations, adolescents across various mammalian species show increases in risk-taking and sensation-seeking, which may include the frequent initiation of alcohol and other drug use, and elevated levels of alcohol consumption relative to those of adults[2].

The prevalence of alcohol drinking in adolescents is high in the United States[3] and is even higher in many European countries[4]. For instance, in the United States, 21%, 42% and 58% of 8th (~13 and 14 year olds), 10th (~15 and 16 year olds) and 12th (~17 and 18 year olds) graders, respectively, report the use of alcohol in the past year[5]. The consumption of five or more alcoholic drinks in males, or four or more alcoholic drinks in females, within a 2 hour period is commonly referred to as binge drinking and is particularly notable among adolescents, with 5%, 16% and 24% of individuals in these age groups, respectively, reporting binge drinking in the past 2 weeks in the United States[6]; rates of such drinking are several-fold higher in European adolescents[4] (FIG. 1). Alcohol consumption rates reach very high levels in some adolescents: among high school seniors (~17 and 18 year olds) in the United States, >10% report consumption of ≥10 alcoholic drinks and >5% report consumption of >15 alcoholic drinks per occasion in the past 2 weeks[7]. Overall, although adults drink alcohol on more days than adolescents do, when adolescents consume alcohol, their consumption levels per occasion are greater than those of adults[8]. Although a variety of factors undoubtedly contribute to the elevated intake of alcohol in adolescents, maturational changes in the brain probably have an important role. Indeed, alcohol consumption is elevated

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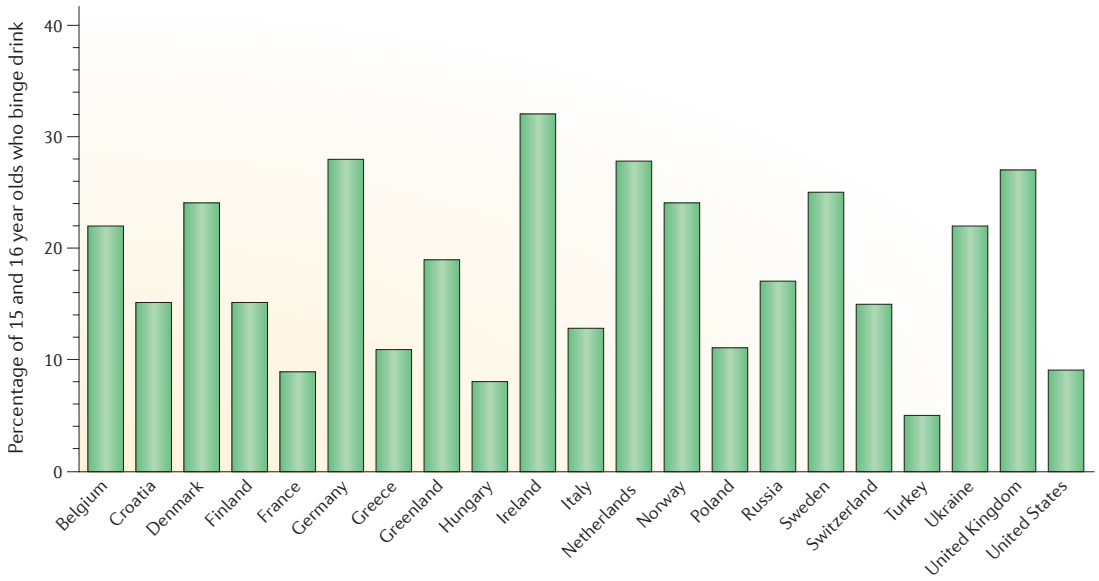

Figure 1 | **Binge drinking in individuals aged 15–16 years from various European countries and the United States.** In this data set, binge drinking was defined as the consumption of at least five drinks on a single occasion at least three times over the past month. Data from REF. 4.

during adolescence relative to adulthood not only in humans but also in laboratory animals such as rodents[9], indicating that biological factors probably contribute to the elevated alcohol intake observed during this developmental period.

Because of the high rates of the initiation and escalation of alcohol use in adolescents, there is substantial interest in exploring the antecedents of these behaviours and the consequences of this exposure on later neurobehavioural function. The goal of this Review is to summarize the effects of alcohol use in human adolescents and in rodent models of adolescence. To set the stage for this discussion, the Review begins with a brief summary of the maturational changes that occur in the adolescent brain, derived from both human and rodent work. The article then explores cognitive and behavioural function in rodents and humans following adolescent alcohol exposure before covering the neural alterations associated with such alcohol exposure, and it ends with a discussion of the relationship between the human and nonhuman animal findings and the potential future directions for this work.

It should be noted that, consistent with the vast majority of the literature to date, this Review emphasizes comparisons between adolescents and adults, leaving in abeyance the issue of the extent to which adolescence represents a developmental dissociation versus a linear transition between juveniles and adults. The issue of pubertal effects on alcohol use is also beyond the scope of this Review, although it should be noted that studies in youths to date have focused primarily on the role of perceived pubertal timing in the initiation and/or escalation of alcohol and substance use[10], and rodent studies have found surprisingly limited effects of the presence or absence of pubertal hormones per se on behaviours that are not strongly sexually dimorphic, including novelty-seeking as well as alcohol preference and intake[11].

Binge drinking
As defined by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), a pattern of alcohol use that results in blood alcohol concentrations in the range of 0.08 g/dl or greater; typically, alcohol concentrations in this range are achieved by consumption of five or more or four or more drinks within a 2 hour period in males and females, respectively.

Adolescent brain changes

Substantial evidence has accumulated over the past several decades that the brain continues to mature through adolescence. Much of this ontogeny appears to have been highly conserved evolutionarily, with the brains of adolescents showing similar developmental changes across mammalian species[12]. These across-species commonalities have proved useful for studies of adolescent brain development, given that the more invasive techniques possible in laboratory animals have yielded substantial data regarding the cellular, synaptic and molecular mechanisms underlying this maturation[13,14]. Much of the research in this area has been reviewed extensively[12,15–17], including in a recent special journal issue devoted to the adolescent brain[18]. Hence, I only briefly highlight maturational changes in the adolescent brain here.

The maturation of the adolescent brain includes notable pruning of the synaptic connections between neurons; indeed, rodent studies indicate a loss of up to 50% of the synaptic connections in some regions of the brain during adolescence[19]. Adolescence in both rodents[20] and humans[21] is associated with reductions in the volume of grey matter (regions enriched in neurons, glia and neuropil). These reductions may be linked in part to the maturational loss of synaptic connections and to developmental increases in the amount of brain partitioning as white matter, given that the skull constrains brain size. Developmental increases in white matter are associated with the continued elaboration of myelin (an insulating sheath that markedly enhances the rate of axonal conductance) around axons during adolescence. Axons in pathways interconnecting distant brain areas are often particularly targeted for myelination during adolescence, thereby increasing the speed of communication between dispersed regions. Indeed, imaging studies examining connectivity in the developing human brain

have revealed that connectivity between distant brain regions is increased relative to more local connectivity during adolescence[17,22].

Brain systems that undergo particularly marked developmental change during adolescence include neurons using dopamine (DA), a neurotransmitter that is critical for the processing of rewarding stimuli — including natural rewards as well as drugs — and the cues associated with these stimuli. Although the development of the DA system is a complex process, there is evidence that activation of mesolimbic DA projections to regions such as the dorsal striatum, nucleus accumbens and amygdala as well as of mesocortical DA projections to the prefrontal cortex (PFC) often peaks during adolescence[23,24]. In rats, the DA neurons in the ventral tegmental area that form these projections reach their highest firing rates during mid-to-late adolescence[25,26], with peaks in DA activity and levels of receptor expression in mesolimbic regions typically occurring earlier in adolescence than in the PFC[27]. Inhibitory tone and the ratio of inhibition to excitation are generally lower in the PFC in adolescence than in adulthood[28], with rodent studies revealing that developmental increases in relative inhibition during adolescence result from notable elimination of excitatory synapses in the PFC[29] and ontogenetic increases in $GABA_A$ receptor-mediated tonic (extrasynaptic) currents[30]. Strong DA D_2 receptor-mediated excitatory stimulation of GABAergic inhibitory interneurons also emerges in the PFC of rodents by late adolescence, which in turn inhibits pyramidal cell activity in the PFC[14]. The maturation of this robust DA-driven inhibition of PFC pyramidal cells has been suggested to enhance the salience of PFC pyramidal outputs that is critical for the maturation of PFC interrelationships with other brain regions[31].

Studies in laboratory animals and humans have found that mesolimbic and mesocortical DA projections are more sensitive to certain reward-related events in the adolescent brain than in the adult brain[32,33]. Indeed, human brain imaging studies show that, in response to reward receipt, adolescents exhibit greater activity in both mesolimbic and mesocortical DA terminal regions than do adults. These effects are not always evident, with both mesolimbic and mesocortical DA terminal regions in adolescents sometimes showing less activation during (and hence lower sensitivity to) reward anticipation than the equivalent regions in the adult brain[32]. Hypersensitivity to the receipt of rewards has been suggested to increase adolescents' drive for risky and novel experiences[33,34]. Studies in rodents have also showed that adolescents exhibit enhanced neural and behavioural sensitivity to positive rewarding stimuli — for example, in the latter case, displaying more goal-directed behaviour towards stimuli and often being willing to work harder to attain these stimuli[34]. In these studies, evidence for synergistic effects of reward-related stimuli have sometimes emerged, with, for instance, the presence of social stimuli markedly enhancing the effectiveness of other rewarding stimuli in adolescents[34]. In humans, adolescents, but not adults, show an increase in risk-taking behaviour for rewards under socially stimulating circumstances[35]. Indeed, social context plays a particularly critical role in alcohol intake during adolescence in humans[36,37] and rodents[38,39]. Although much of the work using rodent models of adolescence has been conducted only in males, some studies have examined high social drinking in adolescents of both sexes. These studies[38,39] found that high-drinking males had greater baseline social activity and were more sensitive to the social facilitatory effects of alcohol than low-drinking males, whereas high-drinking females were socially anxious and particularly sensitive to alcohol's social anxiolytic effects relative to their low-drinking counterparts — findings reminiscent of sex differences in drinking motives reported by human adolescents[36,37].

Adolescent engagement in risk-taking, including the use of alcohol and other drugs, is also thought to be influenced by the protracted maturation of neural systems and networks that are critical for cognitive control and that only slowly reach their adult state late in adolescence[40]. Studies of the emergence of cognitive control during adolescence first focused on delayed maturation within PFC regions that play critical roles in inhibitory control and other executive functions, a developmental delay that contrasts with the earlier maturation of limbic regions such as the nucleus accumbens and amygdala, which are critical for the processing of rewarding and emotional stimuli[40]. Current versions of such dual-system models propose developmental peaks in sensation seeking and processing of rewarding stimuli during mid-adolescence (~14–17 years) that emerge independently from the more linear and protracted development of cognitive control mechanisms, which continues into late adolescence[41]. Other models of adolescent brain development have focused on development of neural circuitry, suggesting that subcortical–subcortical circuits develop early in adolescence, followed later by the emergence of cortical–subcortical and then corticocortical connectivity, with the relative levels of activity observed in these circuits during adolescence influenced by both content (for example, desired actions or emotions) and context (for example, social isolation or the presence of peers, parents or potential threats)[17,42,43]. The circuitry undergoing notable change during adolescence includes the mesocortical DA pathway, which exhibits experience-related increases in DA firing that are thought to trigger both structural and electrophysiological plasticity in the PFC and to contribute to the accumulation of experience-based adaptations during adolescence[17]. Evidence is accumulating that neuroplasticity gradually declines as the brain matures (from childhood to adolescence and into adulthood), resulting in enhanced neural stability, which is thought to adapt the maturing brain to the circumstances and contexts that are encountered by the often experience-seeking juvenile and adolescent[17,22,42].

Thus, the neural changes occurring in the brain during adolescence include both developmental declines in synaptic connections in various brain regions and changes in critical network associations to favour more distributed circuitry over more local circuitry. Mounting evidence indicates that the nature of these adolescent

neural alterations may be, to some extent, experience-dependent, helping to sculpt the adolescent brain into a mature brain that is adapted to those experiences. Many of these developmental changes occur in brain regions that are particularly sensitive to even fairly low doses of alcohol, such as regions of the PFC and subcortical regions that modulate reward and motivational functions[44]. Hence, it is possible that such maturation could be vulnerable to repeated exposure to alcohol during adolescence. Indeed, as detailed below, convincing evidence is emerging from research in humans and laboratory animals that adolescent alcohol exposure induces specific and often persisting cognitive, behavioural and neural consequences.

Alcohol, human youth and cognition

Adolescents with a history of alcohol use differ cognitively from relatively abstinent adolescents: the former exhibit elevations in risky decision-making, as well as poorer performance on attention, visuospatial, working memory and other executive function tasks[45–48]. For instance, in a recent large cross-sectional study of >800 individuals aged 12–21 years, those adolescents that exceeded a no–low drinking threshold exhibited poorer impulse control (indexed via choice of lower delays in a delay discounting task) and decreased accuracy on a balance ('walk-a-line') test assessing postural stability[49]. However, the differences that are observed in cross-sectional studies between groups of adolescents that vary in their alcohol use are not necessarily causal. That is, the observed group differences may have predated alcohol use and contributed to the initiation and escalation of that use rather than reflecting the consequences of such use. These possibilities are not mutually exclusive: some of the differences that predated alcohol use perhaps represent vulnerability factors that promote greater alcohol use after alcohol initiation, thereby precipitating the emergence of more pronounced differences between the groups as alcohol use trajectories diverge. Longitudinal studies that track individuals over time (ideally beginning before alcohol use onset) have proved useful for distinguishing predisposing factors that predict later problematic use from differences that emerge as adolescents begin to diverge in their initiation, use and abuse of alcohol.

Effects predating alcohol use. Prospective longitudinal studies have revealed several neuropsychological, cognitive and personality variables that predate alcohol use and serve as predictors of the later initiation and escalation of alcohol consumption. For instance, from baseline assessments obtained early in adolescence (~11.5–14 years), cognitive and personality factors, including poorer cognitive inhibition[50], elevated impulsivity[51] and deficits in executive function tasks (for example, decreased performance on perceptual portions of the Wechsler abbreviated scale of intelligence)[52], predicted the initiation and frequency of alcohol use and/or the maximum number of alcoholic drinks consumed per occasion 3–6 years later. The accuracy of early-adolescent predictions of individuals who would develop moderate to heavy alcohol use by their late teens was improved when baseline cognitive measures were combined with neural imaging data (see discussion below) and demographic variables (that is, sex and socioeconomic status)[52]. The importance of personality variables in the initiation of alcohol use was also apparent in data obtained by the IMAGEN study, a European longitudinal study of adolescent brain development, genetics and mental health. For example, when adolescents were examined at 14 years of age and again at 16 years of age, personality factors (sensation-seeking, novelty-seeking, impulsivity and extraversion) best predicted alcohol intake in early adolescence, whereas genetic factors predicted increases in alcohol intake over the 2 year period[53]. Indeed, there is evidence from twin studies that genetic factors play a negligible role in the initiation of alcohol drinking in adolescence, although they influence escalation of drinking thereafter, with environmental factors contributing to both the initiation and escalation of alcohol use[54]. Further discussion of the genetics of alcohol use in adolescence can be found in a recent genome-wide association study of genetic risk, personality and adolescent alcohol problems[55].

Consequences of alcohol use. In youths first assessed at 12–16 years of age (when they had minimal, if any, prior alcohol and/or other drug use) and again 6 years later, those that exhibited extreme binge drinking (10 drinks or more per occasion at least once over the 3 months before the second test) performed more poorly on verbal learning and short-delay memory tasks than non-binge drinkers, despite equivalent baseline performance of the two groups[56]. Interestingly, when regression analyses were used to determine the threshold exposure levels for these alterations, essentially a linear dose-dependent relationship emerged, with the number of drinks consumed during peak drinking episodes linearly associated with an increasing deleterious effect on verbal learning and memory, leading the authors to conclude that there was no safe drinking level to avoid these impairments. At the 8-year to 10-year follow-ups of youths with and without alcohol or substance abuse disorder at study enrolment, cumulative alcohol use over the follow-up period was reported to predict deficits in attentional function, and poorer arithmetic[57] and verbal memory[58] performance. Similar results were observed in youths who persisted in using alcohol and those who no longer used alcohol, suggesting that recovery of cognitive function did not occur over the follow-up period, even in those that had stopped use. However, findings from other work provide evidence for recovery of cognitive function following termination of use: over a 2 year follow-up period, university students who exhibited binge alcohol use initially but not at follow-up did not differ cognitively from individuals who did not binge at either time, with both groups exhibiting better verbal memory and less perseveration on a response monitoring task than individuals who continued to binge drink alcohol[59]. Clearly, more work is needed to address the critical issues of the threshold for cognitive effects and the extent of cognitive recovery following the termination of alcohol use.

Prospective longitudinal studies
Studies that track individuals over time, ideally starting before the emergence of the target measure (for example, in this context, before the initiation of alcohol use or problematic alcohol use).

When youths were tested for cognitive function at 12–14 years of age (when they had little or no drinking experience) and again 3 years later when some of the youths had initiated moderate to heavy alcohol use, a higher number of drinking days during the past year was associated with a greater decline in performance on a visuospatial task from baseline to follow-up in girls (but not in boys), whereas the number of hangover symptoms during the past year predicted the magnitude of decline in sustained attention in males (but not in females)[60]. These findings illustrate the emerging sex differences in this literature[61], which are actively being explored, although this topic is beyond the scope of this Review. This study also raises the importance of withdrawal or hangover severity as a predictive measure of outcome magnitude. Indeed, the number of lifetime alcohol withdrawal symptoms has been associated with specific cognitive deficits in cross-sectional studies[62,63]. Moreover, in the 8 year and 10 year longitudinal studies discussed above, although the amount of cumulative alcohol exposure predicted certain neuropsychological impairments, the number of withdrawal symptoms experienced within the previous 2 years was associated with specific deficits in visuospatial function[57] and verbal learning[58]. Thus, the number and severity of withdrawal episodes may have outcomes separable from the amount of alcohol exposure per se. Periods of alcohol abstinence may facilitate the emergence of compensatory neuroadaptations. Indeed, in studies in both adult clinical populations and laboratory animals, multiple alcohol withdrawals have been related to increased severity of a variety of negative outcomes[64], even when total amount and duration of alcohol exposure was controlled in animal studies[65]. Similar effects are seen during adolescence, with the lasting effects of adolescent alcohol exposure being more pronounced in rodents exposed intermittently rather than continuously to alcohol[66,67], and evidence that, although adolescent rats often exhibit fewer hangover or withdrawal symptoms than adults following initial alcohol exposure[68], adolescents appear more sensitive than adults to the exacerbation of withdrawal signs induced by repeated episodes of alcohol withdrawal[69,70].

It should be noted that in these studies and the neuroimaging studies discussed below, adolescents frequently indicated use of not only alcohol but also other drugs such as marijuana or cigarettes. Although findings assessing separate and combined effects of adolescent drug exposure are limited and beyond the scope of this Review, it should be recognized that owing to the concurrent use of drugs other than alcohol, it is often difficult to conclusively relate the observed effects to alcohol use per se. Statistical approaches (such as including other drug use as a covariate) can be used to reduce, but do not eliminate, possible misattribution of consequences to alcohol-specific effects[57]. Thus, one of the advantages of research using animal models of adolescence is that consequences of alcohol exposure alone or in combination with other drugs can be empirically investigated to assess alcohol-specific adolescent exposure effects.

Taken together, the data to date suggest that personality variables, such as externalizing behaviour and impulsivity, as well as lower performance on certain specific inhibitory and executive function tasks, predate and serve as predictors of later initiation and/or escalation of alcohol use, whereas alcohol use during adolescence may precipitate additional cognitive differences that emerge concomitant with that use. Such alterations in verbal learning and memory, attention and visuospatial tasks include some of the major persisting cognitive deficits reported in adults abstaining from alcohol years after undergoing detoxification[71], suggesting that the roots of such lasting deficits are established early in the development of problematic alcohol use. As discussed above, the evidence also suggests that cognitive alterations are associated with not only the amount of alcohol consumption but also the frequency or intensity of withdrawal. The latter could potentially implicate the importance of repeated episodes of ethanol presence and clearance that might accelerate and intensify the induction of alcohol neuroadaptations that contribute to the adverse effects of long-term use[65].

When considering these findings, however, it should be emphasized that, in many of these studies, alcohol-using youths did not exhibit altered performances on the majority of the cognitive tasks examined compared with control individuals, suggesting that there is considerable specificity in the nature of the observed cognitive effects. It should also be noted that the populations studied in many of the longitudinal studies to date have included few individuals with low socioeconomic status, limited educational opportunities, poor home stability and so on. Thus, it remains to be determined whether the consequences of adolescent alcohol exposure would be more pronounced in youths from less-privileged backgrounds. Moreover, it is unclear whether the observed effects would be intensified by challenges later in life, such as exposure to chronic stressors, traumatic brain injury or ageing-related cognitive decline.

Adolescent alcohol effects in rodents

Studies examining the consequences of adolescent alcohol exposure in rodents have typically included measures of not only cognitive functioning but also behaviours such as risk-taking, impulsivity, anxiety and social behaviours. In such studies, the consequences of adolescent exposure to alcohol also have often been assessed in adulthood, well after termination of alcohol exposure, whereas human longitudinal studies have typically assessed individuals in adolescence (or, at the latest, emerging adulthood). Typical exposure models in rodent studies include intermittent exposure to alcohol using an every-other-day or 2 days on–2 days off schedule for varying lengths of time during the broad adolescent period (roughly 28–55 postnatal days)[72]. Various administration routes (intragastric, inhalation, oral and intraperitoneal) have been used at exposure levels usually producing blood alcohol concentrations of approximately 100–150 mg%[44], well into the binge-drinking range (defined as ≥80 mg% by the National Institute on Alcohol Abuse and Alcoholism (NIAAA)) and consistent with levels reported in field studies of adolescents

drinking heavily[73]. Studies that have compared equivalent exposures to alcohol in adolescent and adult animals have found that the effects of alcohol exposure during adolescence are generally not evident or are less pronounced than after comparable alcohol exposure in adulthood[44].

Cognitive studies in rodents generally have revealed that repeated exposure to alcohol during adolescence has minimal effects on later learning and memory of tasks ranging from simple spatial learning tasks[74] to more challenging five-choice serial reaction time tests[75]. However, when the task demands require some degree of cognitive flexibility, deficits have often emerged. For instance, although adult spatial learning was unaffected after adolescent alcohol exposure, when the spatial target was switched to a new location, the previously alcohol-exposed rats took longer to learn the new location than rats not exposed to alcohol during adolescence[76,77]. As adults, rats exposed to alcohol during adolescence also had difficulty learning an operant set-shifting task[78]. Extinction was also delayed in the adolescent alcohol-exposed animals when they were tested in adulthood[78]. In several aversive (but not appetitive[79,80]) tasks, rats exposed to alcohol during adolescence exhibited evidence of behavioural inefficiencies in adulthood. Such inefficiencies included greater time and lower path efficiency when escaping in a water maze (although acquisition of the water maze escape task was unaffected)[74] and delayed latencies to lever press on choice trials in a punishment-based task[80].

Increases in later anxiety-like behaviour after adolescent alcohol exposure have been reported using a variety of tests in rodents. Social anxiety, characterized by decreases in social investigation and social preference, has consistently been observed after adolescent alcohol exposure; this social anxiety is sex-specific as it is evident only in males[81,82]. Anxiogenic effects of adolescent exposure have also been observed in the elevated plus maze, with animals previously exposed to alcohol spending proportionally less time on the open arms than the control animals[83,84] and engaging in more risk-assessment behaviour (for example, stretch-attend postures)[85]. Evidence for increases in anxiety has also come from studies using the light–dark box, with rats exposed to alcohol during adolescence entering the dark compartment more quickly and spending more time in the dark compartment than controls[84,86,87], as well as from marble-burying[87] and open-field tests, with rats and mice previously exposed to adolescent alcohol spending more time on the periphery rather than exploring the centre of the open field[77,88].

However, repeated exposure to alcohol during adolescence has sometimes been found to decrease apparent anxiety-like behaviours, as indexed by the exposed animals spending proportionally more time on the open arms of the elevated plus maze[78,89] and returning to the open, light side of the light–dark box more quickly[90] than control animals. Likewise, in an open-field conflict test, in which desirable food was placed under a bright light that was centred above the field, adolescent alcohol-exposed animals approached the food and ate more quickly than controls when they were tested in adulthood[90–92]. These types of findings have typically been interpreted as reflecting 'disinhibition', impulsivity or even increases in risk-taking rather than as decreases in anxiety. Tests of anxiety are notoriously sensitive to variations in context, and prior manipulations can promote the expression of either anxiety-like behaviour or disinhibition, depending on the test circumstances[93]. It is possible that anxiety and disinhibition may not represent opposite ends of the same continuum but instead can be expressed orthogonally. For instance, in a systematic analysis of stretch-attend postures (commonly used as an index of risk assessment) in non-drug-treated mice in the open field test and elevated plus maze, risk assessment was found to be unrelated to disinhibition (measured via percentage of time spent in the centre of an open field)[94]. Each of these constructs has also been associated with different (not converse) patterns of neural activity[95]. Indeed, after repeated exposure to alcohol during adolescence, rats were found to exhibit increases in risk-taking under rewarding conditions but increases in risk assessment under more adverse circumstances — for example, when tested after exposure to a stressor (30 minutes of restraint)[85]. Other rodent work has likewise shown that increases in risk-taking as a result of adolescent alcohol exposure are evident only when reward (but not punishment) probability is varied[80]. Increases in risk-taking after adolescent alcohol exposure have also been reported in adult rats using an operant probability discounting task, with exposed rats continuing to prefer the risky choice at lower probabilities than were acceptable to controls[96–100]. Moreover, adult mice exposed to alcohol during adolescence showed an increase in risky choices in a modified Iowa gambling task[101].

When attempting to interpret findings of risk assessment versus risk-taking or disinhibition, it may be useful to consider these concepts from an evolutionary perspective. Adolescent risk-taking has been suggested to have evolved in part to encourage dispersal from the home territory around the time of sexual maturation to avoid genetic inbreeding[102]. However, unknown territories are fraught with potential threats to survival. Thus, to the extent that risk-taking, disinhibition and novelty seeking promote dispersal whereas anxiety, risk assessment and vigilance increase the probability of survival as animals emigrate, what might appear at first to reflect conflicting results might in fact reflect compatible findings owing to similar evolutionary pressures. Inclusion of measures of risk assessment in tests of risk-taking, disinhibition and anxiety could help disentangle these effects.

Repeated exposure to alcohol during adolescence has sometimes been reported to increase subsequent voluntary consumption of alcohol in adulthood, effects that are evident following exposure via oral self-administration[87,103–105], or, occasionally, intraperitoneal injections[83,106,107] or vapour inhalation[78], with such increases in intake sometimes not observed in animals receiving similar alcohol exposure in adulthood[108]. In other studies, however, increases in later alcohol intake were not evident after voluntary or experimenter-administered alcohol exposure during adolescence[109–111], or similar consumption increases were seen after repeated alcohol exposure during either

Set-shifting task
A task in which animals are first taught one rule about the stimulus that predicts a rewarded operant response. There is then a rule shift, and the animals must learn to ignore the initial rule and instead use another stimulus to determine which response will be rewarded.

Extinction
Learning not to respond when a reinforcer is no longer received.

Elevated plus maze
A test of anxiety that uses a four-armed, cross-shaped apparatus that is well elevated from the floor. Two of the arms are surrounded by high walls (the 'closed arms') whereas the other two arms do not contain walls (the 'open arms'). Anxiety-like behaviour in this test is indexed by animals spending less time and exhibiting fewer entries into the open arms than typically seen in control animals.

Disinhibition
A lack of restraint, often associated with increases in impulsivity or risk-taking.

Probability discounting
In an operant probability discounting task, animals are given a choice between a 'safe' lever associated with a small but consistent reward versus a 'risky' lever associated with a reward that is greater but less probable. In such tasks, increased risk-taking is indexed by animals persisting in choosing the risky lever even when the probability of receiving the higher reward is low.

adolescence or adulthood[112,113]. The circumstances that led to these different voluntary intake patterns after adolescent alcohol exposure remain to be detailed, although stress level may have been a critical variable. Indeed, female rats given voluntary access to alcohol beginning in adolescence drank more than controls in adulthood only after stressor exposure; a stress-induced escalation in intake was not seen in females when their initial alcohol access was delayed to adulthood[114]. Indeed, exposure to alcohol during adolescence has been reported to influence the development of the hypothalamic–pituitary–adrenal axis in rodents and alter later hormonal responses to stressors[115,116].

Adolescent alcohol exposure has been reported to increase not only later alcohol consumption under some circumstances but also the appetitive properties of, and motivation for, alcohol. Adult rats that drank heavily when voluntarily consuming alcohol during adolescence developed a preference for a flavour when that taste was paired with alcohol consumption in adulthood, whereas animals that were moderate drinkers during adolescence or that were alcohol naive developed an aversion for the alcohol-paired flavour[117]. Likewise, adolescent alcohol-exposed rats but not control rats developed a preference for a test chamber paired with alcohol in adulthood[118]. Similar facilitation of alcohol-induced conditioned place preferences following alcohol exposure during adolescence (but not after comparable exposure in adulthood) was seen in a study in mice, although alcohol exposure at either age increased later alcohol consumption[112]. Likewise, intermittent home cage access to alcohol either during adolescence or in adulthood increased later alcohol consumption, although only adolescents that consumed high levels of alcohol (and not adolescents or adults who consumed lower levels of alcohol) exhibited an increase in motivation for alcohol, as indexed via more rapid completion of an operant schedule to access alcohol[113].

These elevations in alcohol consumption and motivation for alcohol are examples of the persistence of adolescent-like phenotypes in adulthood after adolescent alcohol exposure. Indeed, studies in laboratory animals have shown that alcohol is a very different drug for adolescents than for adults and that many adolescent-typical alcohol sensitivities are maintained in adulthood after alcohol exposure in adolescence (TABLE 1). Adolescents are less sensitive than adults to many of the intoxicating and impairing effects of alcohol that seemingly serve as cues to terminate drinking, including alcohol's motor-impairing, sedative, social-inhibiting, aversive and even its hangover-inducing effects[12]. By contrast, adolescents are more sensitive than adults to several key desired consequences of low doses of alcohol, including its social facilitatory and rewarding effects (see REF. 12 for a review) while also being more sensitive to the disruptive effects of alcohol on spatial memory[119]. Although ethical considerations have largely precluded the conduct of similar studies in underaged youths, the limited data available suggest that similar patterns of increased appetitive and decreased impairing effects of alcohol are evident in human adolescents as well, effects that could help promote the high levels of alcohol consumption that are prevalent in adolescents[2,120]. Many of these adolescent-typical sensitivities to alcohol are retained into adulthood after repeated adolescent alcohol exposure[121] and hence could potentially contribute to the increased voluntary intake of alcohol that is often seen in adults after adolescent exposure to alcohol. For instance, as adults, former adolescent alcohol-exposed animals still exhibit 'adolescent-like' insensitivities to alcohol's motor-impairing, sedative and aversive effects[122–124] while retaining adolescent-typical increased sensitivities to alcohol's disrupting effects on spatial memory[125] and to alcohol's locomotor stimulant and rewarding effects[123,126]. Similar evidence for 'adolescentization' of the adult brain after adolescent alcohol exposure will be discussed below.

Alcohol and the human adolescent brain

MRI studies have showed that the brains of adolescents who have a history of substantial alcohol use differ from those without this exposure in various ways, although, as mentioned above, cross-sectional studies cannot be used to infer causality. For example, adolescents with alcohol

Table 1 | **Adolescent-typical alcohol sensitivities determined from rat studies**

Effect of alcohol intake	Sensitivity to effects in adolescents relative to adults	Persistence of adolescent-typical sensitivity into adulthood following repeated adolescent alcohol exposure
Social facilitation (at low doses)	More sensitive	Yes
Rewarding effects	More sensitive	Yes
Impairment of spatial memory tasks	More sensitive	Yes
Social inhibition (at higher doses)	Less sensitive	Yes
Aversive effects	Less sensitive	Yes
Sedation	Less sensitive	Yes
Discriminative stimulus effects	Less sensitive	Unknown
Analgesia	Less sensitive	Unknown
Anxiolysis	Less sensitive	Yes
Acute withdrawal (hangover)	Less sensitive	Yes

use disorder or who frequently engage in binge drinking alcohol exhibit decreases in grey matter volume in various brain regions. The affected areas typically include portions of the frontal, parietal and temporal cortices, as well as limbic regions such as the hippocampus and the cerebellum[127–131], although there is some variation in the precise regions affected across studies. Diffusion tensor imaging studies have also reported decreases in white matter integrity and efficiency in adolescents with alcohol use disorders or a history of binge drinking relative to adolescents without these use patterns[132–135]. Functional MRI (fMRI) studies that were conducted on individuals while they performed cognitive tasks have also revealed notable differences in brain activation between adolescents with and without alcohol use disorders or a history of binge drinking even when task performance was similar across groups. Yet, whereas some studies have showed that individuals with a history of adolescent alcohol use exhibit lower activation in task-relevant regions, others have reported that such individuals exhibit higher activation in those regions or certain task-irrelevant regions[136–139]. These decreases and increases in activation have been suggested to reflect reduced neural recruitment during task performance or compensatory responses, respectively (see discussion below). Longitudinal studies and studies examining youths at heightened risk of developing alcohol use disorders (for example, studies examining youths with a family history of alcoholism (FH^+ youths) versus peers without such a family history (FH^- youths)) have shown that some of these neural features predate onset of alcohol use whereas others are consequences of that use, data to which we now turn.

Effects predating use. Prospective studies beginning in adolescents before initiating marked alcohol use have revealed that the grey matter volumes in brain regions such as the amygdala and portions of the frontal cortex are often smaller before alcohol use initiation in individuals who develop later problematic alcohol use[52]. For example, a decrease in the volume of the anterior cingulate cortex at 12 years of age predicted the emergence of alcohol use problems over the following 4 years[140], whereas decreases in cortical and amygdala volume predicted alcohol drinking 1 year later in a study population of individuals aged 15–17 years[141]. Smaller orbitofrontal cortex[142] and dorsolateral PFC[143] volumes in early adolescence were also found to predict the emergence of binge drinking, alcohol or alcohol–marijuana disorders by late adolescence. Family history studies have also revealed that the volumes of the amygdala and portions of the hippocampus are smaller in FH^+ youths than in FH^- youths[144–146], although occasional reports have documented increases in limbic volumes in the former: one study reported an increase in hippocampal volume in male FH^+ youths[147] and another showed that the volume of the nucleus accumbens correlated with the familial density of alcohol use disorders[148].

Alterations in connectivity between cortical and limbic regions may also be related to later adolescent alcohol consumption. For example, reduced amygdala–orbitofrontal cortex connectivity in a longitudinal study population of individuals aged 12–27 years (recruited from schools and advertisements) predicted alcohol use 2 years later[149], and FH^+ youths showed decreased white matter integrity in various tracts that connect frontal and parietal cortical regions with other brain areas[150,151]. Other work has shown that FH^+ youths exhibit less functional connectivity between the nucleus accumbens and the orbitofrontal cortex than FH^- youths, indicative of poorer integration within the reward network and potentially disrupted maturation of the connectivity between the nucleus accumbens and the orbitofrontal cortex[152].

Prospective fMRI studies have found that youths who later transition into heavy alcohol use or binge drinking often exhibit attenuated activation in task-relevant brain regions during executive function (working memory or inhibitory) tasks (along with sometimes increased activation of task-irrelevant regions) before alcohol use initiation, generally in the absence of task performance deficits[153,154]. Likewise, FH^+ youths have sometimes[152,155] but not always[156,157] been reported to exhibit less brain activation in frontal and/or parietal regions under emotional circumstances or during tasks requiring inhibitory control than FH^- youths. Decreases in frontal activation during a risky decision-making task[158] and in temporal and parietal activation in response to emotional faces[152,159] have also been reported in FH^+ youths relative to FH^- youths. The often-blunted neural responses that have been observed in FH^+ youths are not evident under all circumstances; for example, such individuals generally show no notable alterations in neural activation during the processing of rewarding stimuli[160,161].

Thus, before the onset of alcohol use, the brains of individuals who are at increased risk of alcohol use initiation owing to a family history of alcoholism, or who are known from prospective studies to later transition into heavy drinking, differ from the brains of other youths. These differences that predate use initiation include smaller grey matter volumes, decreased connectivity among a number of brain regions (particularly frontal and parietal cortical regions and limbic areas) and often-blunted neural activation during the performance of inhibitory, risky or emotionally arousing tasks.

Consequences of alcohol use. Studies assessing brain development in youths beginning before alcohol use initiation and continuing through the transition into heavy (or sometimes even moderate) drinking have consistently revealed regionally specific alterations in developmental trajectories, with accelerated developmental decreases in grey matter volume contrasting with generally delayed developmental increases in white matter maturation. However, at this early stage in longitudinal investigations, a reliable consensus has yet to be reached regarding which brain regions and tracts are the most vulnerable to adolescent alcohol exposure, although some commonalities are beginning to emerge.

Several studies have reported exaggerated developmental declines in grey matter among youths after they transition to regular or heavy alcohol use[162,163]. The affected cortical regions include areas critical for executive functioning, cognitive control, attention, sensory

Diffusion tensor imaging
Type of MRI that examines the diffusion of water molecules (which move more rapidly along, rather than across, myelinated axon pathways) to assess the functional integrity of white matter fibre bundles and to index their neuropathology.

Pons
A sensory relay area in the brainstem that helps regulate arousal, sleep and autonomic processes.

integration and language processing, such as the middle frontal gyrus[163], left and middle temporal gyrus[130], and frontal, lateral frontal and temporal cortical regions[162]. Accelerated developmental declines in grey matter volume have also been reported in subcortical regions, including the ventral diencephalon, caudate and brainstem[130]. Volumetric declines in grey matter have been observed not only in adolescents who transitioned to heavy drinking and whose brains differed from controls at baseline (see section above)[130] but also in individuals who began to use alcohol regularly but did not transition to heavy use and whose brains did not differ at baseline from those not initiating alcohol use[163].

Longitudinal studies have also revealed evidence for disruptions in white matter development with adolescent alcohol use. Over an approximately 2–3 year period, adolescents who initiated heavy drinking exhibited attenuated developmental increases in white matter in various cortical regions, including the precentral gyrus, anterior cingulate cortex and middle temporal gyrus[163], and in the pons and the corpus collosum, the massive collection of fibres interconnecting neurons on the left and right sides of the neocortex[162]. Through use of diffusion tensor imaging, studies in alcohol-drinking adolescents have revealed attenuations in white matter integrity in a number of tracts interconnecting various cortical regions (for example, the superior longitudinal fasciculus and the fronto-occipital fasciculus) and subcortical regions (for example, caudate–thalamic white matter connections)[163,164], although increases in axial diffusibility (often consistent with greater axonal integrity) were conversely observed in portions of the corona radiata interconnecting prefrontal and limbic regions[164].

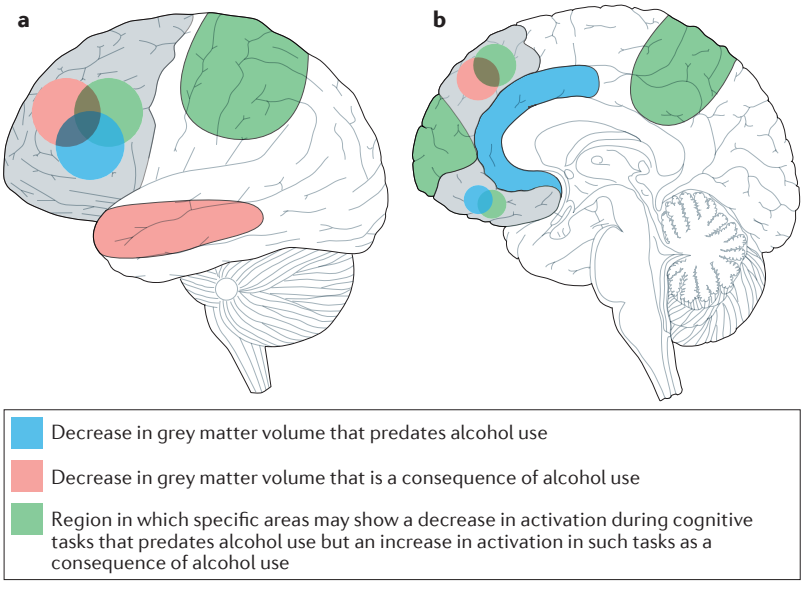

Figure 2 | **Alterations in cortical grey matter volume and task-related brain activation that predate adolescent alcohol use or emerge as a consequence of that use.** The figure shows lateral (part **a**) and midline (part **b**) views of the human neocortex. Note that areas within frontal and parietal regions may show decreases in activation during cognitive tasks that predate use and increases in activation during cognitive tasks that sometimes emerge as a consequence of use.

Overall, the data to date suggest that adolescent use of alcohol generally attenuates maturational increases in white matter volume and the microstructure or integrity of white matter, with some regional specificity in these effects. As discussed above, adolescents who drink alcohol heavily often use other drugs; hence, it can be difficult to attribute neural differences in these individuals to their use of alcohol per se. However, it is interesting to note that, in one study[164], changes in white matter integrity were associated with greater use of alcohol — but not use of marijuana — over the 18 month follow-up period, suggesting some specificity in drug effects.

Several studies have reported that as vulnerable youths begin to drink heavily, the neural responses observed during cognitive tasks change from the blunted task-related neural activation predating alcohol use (discussed above) to a pattern of increased task-related neural activation[153,154]. This later emerging increase in activation has been interpreted as a reflection of less-efficient memory processing and an increasing need to recruit more neural activity for successful task performance[153,154]. For example, one study examined 12–16 year old youths before beginning significant alcohol use and again 3 years later, comparing those adolescents who had transitioned into heavy drinking with those who had not[153]. At baseline, future drinkers showed lower activation in frontal and parietal regions during a working memory task than controls; however, 3 years later, after the former had transitioned to heavy alcohol use, they showed greater activation in these regions than the latter during this task. A different study, using a go–no-go task, reported a similar pattern of a decrease in baseline activation and then an elevation in activation in frontal, parietal and cerebellar areas following a transition to heavy drinking, although performance on the inhibitory task improved similarly between alcohol-using and non-drinking youth across the 3 year span in mid-adolescence[154]. These initial, intriguing longitudinal findings are ripe for replication and further investigation.

Taken together, the imaging data provide evidence that the brains of young adolescents who are at risk of initiating and escalating alcohol use differ from their less vulnerable counterparts in showing regionally specific decreases in grey matter, attenuated connectivity and integrity in white matter tracts and initial signs of decreases in brain activation in task-relevant regions during the performance of cognitive or emotional tasks. Over time, regionally specific developmental decreases in grey matter volume become more pronounced in youths who initiate heavy alcohol consumption and, although work in this area is in its early stages, several studies have reported that blunted task-related activation seen in such individuals before alcohol initiation contrasts with later increases in task-related neural activation with the transition to heavy drinking (FIG. 2). In contrast to the exaggerated developmental decreases in grey matter volume that are observed in heavily drinking adolescents, these youths show attenuated developmental increases in white matter volume and integrity, especially in tracts connecting frontal cortical regions with other areas.

New findings regarding the effects of repeated alcohol exposure on the human adolescent brain should accumulate rapidly owing to two major longitudinal efforts studying youths, beginning before initiation of alcohol use and continuing as some individuals transition to heavy alcohol use. The NIAAA-funded National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) is using an accelerated longitudinal design to sample individuals aged 12–21 years at baseline (with oversampling of individuals aged 12–15 years) from multiple sites. This combined within-subject and between-subjects approach is designed to assess the effects of alcohol use on the adolescent brain and neural characteristics predicting later problems on an accelerated timescale[165]. The other study is the Adolescent Brain Cognitive Development (ABCD) initiative, which was launched in 2015 and is funded by several institutes of the National Institutes of Health. This study is a 10 year, longitudinal, multisite investigation of brain development and child health involving ~10,000 children who were recruited to the project at the ages of 9 or 10 and includes brain imaging studies as well as examination of the initiation of alcohol and other substance use. These new studies will generate critical new knowledge regarding neural antecedents and consequences of adolescent use of alcohol versus other substances, findings complemented by the rapid rise in empirical studies using laboratory animals to assess the lasting neural effects of exposure to such drugs.

Alcohol and the rodent adolescent brain

Across-species comparisons. By and large, notably different levels of analysis have been used in studies of the neural consequences of adolescent alcohol exposure in humans (for example, imaging studies) versus laboratory animals (systems-level, cellular, electrophysiological and molecular analyses), thereby limiting the scope to make across-species comparisons of findings. However, some rodent studies have started to use measures to probe the neural consequences of adolescent alcohol use that are similar to those used in human studies (such as assessment of myelination or white matter integrity, cortical thickness or volume, resting-state connectivity and electroencephalography (EEG) or sleep measures), and, from these studies, the evidence for across-species similarity in findings is building. For instance, evidence of poorer white matter integrity in adult rats following adolescent alcohol exposure has been observed using diffusion tensor imaging[166] as well as when indexed via decreases in gene expression and levels of proteins essential for myelin integrity[167–170], a conclusion similar to that derived from work conducted in human adolescents with a history of alcohol use, as discussed above. Again, reminiscent of MRI findings of attenuated developmental increases in white matter in human adolescents who began to drink heavily[162], the volume of portions of the corpus collosum was also found to be decreased in adult rats after voluntary consumption of alcohol during adolescence, with these decreases inversely correlated with the amount of later relapse drinking[168]. In other work, both regionally specific increases and decreases in cortical thickness or volume were observed in rats after repeated exposure to alcohol during adolescence, including an attenuated thickness in the PFC[88], findings reminiscent of the decreases in cortical thickness reported in the PFC in human studies[171,172]. Again, bearing similarity to findings from MRI studies of human adolescents, a recent resting-state connectivity MRI study in adult rats observed that rats exposed to alcohol during adolescence exhibited long-lasting decreases in connectivity between regions in the PFC, along with decreases in connectivity between various frontal and mesolimbic regions (nucleus accumbens and dorsal striatum)[173].

The use of EEG to assess event-related potentials and sleep provides an additional opportunity for across-species evaluation, as indicated above. Studies of event-related potentials in humans and laboratory animals have often assessed P300, a positive potential occurring about 300 ms after stimulus onset, to index the processing of sensory stimuli. Adolescent rats repeatedly exposed to alcohol during adolesence[174,175] and youths with alcohol dependence[176] display decreases in P300 amplitudes, findings consistent with a disruption in hippocampal development[175]. Long-lasting alterations in sleep, including disruptions in the duration of slow-wave sleep, have been reported in rats exposed to alcohol during adolescence[177]. Although little studied in human adolescents after alcohol exposure, lasting sleep disruption has been reported in abstinent adults with alcoholism[178].

Dopamine and other neurotransmitters. Given the marked developmental transformations that occur in reward-sensitive components of the DA system during adolescence (as discussed above), it is not surprising that these regions appear particularly sensitive to alcohol exposure during adolescence and that alterations in these areas may serve as risk factors for later initiation of alcohol use. With respect to the latter, among early-adolescent youths, reduced recruitment during reward anticipation in DA neurons projecting to mesolimbic and mesocortical regions precedes, predicts and hence may serve as a risk factor for the development of subsequent problematic patterns of drug use[179]. Whether the DA system is further disrupted following alcohol exposure has been little studied in human adolescents, but it has received considerable attention in studies of laboratory animals, from which complex patterns of long-lasting DA alterations have been detected.

For instance, even when using an exposure protocol that produced blood alcohol concentrations well below the binge-drinking threshold in rodents, a study found that alcohol exposure during adolescence increased GABA-induced inhibitory tone onto DA neurons in the ventral tegmental area[180]. This increase in inhibition is postulated to decrease activity in the DA projections emanating from there, lowering tonic (basal) DA levels in terminal regions such as the nucleus accumbens[180]. In turn, this decrease in tonic activity may increase the signal-to-noise ratio of phasic-to-tonic DA stimulation, resulting in exaggerated phasic (stimulation-induced) DA release in response to risky stimuli. Indeed, the aforementioned study not only

showed that tonic DA levels in the nucleus accumbens negatively correlated with risk-taking but also revealed that pharmacological reversal of these decreases in tonic activity blocked the elevation in risk-taking that was evident in adult rats after adolescent alcohol exposure[180]. The increase in phasic DA signalling after adolescent alcohol exposure is situation-specific, evident when the outcome that was received was better than expected but not when the outcome was less than anticipated[181]. These findings are remarkably similar to data from other rodent research showing that adolescent alcohol exposure increases risky decision-making when animals are faced with choosing between low-probability but high-magnitude rewards versus higher-probability but lower-magnitude rewards[96–100]. However, it should be noted that differences in risky decision-making in adult rats were not seen after adolescent alcohol exposure in a task in which increased levels of food reward were paired with increased probability of foot-shock punishment[80]. From such data, it is tempting to suggest that under some circumstances, adolescent exposure to alcohol enhances later reactivity to rewards but not to punishment, but this possibility needs further study.

The consequences of adolescent exposure to alcohol on later DA signalling are complex in other ways as well. For instance, although baseline DA levels in the nucleus accumbens measured via microdialysis are often[106,182,183], but not always[184], found to be elevated after adolescent alcohol exposure compared with those in controls, the activity in mesocortical DA terminal regions sometimes appears to be attenuated[185]. Moreover, although decreases in the levels of DA neuron markers have been reported after such exposure in the prelimbic portion of the PFC[99,185], whether these decreases reflect an attenuation in DA neuron activation is unclear. For instance, one protein found in DA neuron terminals that has been used to determine DA terminal density is catechol *O*-methyltransferase (COMT). On the one hand, decreases in COMT expression following adolescent alcohol exposure could reflect fewer DA terminals and hence attenuated DA neuron activity. On the other hand, given that COMT is critical for DA metabolism, downregulation of this enzyme in DA neuron terminal regions could result in elevated DA levels, thereby reflecting a hyper-DA state rather than attenuated DA neuron activity[185]. Similar challenges in the interpretation of DA-related data are abound throughout the literature.

Box 1 | **Neurogenesis and neurotrophic factors: developmental perturbations**

Neurogenesis is critical for nervous system development but continues at notably lower rates in adult life in two neurogenic zones (within the hippocampal dentate gyrus and the lateral ventricles)[212]. The survival of later-formed new neurons and their successful integration into functional neural networks are thought to depend on 'effortful learning', which allows new experiences to become incorporated with past memories[213]. Rates of neurogenesis are influenced by multiple environmental factors, including physical exercise, sexual behaviour and exposure to drugs. Developmental disruptions such as repeated alcohol exposure during adolescence can inhibit the rate of formation or survival of new neurons, and such changes may be evident long after the chronic exposure period has terminated[192–194]. The induction of neuroinflammation (BOX 2) and alterations in epigenetic regulation (BOX 3) are potential factors that underlie the suppression of neurogenesis.

Repeated alcohol exposure during adolescence may also change the responsiveness of the mesocorticolimbic DA system to alcohol later in life, although there is no consensus yet on the nature of these alterations. Studies report that such exposure enhances alcohol-induced increases in the firing rates of a subset of DA neurons in the ventral tegmental area[186] while attenuating[183,187], but prolonging, alcohol-related increases in DA efflux in the nucleus accumbens[106,183,184]. Adolescent exposure to alcohol has been reported to attenuate D_2 DA receptor expression in the PFC, hippocampus, striatum and nucleus accumbens and expression of D_1 DA receptors in frontal cortical regions[106]. Adolescent alcohol-exposed rats have been reported to lose the capacity to respond to D_1 receptor stimulation in the prelimbic area of the PFC, with adult-typical D_1, but not D_2, receptor modulation of pyramidal cell activity blocked by such exposure[185].

Studies using increases in expression of the immediate-early gene proto-oncogene FOS to determine neuronal activation to later alcohol challenge have varyingly reported lasting increases in FOS activation in the nucleus accumbens[188] or lower FOS activation in the shell but not the core of the nucleus accumbens[107] in adolescent-exposed rats relative to controls. Attenuated alcohol-induced increases in FOS activation after such exposure also have been reported in the PFC and amygdala[188]. Numerous brain regions including portions of the PFC, dorsal and ventral striatum, and amygdala showed increases in expression of the transcription factor ΔFOSB following repeated alcohol exposure during adolescence that are more notable than those seen after equivalent alcohol exposure in adulthood[105]. These findings are of particular interest given the importance of ΔFOSB in neural plasticity mechanisms that are induced by repeated drug exposures.

Adolescent exposure to alcohol also disrupts other neurotransmitter systems, including the serotonergic and cholinergic systems[44], with cholinergic neurons of the basal forebrain being particularly vulnerable. These cholinergic neurons continue to mature through adolescence[44] and have major projections to the hippocampus and cerebral cortex, where they play critical roles in cognitive functions, including learning and memory. Multiple studies have shown that repeated exposure to alcohol during adolescence reduces the number of neurons showing immunoreactivity to choline *O*-acetyltransferase (ChAT; the enzyme responsible for acetylcholine synthesis) in the basal forebrain[76,88,91,99,189,190], an effect that was associated with decreases in the level of acetylcholine efflux[190] and that was not evident after comparable alcohol exposure in adulthood[88]. This decline in ChAT immunoreactivity was correlated with greater disinhibitory behaviour[91], an increase in risky-choice behaviour[99] and decreased performance on a set-shifting task[190], suggesting that adolescent exposure to alcohol leads to loss of cholinergic tone, which in turn has lasting functional consequences.

Disrupted neurogenesis. Although neurogenesis is a hallmark of brain development, the formation of new neurons continues to a limited extent throughout life in a few brain regions of both humans and rodents, particularly in the hippocampal subgranular zone (BOX 1).

Dendritic spines
Protuberances on neuronal dendrites that are specialized for receiving synaptic inputs.

Multiple studies have showed that adolescent exposure to alcohol induces long-lasting decreases in hippocampal neurogenesis that, when studied, were not evident after comparable exposure to alcohol in adulthood[191–194]. The mechanisms underlying this persisting disruption in the emergence of new neuronal populations after adolescent exposure have yet to be detailed. The attenuated cholinergic activity in the basal forebrain discussed above could play a role, given that stimulation and disruption of these cholinergic neurons facilitates and disrupts neurogenesis, respectively[195]. The suppression of neurotrophins such as brain-derived neurotrophic factor (BDNF), which are key regulators of the survival and differentiation of newly generated neurons, may also contribute to the lasting decrease in neurogenesis after adolescent exposure to alcohol. Indeed, such exposure exerts persisting decreases in BDNF expression in the hippocampus[84,191,196,197]. Evidence for a role of BDNF suppression in the long-lasting disruptions in neurogenesis induced by adolescent alcohol exposure includes a study showing that administration of a BDNF agonist (tyrosine kinase B) rescued neurogenesis and reversed the behavioural deficits observed during withdrawal and abstinence following repeated adolescent alcohol exposure[191]. Such persisting disruptions in neurogenesis may also be influenced by the induction of neuroinflammation, discussed below.

Induction of neuroinflammation. Repeated exposure to alcohol during adolescence induces long-lasting neural and behavioural changes via the induction of neuroinflammation (BOX 2). Through complex signalling cascades[198,199] that include high mobility group protein B1 (HMGB1) activation of Toll-like receptors (such as TLR4) in microglia and stimulation of nuclear factor-κB (NF-κB), alcohol stimulates release of innate pro-inflammatory cytokines (for example, IL-1, IL-6 and tumour necrosis factor (TNF)) that can ultimately disrupt synaptic plasticity and lead to neuropathology and cell death[198,199]. The evidence relating these neuroimmune responses to the consequences of adolescent alcohol exposure includes the finding that lipopolysaccharide, which is an agonist of TLR4 that induces pro-inflammatory genes, reduced adult hippocampal neurogenesis to an extent comparable to that induced by alcohol exposure during adolescence[200]. Conversely, administration of an anti-inflammatory drug (indomethacin) prevented the neuronal cell death and behavioural deficits that were evident after adolescent alcohol exposure[201]. Moreover, the adolescent alcohol exposure-associated increases in anxiety-like behaviour, elevations in alcohol preference and heightened reward properties that were observed in wild-type (non-genetically manipulated) mice were not evident in transgenic mice with disrupted TLR4 expression[202].

Persistence of adolescent-like states. Evidence for the persistence of certain adolescent-like phenotypes into adulthood after adolescent exposure to alcohol was first observed electrophysiologically. Adolescent rodents normally exhibit more hippocampal long-term potentiation, a type of electrophysiological plasticity[203], than adults do; this greater potentiation was retained in adulthood after adolescent alcohol exposure[204]. By contrast, adolescents exhibit lower baseline levels of $GABA_A$ receptor-meditated tonic inhibition (inhibitory tone) in the hippocampal dentate gyrus[205] and onto pyramidal neurons of the prelimbic portion of the PFC[30] than adults do. In both regions, adolescent exposure to alcohol maintained these adolescent-typical low levels of $GABA_A$ receptor-meditated tonic inhibition into adulthood, evidence of arrested developmental maturation of GABA-induced inhibitory tone[30]. Indeed, it has been hypothesized that repeated exposure to alcohol during adolescence may result in the maintenance into adulthood of an immature, heightened ratio of excitation to inhibition[121].

Adolescents also typically differ from adults in showing greater enhancement of $GABA_A$ receptor-meditated tonic inhibition upon acute administration of alcohol. Given that enhancing tonic inhibition typically disrupts learning and memory[206], these findings are thought to contribute to the greater sensitivity of adolescents than adults to the memory-disrupting effects of acute alcohol challenges[119]. This greater enhancement of tonic inhibition following alcohol challenge is likewise maintained into adulthood after repeated adolescent alcohol exposure[206]. Similar persistence of adolescent-like electrophysiological alterations after adolescent alcohol exposure has been reported in terms of blunted ethanol-induced increases in electroencephalographic variability[207] and in latencies of P300 event-related potentials[208]. Moreover, studies show that adult rats with a history of adolescent alcohol exposure have more hippocampal dendritic spines with an immature morphology and fewer with a mature morphology than animals not pre-exposed to alcohol during adolescence[204]. Decreases in spine density and disruptions in spine morphology have also been reported in the infralimbic cortex and the amygdala after adolescent alcohol exposure, although these changes may

Box 2 | **Neuroinflammation and brain damage**

Although the nervous system was long thought to be relatively protected from notable actions of the immune system, it is now clear that the innate immune system in the brain can be activated in response to pathogens, drugs and other potential toxins. In response to pathogens, pro-inflammatory cytokines such as interleukin-1 (IL-1) and IL-6, tumour necrosis factor (TNF) and monocyte chemoattractant protein 1 (MCP1; also known as CCL2) are released into the nervous system and are detected by various pattern recognition receptors, including Toll-like receptors and the receptor for advanced glycosylation end products (RAGE; also known as AGER). Neuroimmune activation can also stimulate the release of endogenous agonists for these receptors such as the Toll-like receptor–RAGE agonist high mobility group protein B1 (HMGB1). Stimulation of these receptors activates transcription factors, such as nuclear factor-κB (NF-κB), which precipitate further release of pro-inflammatory cytokines. Via such signalling cascades, low levels of inflammatory cytokines influence the release of neurotransmitters and hormones in ways that are thought to promote neuroplasticity and neurogenesis. However, overactivation of the neuroimmune system results in sustained inflammation that impairs neuronal processes, contributing to neuropathology and neuropsychiatric disorders including drug addiction (see REF. 202 for a review). Evidence is mounting that a variety of developmental experiences, including adolescent alcohol use, can induce neuroinflammation and contribute to the lasting neuropathology seen after these experiences[44].

not reflect the retention of an immature adolescent phenotype per se[209]. Thus, overall, numerous behavioural and neural examples exist of the retention of adolescent-like phenotypes into adulthood after adolescent alcohol exposure[121].

Altered epigenetic landscape. Long-lasting consequences of developmental experiences can be exerted via altering the transcription of DNA through epigenetic programming (BOX 3). Indeed, repeated exposure to alcohol during adolescence induces long-lasting increases in global histone deacetylase (HDAC) activity and more-specific increases in HDAC activity regulating *Bdnf* transcription in the amygdala and the hippocampus, thereby potentially contributing to the decreased BDNF expression, decreased dendritic spine density, suppressed neurogenesis and other long-term consequences of adolescent alcohol exposure[210]. Indeed, administration of the HDAC inhibitor trichostatin A not only reversed the decreases in hippocampal neurogenesis and BDNF that were evident following adolescent alcohol exposure[84] but also attenuated adolescent alcohol exposure-related increases in anxiety-like behaviours and elevated alcohol intake[83]. Thus, epigenetic effects probably contribute to and interact with other lasting neural consequences of alcohol exposure during adolescence in perhaps reciprocal ways with, for instance, the alcohol-related epigenetic alterations in *Bdnf* expression posited to contribute to increased neuroimmune gene expression and vice versa[44]. Research is ongoing in the areas of normal epigenetic programming, alterations in this programming associated with alcohol exposure during adolescence and the relationship of epigenetic reprogramming to other lasting effects of adolescent alcohol exposure.

Perspectives and conclusions

Although research examining the predictors and consequences of adolescent alcohol exposure is still in its the early stages (FIG. 3), the evidence is mounting from human prospective studies that some neural and cognitive or personality attributes associated with heavy use of alcohol in adolescence may predate that use and serve as risk factors for increasing the probability of later use.

Box 3 | **Epigenetic regulation of DNA expression**

Experiences encountered throughout life, including alcohol or other drug exposure, can influence the probability of expressing particular genes by chemically modifying the material around which DNA is wrapped (histones) or the DNA itself. Such epigenetic modifications include alterations in DNA methylation (which normally serves to inhibit gene transcription), histone acetylation (which normally activates transcription of the associated DNA sequence), histone deacetylation (which normally exerts repressive effects on transcription) and histone methylation (which can repress or activate transcription depending on which specific protein residue of the histone is modified)[210]. Such epigenetically induced alterations in gene transcription play a critical role in guiding developmental processes while also being dynamically influenced by experiences throughout life to alter ongoing expression of neuroadaptations and plasticity. Perturbation-induced epigenetic changes in normal developmental programming probably contribute to the long-term consequences of challenges to normal development induced by adolescent exposure to alcohol, other drugs or stressful experiences.

Whether individual differences in neural or behavioural characteristics similarly serve as risk factors for adolescent drinking in laboratory animals is largely uncharted territory, except for recent work showing sex-specific associations between the level of baseline social activity and the magnitude of social drinking in adolescent male rats, and between social anxiety level and the magnitude of social drinking in adolescent females[38,39]. As discussed above and summarized in FIG. 3, substantial evidence from work in humans and laboratory animals indicates that adolescent alcohol exposure has highly specific cognitive and neural consequences. The dependent measures examined in such studies, however, have often differed notably across species, thus limiting comparisons of findings across species. Nevertheless, studies employing similar measures to assess the effects of adolescent alcohol exposure have revealed several emerging concordances in neural findings, including disruptions in myelination and poorer white matter integrity, alterations in connectivity between frontal and limbic brain regions and changes in EEG results.

As research in these areas continues to accelerate, several important issues need to be resolved in future work in humans and laboratory animals. More data are needed to determine whether regional vulnerabilities to alcohol vary at different points during adolescence, what the exposure thresholds are for these effects and the degree to which recovery can occur. Given that adolescents frequently use drugs in addition to alcohol, further work is needed to determine whether the observed neural and functional consequences evident in alcohol-using human adolescents are related to the effects of alcohol per se[57]. Addressing these issues would benefit not only from ongoing longitudinal studies in humans but also from empirical research using laboratory animals in which alcohol exposure levels, timing, exposure to other drugs and recovery periods can be carefully controlled. Although rodent studies have revealed substantial evidence of alterations in the DA system and in reward processing following adolescent alcohol exposure, assessment of reward processing in alcohol-using human adolescents has received little attention. To date, studies of the functional consequences of adolescent exposure to alcohol in human adolescents have largely focused on neuropsychological measures; the extension of such studies to include indices of disinhibition, anxiety, cognitive flexibility, sleep disturbances and other measures found to be sensitive to adolescent exposure effects in laboratory animals could prove valuable. An area that is ripe for additional study in laboratory animals, as there has been little investigation thus far, is the potential effects of adolescent alcohol exposure on the pruning process — a hallmark of adolescent brain maturation. As mentioned earlier, there is also a dearth of studies using nonhuman animals to examine the contribution of individual differences (including genetic background) to risk factors for higher levels of alcohol drinking in adolescence. One area of ongoing research in laboratory animals that should remain a critical focus in future studies is work to examine the efficacy of environmental (for example, exercise) and pharmacological

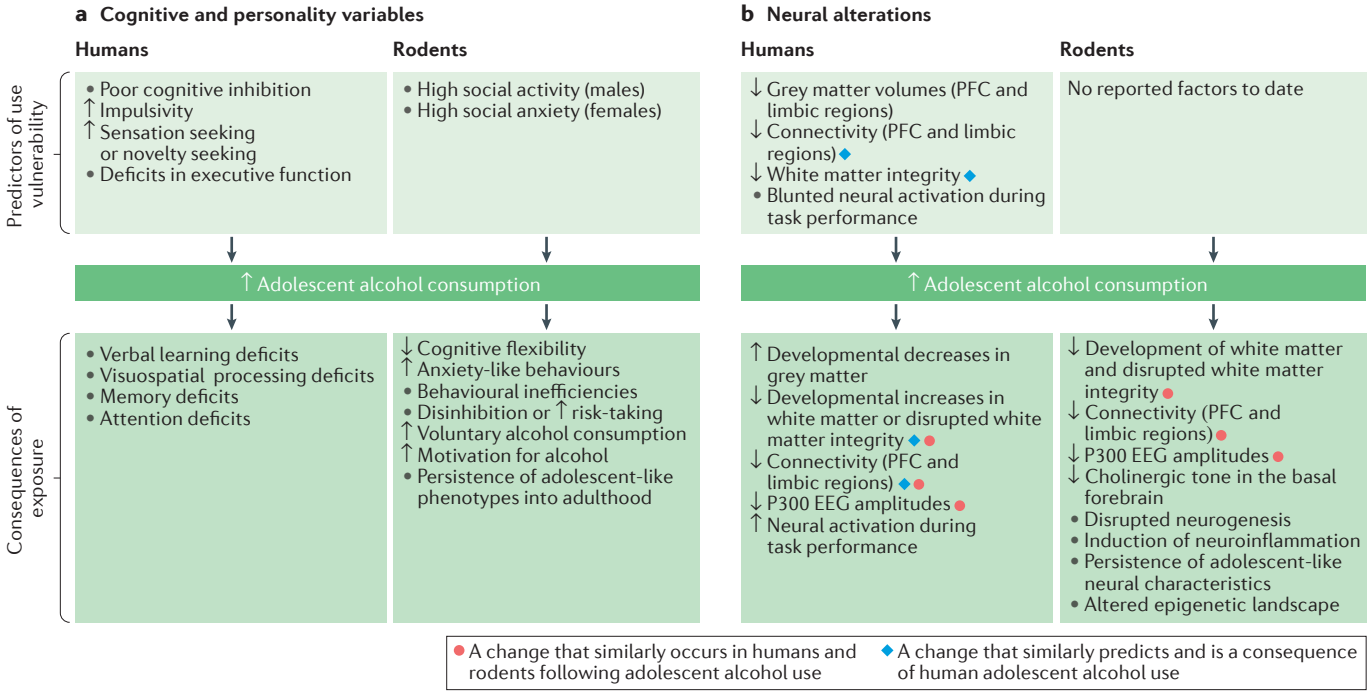

Figure 3 | **Predictors and consequences of alcohol exposure in adolescent humans and rodents. a** | Various cognitive and personality variables predict the use of alcohol in adolescents or may be changed in the long term by alcohol exposure during this period. Note that, in rodents, the social measures are predictive of future adolescent alcohol drinking only in social circumstances. **b** | Various neural measures have also been shown to predict adolescent alcohol consumption or result from adolescent alcohol exposure. Blue diamonds highlight similarities in the predictors and consequences of adolescent alcohol use in human studies, whereas the red circles highlight similarities in the consequences of adolescent alcohol exposure that have been found across studies in human adolescents and studies in rodent models of adolescence. EEG, electroencephalography; P300, positive potential occurring about 300 ms after stimulus onset; PFC, prefrontal cortex.

manipulations to reverse the neural and functional consequences of adolescent alcohol exposure. Such efforts to 'rescue' normal neurobehavioural function after adolescent alcohol exposure through targeting epigenetic alterations, neuroinflammation, neurogenesis, levels of neurotrophic factors and so on are important not only to address potential causal relationships but also to provide essential background for translational efforts that will be critical for the development of future prevention and intervention efforts.

The evidence for relatively long-lasting effects of adolescent exposure to alcohol on later neurocognition and drinking behaviour seems disconnected from the often ostensibly sanctioned and rampant use of alcohol by young people. Is this issue simply due to a lag between the accumulation of scientific data and the initiation of efforts to inform the public? This is a possibility, given that, traditionally, there has been limited communication between scientists and the public. However, the issue appears to be more complicated than that and may have important implications for prevention science. In many places in Europe and the United States, alcohol use by adolescents is typically largely accepted or at least condoned by adults as a 'rite of passage'. The long-term consequences of such behaviour are little acknowledged and parents often recollect their own adolescent use of alcohol, noting that 'they turned out OK'. Most educational efforts to date that have aimed to reduce alcohol intake by adolescents and college students have focused on getting youths to change their behaviour, a strategy that has consistently proved ineffective[211]. Rather than trying to "change teenagers into something they are not" (REF. 211), educational efforts regarding lasting neurobehavioural consequences of adolescent alcohol exposure would perhaps be more effective if they were tailored to include the general public. The use of public media, other communication venues and education efforts focusing on parents, family members, friends, neighbours and legislators may all ultimately be necessary to change the zeitgeist of alcohol use from a rite of passage for adolescents to something that should be explicitly discouraged. Indeed, such a change in thinking would ultimately be necessary to facilitate policy changes that are directed towards successfully limiting alcohol access to youths — strategies such as increasing peer influences and social norms against drinking by youths, greater enforcement of legal drinking ages, reductions in alcohol availability near schools and other places where youths congregate, provision of cost disincentives and so on. Such changes, however, will probably take place slowly. As we have learned from other potential health-related and survival-related issues (for example, sports-related concussion injuries, as well as mass shootings and gun laws), even compelling science often produces at best torturously slow change. The adoption of measures to decrease smoking in public places in the United States, although ultimately largely successful, was a long time in coming.

There is strong evidence that the developing brain increases the propensity for adolescents to engage in risk-taking and to seek new experiences, including alcohol and drug use, with these behaviours pursued particularly avidly under social circumstances. Working against this biology to try to convince adolescents to avoid risks, parties, alcohol and drugs may ultimately prove unrealistic. Given the biological bases of these predispositions to seek new and exciting experiences, rather than trying to eliminate risk-taking or drug-taking per se, prevention efforts might be more usefully directed towards limiting access to particularly harmful risk-taking situations while promoting 'safer' risk-taking via allowing adolescents to experience novel, challenging and exciting stimuli in social, alcohol-free and drug-free contexts that minimize the chances for harm. Positive youth development programmes focusing on strengthening the self-regulation of adolescents and moderating the levels of stress produced by stimulating and emotional social contexts may provide another approach to help adolescents resist binge drinking and other types of excessive risk-taking behaviours[212]. Such prevention strategies would appear more likely to be efficacious than later intervention efforts aimed at reversing the long-lasting and undesired neurobehavioural consequences of adolescent alcohol and drug use.

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