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Adolescents and Alcohol: Acute Sensitivities, Enhanced Intake, and Later Consequences*

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Abstract

Adolescence is an evolutionarily conserved developmental period characterized by notable maturational changes in brain along with various age-related behavioral characteristics, including the propensity to initiate alcohol and other drug use and consume more alcohol per occasion than adults. After a brief review of adolescent neurobehavioral function from an evolutionary perspective, the paper will turn to assessment of adolescent alcohol sensitivity and consequences, with a focus on work from our laboratory. After summarizing evidence showing that adolescents differ considerably from adults in their sensitivity to various effects of alcohol, potential contributors to these age-typical sensitivities will be discussed, and the degree to which these findings are generalizable to other drugs and to human adolescents will be considered. Recent studies are then reviewed to illustrate that repeated alcohol exposure during adolescence induces behavioral, cognitive, and neural alterations that are highly specific, replicable, persistent and dependent on the timing of the exposure. Research in this area is in its early stages, however, and more work will be necessary to characterize the extent of these neurobehavioral alterations and further determine the degree to which observed effects are specific to alcohol exposure during adolescence.

Keywords

Adolescent; Alcohol; Acute tolerance; NMDA-receptor systems; Rodent model; Social anxiety; Fear conditioning; Incentive salience

1. Introduction

Over the past several decades, convincing evidence has accumulated that brain development is a protracted process, with often striking neural alterations occurring during adolescence (see Casey et al, 2008; Spear, 2010, for reviews). It is also during this time of marked neural transformation that experimentation with and use of drugs, especially alcohol, is often initiated. By about 14 years of age, alcohol use has become normative among youth in the United States, with a majority of young teens reporting that they have at least tried alcohol (e.g., Johnston et al, 2008). And when adolescents drink, their consumption often reaches

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relatively high levels. Adolescents drink twice as much on average per drinking episode than do adults (Substance Abuse and Mental Health Services Administration, 2008). Among 8th grade and 12th grade students, in the United States, 10% and 25%, respectively, report consuming 5 or more drinks within a drinking episode within the past 2 weeks (Johnston et al, 2008). Binge drinking rates are even 2–3 fold higher among adolescents in some European countries than among adolescents in the United States (Ahlström & Sjöström, 2004).

Adolescents may drink relatively heavily when compared to adults in part because of age-specific sensitivities to alcohol. That is, many of the neural systems that undergo transformation during adolescence are alcohol sensitive, and likely contribute to notable differences between adolescents and adults in their sensitivity to alcohol, and to the propensity of adolescents for engaging in relatively high levels of alcohol use. In turn, such high levels of use could influence these ongoing neural transformations in the adolescent brain, with perhaps long-lasting consequences. After brief consideration of adolescent neurobehavioral function from an evolutionary perspective, this review will then turn to examination of these issues using data from basic animal research, with a focus on work from our laboratory.

2. Adolescence from an evolutionary perspective: physiological and neural characteristics, and behavioral implications

Adolescence is a developmental period that has been highly conserved across species during mammalian evolution. When defined as the transition from dependence on one or more parents to a time of relative independence, adolescence is an ontogenetic journey taken by all developing mammalian organisms. Adolescents across mammalian species are faced with the common goals of gaining the skills necessary for survival in adulthood and for reproductive success, thereby ensuring the passage of one's genes to the next generation. During this developmental passage, adolescents across a variety of mammalian species undergo similar biological changes. Included among these physiological transformations are the processes of puberty which occur over a relatively restricted time during the broader adolescent period, with a timing that varies as to when it occurs during adolescence both within and across species. Other hormonal changes are seen as well, including some evidence for developmental changes in rates of release of stress hormones (Klein & Romeo, 2013). Adolescence is also associated with dramatic changes in body appearance, including the pubertal-associated development of secondary sexual characteristics prominent in humans and certain other species, as well as a growth spurt (see Spear, 2000, for discussion).

Although these changes in body size and appearance are more obvious, they are no more dramatic than the physiological changes occurring in the brain. Adolescent-typical transformations of the brain include some that are regressive, such as notable synaptic pruning in some brain regions (Rakic et al, 1994), along with progressive changes that include, e.g., axonal myelination of pathways that often interconnect distant brain regions, speeding information flow across these areas (Paus, 2005). Continued elaboration, modification and refinement of regional brain activity and of neurotransmitter signaling systems also occur at this time (see Spear, 2000, 2010; for reviews). The brain transformations seen during adolescence are region- and system-specific, and extend well beyond the delayed maturation of frontal regions such as the prefrontal cortex (PFC) that has received much attention in the literature (e.g., Crews et al, 2007; Casey et al, 2008). Other prominent regional alterations include unusually strong links between subcortical regions critical for processing rewarding stimuli (e.g., nucleus accumbens) and those processing aversive, arousing and emotionally provoking stimuli (e.g., the amygdala) during adolescence, with both of these regions demonstrating greater reactivity under some

circumstances to rewarding and emotional/affective stimuli than is evident in adulthood (see Spear, 2011). With the rise in the emphasis in imaging studies on networks of functionally interconnected brain regions that are activated under different circumstances, exciting work is focusing on the maturation of network patterns during childhood, adolescence and adulthood (e.g., Fair et al, 2007).

Not only have the basics of brain structure and regional composition been conserved across mammalian species, but these normal developmental transformations in the brain also generally occur at the same relative times during development across species as well. That is, to the extent that across-species data are available, similar patterns of neural differences between adolescents and adults have generally been seen across mammalian species (see Spear, 2000, 2010, for review), similar to the across-species similarities seen in other physiological, hormonal, and behavioral characteristics of this ontogenetic transition. The timing and duration of adolescence, however, varies notably across species and appears roughly proportional to the species' life-span. For instance, although the precise timing of onset and offset of adolescence is somewhat variable within any species, adolescence in humans has sometimes been characterized as the second decade of life (e.g., Petersen et al, 1996), with the age span from 20 to 25 (or 30) years sometimes termed late adolescence/ "emerging adulthood" (e.g., Baumrind, 1987; Arnett, 2004). Among much shorter-lived rats, in contrast, prototypic adolescence was proposed to subsume approximately the two week period from postnatal days (P) 28–42 (Spear, 2000), with a late adolescent/ "emerging adulthood" period perhaps extending from about P42 to P55 (Vetter; O'Hagen & Spear, 2012b).

Adolescent-typical neural transformations are likely significant for the adolescent in a number of ways. Ultimately, these brain changes must support adult-appropriate neurobehavioral development, including cognitive/emotional maturation. Some of the neural changes in brain, particularly in hypothalamic areas that modulate hormone release and associated forebrain regions that project to these areas, also undoubtedly contribute to the hormonal reawakening of puberty, with many candidates for key roles in the onset of puberty still under investigation (e.g., see Moguilevsky & Wuttke, 2001; Goodman & Lehman, 2012; Hemond et al, 2013). Brain-hormonal relationships during adolescence are bidirectional, though. That is, there is evidence that pubertal rises in hormones such as testosterone and estrogen can exert additional organizational influences on brain sexual differentiation beyond those initiated much earlier in life by prenatal and perinatal surges of gonadal hormones (Sisk & Zehr, 2005). Changes occurring in adolescent brain are also thought to help transform the highly plastic, but not particularly efficient immature brain into a more efficient, albeit less plastic adult brain. It has often been asserted that the gradual waning of neuroplasticity during adolescence may provide a special window of vulnerabilities and/or opportunities to match the maturing brain to environmental circumstances. Such plasticity-sensitive circumstances could range from enhanced artistic, athletic or educational opportunities to stressors and alcohol/drug use, although more work is needed to determine the actual prevalence of such postulated neuroplasticity and its implications for future functioning (see Spear, 2010, for discussion).

In addition to supporting the emergence of adult-appropriate neural function and behavior, adolescent-associated brain transformations must also, of course, mediate age-appropriate behaviors of the adolescent. As mentioned above, prominent among the brain regions undergoing adolescent transformation are areas such as the PFC, nucleus accumbens and amygdala that form interrelated, overlapping and critical nodes in brain systems modulating cognitive control functions, reward systems and affective/socioemotional systems. Given the dramatic brain changes seen in the regions, it would be surprising if adolescents did not differ from those at other ages in their behavior. And, indeed, they do, as illustrated here

using two examples: (a) Social interactions and affiliations with peers take on increasing importance during adolescence across a variety of species. Human adolescents spend about four times more time interacting socially with peers than with adults (parents and teachers) (Csikszentmihalyi et al, 1977). Likewise, adolescent rats spend more time interacting socially with peers and find these social interactions more reinforcing than do adults (e.g., Douglas et al, 2004). In many species, such social interactions seemingly help guide decisions such as food choices, and provide the opportunity to practice and model adult-typical behavior patterns (Galef, 1977; Smith, 1982). (b) Adolescents from a broad range of species including humans also exhibit an increased propensity for a group of related (albeit not synonymous) behaviors that include risk-taking, sensation-seeking, novelty-seeking and reckless behavior. Like social stimuli, novelty has also been shown in laboratory animals to be more reinforcing for adolescents than adults (Douglas et al, 2003). Risk-taking and novelty- and sensation-seeking can be perilous, with mortality rates (especially among males) rising 2–4 fold during adolescence in humans and a variety of species (e.g., Crockett & Pope, 1993; Irwin & Millstein, 1992); these elevated death rates are largely attributable to behavioral causes, prominently including risk taking (Heron & Smith, 2007). Despite its high cost, risk-taking may have been evolutionarily preserved across species for a number of reasons that include enhancing the probability of reproductive success in males of a variety of species (see Steinberg & Belsky, 1996) and providing the opportunity to explore adult behaviors and privileges (Sibereisen & Reitzle, 1992). The desire to seek out risky and novel stimuli could also help to promote emigration away from the home territory and hence away from those with whom the adolescent is genetically related. This would help avoid inbreeding—i.e., the lower viability and other damaging effects associated with expression of recessive genes in offspring derived from the mating of closely related individuals (e.g., Bixler, 1992). In most mammalian species, males (or less commonly, females or both sexes), leave the natal area around the time that they begin to become sexually mature (e.g., Keane, 1990; Schlegel & Barry, 1991).

Adolescent-associated neural changes may have ancillary consequences as well. Many of the brain regions undergoing developmental change during adolescence are highly sensitive to drugs such as alcohol, and hence may contribute to the initiation and progression of alcohol and other drug use during adolescence (e.g., see Guerri & Pascual, 2010, for review). If increases in drinking during adolescence are indeed related in part to adolescent-typical neural characteristics that have been conserved across mammalian species, then it might be expected that not only human adolescents but their counterparts in other species might voluntarily consume more alcohol per occasion than do adults. Indeed, even when using an animal model of adolescence in the rat, adolescents have often been found to voluntarily consume 2–3 times more alcohol than adults under a variety of home cage or limited access situations (Brunell & Spear, 2005; Doremus et al, 2005; Vetter et al, 2007, but see Bell et al, 2006)—findings that are reminiscent of the generally 2 fold greater per occasion intakes reported in human adolescents than adults (Substance Abuse and Mental Health Services Administration, 2008). This age-specific elevation in consumption is accompanied by marked differences between adolescents and adults in their sensitivity to various effects to alcohol, a topic to which we now turn.

3. The acute response of adolescents to alcohol

3.1 Age differences in alcohol intake and sensitivity

Acute exposure to alcohol (ethanol [EtOH]) induces a diversity of effects ranging from a stimulation of social behavior at low doses of EtOH to motor impairment, aversive effects and sedation at higher doses. Using rodent models of adolescence, we and others have shown adolescents to differ markedly from mature animals in their sensitivity to these various acute effects of EtOH, although whether adolescents are more or less sensitive to

EtOH than are adults varies notably with the EtOH effect that is being assessed. On the one hand, adolescents are more sensitive than adults to a few restricted EtOH effects. Swartzwelder and his group have found adolescent rats to be more vulnerable than adults to the memory-disrupting effects of EtOH and to EtOH-induced disruptions in brain plasticity indexed via long-term potentiation (e.g., Markwiese et al, 1998; Pyapali et al, 1999). In our lab, we have consistently found adolescent rats to display notable social facilitation in response to low doses of EtOH, with these increases in social behavior seen not only with adolescent-typical play behavior but also with the more adult-prevalent social behavior of social investigation (sniffing of another animal) (e.g., Varlinskaya et al, 2001). This stimulation of social behavior by EtOH is not associated merely with general locomotor stimulation in that low doses of EtOH increase social interactions of adolescents without increasing general motor activity during testing; moreover, no ethanol-induced stimulation of interactions is seen to an inanimate novel object (Varlinskaya et al., 2001). EtOH-induced social facilitation is most marked early in adolescence and declines later in adolescence (Varlinskaya & Spear, 2006a), and is no longer evident under normal circumstances in adult animals (e.g., Varlinskaya & Spear, 2002). Although the data are more mixed, there is also some evidence that adolescents may also be more sensitive than adults to the rewarding effects of EtOH (e.g., Pautassi et al, 2008; Ristuccia & Spear, 2008; but see also Dickinson et al, 2009).

Adolescents, however, are generally less sensitive than adults to other EtOH effects, as indexed via being less impaired than adults at a given EtOH exposure level or via the need for more EtOH to exhibit a given EtOH-associated effect relative to adults. For instance, adolescents are less sensitive than adults to the social impairing effects that emerge at higher doses of EtOH (Varlinskaya & Spear, 2002), with this insensitivity being particularly marked in young relative to older adolescents (Varlinskaya & Spear, 2006a). Adolescents are also relatively insensitive to the aversive effects of EtOH, requiring higher EtOH doses to develop a an aversion to a novel taste paired with an injection of EtOH – i.e., a EtOH conditioned taste aversion (CTA) – than their mature counterparts (Anderson et al, 2010; Vetter-O'Hagen et al, 2009). Ethanol also serves as a less effective discriminative cue for adolescents than for adults, suggesting that adolescents are less able to detect interoceptive effects of EtOH than are adults (Anderson & Spear, in press). Adolescents likewise are less sensitive than adults to EtOH's motor impairing, anxiolytic, and sedative effects (e.g., Sliveri & Spear, 1998; Varlinskaya & Spear, 2002; Ramirez & Spear, 2010a) and to EtOH-induced context retention deficits in a fear-conditioning task (Broadwater & Spear, 2013a). Adolescent rats have even been found to exhibit attenuated sensitivity to some "hangover" effects during the recovery period following a large dose of EtOH (Doremus et al, 2003).

3.2 Contributors to these adolescent-typical EtOH sensitivities

There are a number of possible contributors to these adolescent-typical EtOH sensitivities. One possibility is that adolescents may differ from adults in how quickly EtOH is absorbed, distributed, and metabolized in the body,, although it seems unlikely that age differences in pharmacokinetics alone could be responsible for both adolescent-typical attenuated and accentuated EtOH sensitivities. Consistent with the generally faster metabolic rate of adolescents than adults, under some circumstances adolescents do tend to metabolize EtOH slightly faster than do adults, thereby resulting in slightly but sometimes significantly lower levels of EtOH in adolescents than adults at some time points after EtOH challenge. These differences alone, however, have generally been found to be insufficient to account for the attenuated sensitivities of adolescents to EtOH; thus, age differences in acute sensitivities to EtOH are thought to reflect pharmacodynamic rather than pharmacokinetic factors (see Spear, 2007). For instance, when given a sedative dose of EtOH, adolescents not only generally recover their righting response about twice as rapidly as do adults but, importantly,

recover with significantly higher levels of EtOH in their brains than adults – compelling evidence that their brains are less sensitive to EtOH's sedative properties than are the brains of adults (Silveri & Spear, 1998). Yet, because of the tendency for slight age differences in pharmacokinetics, it is prudent to continue to monitor EtOH levels in studies of age differences in sensitivity to various effects of EtOH.

One notable way that adolescents have been found to differ from adults is the unusually rapid adaptation that their brains develop to the presence of EtOH during a single EtOH challenge period. This phenomenon is termed “acute tolerance” (Mellanby, 1919), and is defined as an attenuation in EtOH sensitivity that emerges during the course of a single period of EtOH intoxication. Using a variety of ways of assessing acute tolerance, juveniles and adolescents have been shown to exhibit more acute tolerance than adults (e.g., Silveri & Spear, 1998; Varlinskaya & Spear, 2006b). This rapid, within-session adaptation to EtOH likely contributes to the attenuated sensitivity shown by adolescents to many of EtOH's intoxicating effects. Yet, acute tolerance alone is not entirely responsible for the attenuated EtOH sensitivities of adolescents given that blocking expression of acute tolerance (with an antagonist of one of the primary receptor subtypes of the glutaminergic neurotransmitter system: N-methyl-D-aspartic acid receptors [NMDA-R]) did not eliminate age differences in these EtOH effects (Silveri & Spear, 2004; see also Ramirez et al, 2011).

There are a variety of other potential contributors to age differences in EtOH sensitivities. One possibility is that increases in the release of gonadal hormones at puberty may act on hormone-sensitive brain regions to alter EtOH responsiveness, thereby exerting an *organizational role* for the emergence of adult-typical EtOH sensitivities. Yet, in a series of studies we have found little evidence for a notable contribution of puberty-related increases in gonadal hormones to the emergence of adult-typical EtOH sensitivities. For instance, although gonadectomy in male (but not female) rats was effective in increasing later EtOH intake, these increases in EtOH intake were seen when the testes were removed either pre-pubertally or in adulthood (Vetter-O'Hagen & Spear, 2011), and were largely reversed by testosterone replacement (Vetter-O'Hagen et al, 2011). Collectively, this pattern of findings is consistent with an *activational* rather than *organizational role* for testosterone in moderating EtOH intake in male rats. That is, the gradual ontogenetic decline in EtOH intake observed around P40 in males (Vetter et al, 2007) may not be a result of testosterone-sensitive brain maturational processes, but may be related to rises in gonadal hormones, with rising levels of testosterone likely playing a suppressant role on EtOH consumption in male rats as they mature, lowering their EtOH intake to levels below that seen in adult female rats. The means by which gonadal hormones influence EtOH consumption in males is still unclear. EtOH intake is typically inversely associated with sensitivity to EtOH's aversive effects (while being positively associated, to a lesser extent, with its rewarding properties) (Green & Grahame, 2008). Yet, we have found that neither pre-pubertal nor adult gonadectomy influenced sensitivity to EtOH's social inhibitory effects (Vetter-O'Hagen & Spear, 2012a) or its aversive consequences (indexed via CTA–Vetter-O'Hagen et al, 2009; Morales & Spear, 2013), although gonadectomy at either age altered the microstructure of social behavior (Vetter-O'Hagen & Spear, 2012a). Thus, although close relationships have been reported between pubertal-related gonadal changes and the emergence of a variety of sexually-dimorphic adult-typical behaviors (e.g., see Schultz & Sisk, 2006, for review), our data to date suggest that age-related differences in EtOH sensitivities that emerge between adolescence and adulthood appear largely independent of maturational changes induced by gonadal hormones.

Other major contributors to adolescent-typical EtOH sensitivities are undoubtedly related to developmental changes that occur in the neural substrates underlying EtOH's effects. EtOH affects a variety of neural systems, including glutamatergic, gamma-amino-butyric acid

(GABA), dopaminergic, serotonergic, cholinergic and opioid systems (see Eckardt et al, 1998), with many of these neural systems undergoing sometimes marked developmental change during adolescence (e.g., see Spear, 2000, for review). For instance, NMDA-R associated with the major excitatory neurotransmitter system in the brain – the glutamatergic system – exhibit developmentally enhanced activity during adolescence in certain brain regions (e.g., Kasanetz & Manzoni, 2009), whereas various components of the primary inhibitory neurotransmitter in brain – the GABA system – are still developmentally immature in adolescents (e.g., Brooks-Kayal et al, 2001; Yu et al, 2006). Given that EtOH's effects are mediated in large part by NMDA-R antagonistic and GABA stimulatory actions, developmental changes in these systems could play a critical role in influencing adolescent responsiveness to EtOH. If so, it would be expected that adolescents would be less sensitive than adults not only to the intoxicating effects of EtOH, but also to the effects of GABA agonists and NMDA-R antagonists. Assessments of the psychopharmacological effects of the GABAergic system during development, however, have proved challenging due to notable sedative effects of most GABA agonists; nevertheless, we have found adolescents to be less sensitive than adults to the anxiolytic effects of a partial $\alpha 2/3/5$ GABA_A receptor agonist, L-838,417, even when analyses of covariance were used to control for locomotor effects (Morales et al, 2013a).

Studies with NMDA receptor antagonists such as MK-801 and subtype-specific NR2A and NR2B antagonists have proved more fruitful. For instance, we have observed that, reminiscent of the biphasic effect of EtOH on adolescent social behavior (i.e., low doses stimulating and higher doses suppressing this behavior), MK-801 and the NR2B antagonist ifenprodil likewise induced biphasic effects in adolescents, with facilitation of social behavior seen at low doses (Morales et al, 2013b) and social inhibition evident at higher doses (Morales & Spear, 2013). Although adolescents required higher doses of MK-801 and ifenprodil to inhibit social behavior than in mature animals, they were conversely more sensitive than adults to the social inhibitory effects of the NR-2A antagonist, PEAQX (Morales & Spear, 2013). Given that receptor abundance typically requires higher antagonist doses for functional blockade, these data are consistent with the gradual developmental shift seen in many (albeit not all brain regions) from higher to lower expression of NR2B-, but lower to higher expression of NR2A-subunit-containing receptors (e.g., Sheng et al, 1994). A similar attenuated response to ifenprodil among adolescents relative to adults was observed in terms of its motor impairing effects (Ramirez et al, 2011) and in terms of its aversive effects indexed via CTA (Ramirez et al, 2010b). These data support the suggestion that greater expression of NR2B receptors through adolescence in one or more brain areas could potentially contribute to the relative resistance of adolescents to social inhibitory, motor impairing and aversive effects of EtOH.

Notable developmental changes in mu and kappa opioid systems also likely contribute to adolescent-typical EtOH sensitivities. Ethanol-induced facilitation of social behavior seen during adolescence appears mediated in part through ethanol-induced facilitation of mu opioid receptors, with the nonselective opiate antagonist naloxone and the mu-selective opiate antagonist CTOP blocking adolescent-specific induction of social play by EtOH (Varlinskaya & Spear, 2009). In contrast to socially facilitating effects of the mu opioid system, stimulation of the kappa opioid system has been shown to have aversive and anxiogenic properties. Adolescents are often more resistant to these kappa opioid effects than are adults. For instance, adolescents are less sensitive than adults to the aversive properties of the kappa agonist U62,066 indexed via CTA (Anderson et al, 2013) – age differences that were further exacerbated by chronic stress (Anderson et al, 2012).

Collectively, these data support a role for a variety of neurotransmitter systems in the myriad of developmental differences in EtOH sensitivities seen between adolescents and adults.

Immaturities in the GABA and kappa systems may be related to adolescent-typical attenuations in low dose anxiolytic and higher dose aversive and anxiogenic effects, respectively. In contrast, enhanced expression of NR2B and mu receptor activation may contribute to adolescent-typical EtOH-induced social facilitation, with developmentally enhanced NR2B-but immature NR2A-containing receptor systems contributing to the adolescent resistance to social inhibitory effects. It should be noted that little is yet known of the regional specificity for these effects, and the degree to which other neural systems may also be involved in the complex developmental pattern of changing EtOH sensitivities. As but one example, it is possible that certain adolescent-typical EtOH sensitivities may reflect developmental alterations in dopamine projections to target areas such as the nucleus accumbens, prefrontal cortex, and amygdala that influence responding to a broad variety of drug and natural rewards (e.g., Robinson et al, 2011; see Doremus-Fitzwater et al, 2010, for review). Indeed, as discussed in the next section, in some respects adolescent-associated alterations in sensitivity to the rewarding and aversive effects of EtOH are similar to developmental findings seen with drugs other than alcohol and with natural rewards.

3.3 Generalization to other drugs and stimuli

Adolescent animals may differ from adults not only in their sensitivity to EtOH, but in their sensitivity to other drugs as well. This has been best studied in terms of drug sensitivity to rewarding and aversive properties. For instance, when assessed via CTA or conditioned place aversions (avoiding a place previously paired with drug exposure), we and others have shown that adolescents are less sensitive than adults not only to the aversive effects of EtOH, but also to the aversive effects of nicotine (Wilmouth & Spear, 2004; Shram et al, 2006; Torres et al, 2008), tetrahydrocannabinol (Schramm-Sapota et al, 2007), and amphetamine (Infurna & Spear, 1979). Conversely, enhanced sensitivity to rewarding effects may be seen during adolescence not only to EtOH, but to other drugs as well. These studies have typically used a conditioning technique called conditioned place preference to index reward sensitivity, a procedure that involves assessing the development of a preference for a location previously paired with drug exposure relative to another location to which animals had received equivalent exposure in the absence of the drug. Using conditioned place preference, adolescent rats were found to be more sensitive than their adult counterparts to the rewarding effects of nicotine (Vastola et al, 2002; Shram et al, 2006; Torres et al, 2008), and stimulants such as cocaine and amphetamine (Badanich et al, 2006; Brenhouse et al, 2008a,b; Zakharova et al, 2009a,b), although these results are not ubiquitous (Campbell et al, 2000; Aberg et al, 2007). Similar adolescent-typical sensitivities may be seen with some non-drug stimuli as well. As mentioned previously, adolescents have been found to be more sensitive than adults to the rewarding effects of social stimuli and novelty using similar place preference conditioning procedures as used with psychoactive drugs (Douglas et al, 2003, 2004). And when using taste reactivity as an index of hedonic sensitivity, adolescent rats were found to exhibit evidence of both greater positive taste reactivity to sucrose and attenuated reactivity to quinine (Wilmouth & Spear, 2009). Thus, in studies using animal models of adolescence, this age period was often found to be associated with a general bias toward enhanced rewarding and attenuated aversive properties to a variety of drug and natural stimuli.

3.4 Possible implications for human adolescents

Studies discussed above using an animal model of adolescence in the rat have shown that alcohol is experienced differently by adolescents relative to adults, with adolescents being particularly sensitive to the social-facilitating (and perhaps rewarding) effects of ethanol, but more resistant than adults to many intoxicating effects of EtOH, including its aversive, motor- and social-impairing, and sedative effects. There is a dearth of similar investigations in human adolescents due to ethical issues involved in administering EtOH to underage

youth. Yet, from the limited literature that is available, there are hints that human adolescents may exhibit similar developmentally-related patterns of ethanol sensitivity. For instance, human adolescents are particularly prone to drink alcohol for its socially facilitating effects (e.g., Beck, Thombs & Summons, 1993), reminiscent of the EtOH-induced social facilitation seen in our rodent model. And in a rare, older study where 8–15-year-old adolescent boys were challenged with EtOH and given a variety of objective and subjective tests of alcohol intoxication, the authors noted that they “were impressed by how little gross behavioral change occurred in the children...after a dose of alcohol which had been intoxicating in an adult population” (Behar et al, 1983, p.407). These findings are reminiscent of the adolescent attenuation in sensitivity to intoxicating effects of EtOH often observed in rodent studies.

To the extent that similar patterns of ethanol sensitivities are evident in human adolescents as seen in developmental studies with rodents, these ontogenetic patterns could serve to promote relatively high levels of EtOH use, including the binge-like patterns of EtOH consumption that are especially prevalent during adolescence (Ahlström & Sjöström, 2004; Johnston et al, 2008). That is, ethanol drinking could be encouraged due to EtOH-induced facilitation of social behavior (in conjunction with potentially greater rewarding effects), with relatively high consumption levels permitted because of the attenuated sensitivity of adolescents to aversive, motor-impairing, socially-impairing and sedative consequences of EtOH that seemingly serve as negative feedback cues to terminate drinking (see Spear & Varlinskaya, 2005, for further discussion). Indeed, an insensitivity to intoxicating effects of EtOH (with perhaps an increased sensitivity to its euphoric and rewarding effects – e.g., see King et al, 2011) is a major risk factor for problematic alcohol use, “perhaps through increasing the chances that a person will drink more heavily” (Schuckit, 1994, p.184). For instance, individuals with a family history of alcoholism (e.g., Schuckit, 1994) as well as rodent lines exhibiting high alcohol intakes (see Green & Grahame, 2008, for review) characteristically exhibit an insensitivity to intoxicating, aversive and sedative effects of EtOH. These EtOH effects may be attenuated further by repeated exposure to stressors and a prior history of EtOH use (Varlinskaya & Spear, 2010; Varlinskaya et al, 2010). Thus, a genetic-based insensitivity to EtOH when combined with ontogenetic insensitivities of adolescence and further insensitivities induced by environmental stressors and/or a history of prior EtOH use may serve as multiple vulnerabilities to precipitate heavy drinking when genetically at-risk adolescents undergo stressful circumstances and begin to drink. Such patterns of elevated use may have long-lasting consequences. Indeed, as discussed in the next section, there is emerging evidence from basic animal studies that repeated exposure to EtOH during adolescence may have specific consequences that persist into adulthood.

4. Adolescence as a vulnerable period for persisting effects of repeated alcohol exposure

There is substantial evidence in the human research literature that the younger individuals are when they begin to drink, the more likely they are to develop problematic patterns of alcohol use, including stress-reactive drinking and alcohol dependence later in life (e.g., see Dawson et al, 2008; Lee et al, 2012). Youths that have been binge drinking for some time exhibit alterations in regional brain volumes, integrity of white matter, and patterns of brain activation during cognitive tasks (e.g., Squeglia et al, 2009). From such studies, it is difficult to determine conclusively whether these neurobehavioral alterations are a result of toxicity associated with the adolescent EtOH exposure per se or whether they reflect pre-morbid characteristics that increase the risk for early alcohol use (e.g., De Bellis et al, 2005). Issues of causality can be addressed in human studies through longitudinal assessments that are initiated prior to the time that youth begin drinking. Work in this area has begun (e.g., Wetherill et al, 2013). In addition to these long-term and costly human longitudinal studies,

controlled experiments in laboratory animals can also be used to determine whether subsequent brain and behavioral function is particularly vulnerable to alcohol exposure during adolescence.

In our laboratory, we have begun to investigate effects of repeated adolescent exposure to EtOH on later neurobehavioral functioning. Our findings to date suggest that the effects of adolescent intermittent exposure to EtOH are replicable, specific, and dependent on timing of the EtOH exposure. Unlike research examining consequences of prenatal drug exposure where there is an inherent “other age” exposure group (i.e., the dam), in adolescent exposure studies it is necessary to include another-aged exposure group to determine if consequences are adolescent-specific. Using this approach, in our work to date we have generally not seen the same effects with comparable exposures in adulthood. Indeed, timing of exposure may matter even within the broad adolescent period, with early adolescents being especially vulnerable. Recent findings of our group leading to these conclusions are briefly summarized below.

4.1 Social anxiety

Adolescent exposure to EtOH during early/mid adolescence induces a replicable increase in social anxiety in male rats that is evident weeks after termination of exposure. In these studies, male and female Sprague-Dawley rats were given either 0 (water) or 3.5 g/kg EtOH intragastrically (i.g.) every other day during early/mid adolescence (P25–45) or late adolescence/emerging adulthood (P45–65) (Varlinskaya et al, submitted). Twenty-five days later in adulthood (at P70 or P90), animals were tested for social behavior under baseline conditions or after acute challenge with 0, 0.5, 0.75 or 1.0 g/kg EtOH given via an intraperitoneal injection. Thirty min. following injection and placement in the test apparatus, an unfamiliar, non-manipulated partner was added and social interactions between the test animal and partner were videotaped for 10 min. and later scored for various indices of social behavior. At testing 25 days after EtOH exposure in early/mid adolescence, previously EtOH-exposed males exhibited lower baseline levels of social behavior than control animals. Behavioral alterations included reductions in social play as well as decreases in two measures that have been shown to be particularly sensitive to anxiogenic/anxiolytic manipulations: (a) social investigation (sniffing of the partner) and (b) a coefficient of social preference/avoidance (that reflects approaches towards or away from the partner and is used as an index of social motivation). The suppressed levels of social investigation and play behavior were reversed upon challenge with EtOH, restoring normal levels of social interactions (evidence of EtOH-induced anxiolysis) and elevating EtOH-precipitated play to the high levels typically seen in adolescent animals (but not normally evident at the time these animals were tested in adulthood). The social suppression induced by early/mid-adolescent EtOH exposure and its reversal by EtOH challenge was evident in males but not females, and was not seen in either sex after EtOH exposure during late adolescence. Similar age specificity in exposure effects has also been reported by the Naassila group when examining later voluntary home cage EtOH intake (Alaux-Cantin et al, 2013) where they found that this intake was increased by intermittent EtOH exposure from P30–43 whereas comparable exposure from P45–58 had no effect.

4.2 Disrupted fear conditioning retention

We have broadened our studies of negative affect after adolescent exposure to EtOH to include not only tests of social anxiety but also fear conditioning, retention and extinction. In this experimental series, different groups of male rats were intragastrically intubated with 0 (water) or 4 g/kg EtOH i.g. every other day from P28–48 (early/mid adolescent exposure), P35–55 (mid/late adolescent exposure) or P70–90 (adult exposure). Twenty-two days later, animals were given three, 1-sec, 0.5 mA footshocks that were either immediately preceded

by a 10 sec. tone (tone conditioned animals) or presented at the same intervals in the context alone (for the context conditioning groups). Twenty-four and 48 hrs later, animals were tested for fear retention to the tone or context, respectively, consistent with their training group assignment (Broadwater & Spear, 2013b). Context fear retention, a task thought to be hippocampally-dependent, was disrupted only by early/mid adolescent EtOH exposure. In contrast, both the mid-late adolescent and adult exposure groups exhibited disruptions in context extinction (a task where PFC function has been implicated) that were not evident in the early/mid adolescent exposure group. No exposure effects were seen in any of the age groups for tone measures thought to be relatively amygdala-sensitive. Although we have just begun to examine exposed animals neuroanatomically, in our initial forays adolescents exposed to EtOH during early/mid adolescence were found to show reduced doublecortin, a microtubule-associated protein that is expressed in immature neurons and used as a marker of neurogenesis. This EtOH-associated decrease in doublecortin was seen in the dentate gyrus of the hippocampus and was evident 3½ weeks following termination of the exposure period, suggesting persistent suppression in neurogenesis following the developmental exposure to EtOH (Broadwater, Crews & Spear, in preparation). Similar declines in doublecortin in this brain region after adolescent EtOH exposure were recently reported 8 weeks following termination of EtOH by Ehlers and colleagues (2013). Intriguingly, in our study, when animals were exposed to comparable amounts of ethanol in adulthood, no change in doublecortin levels were subsequently observed; thus, this long-lasting suppression in hippocampal neurogenesis was specific to EtOH exposure during adolescence. These age specific effects are consistent with the impaired context fear retention seen in animals exposed intermittently to EtOH as adolescents but not as adults, given evidence that this hippocampally-dependent task requires formation of new neurons (e.g., Wojtowicz et al, 2008). It remains to be determined whether the fear context extinction deficits seen after adult (but not adolescent) exposure to EtOH are associated with detectable, age-related neuroanatomical alterations in other brain regions such as the PFC.

4.3 Increased incentive salience

Robinson and Berridge (1993; see also Berridge and Robinson, 2003) have defined incentive salience as the motivational drive to approach natural or drug rewards as well as cues associated with these rewards and have found this index of incentive motivation (“wanting”) to be distinguishable functionally and in neural substrates from hedonic “liking”. Given that increased incentive salience is thought to be a marker of drug addiction vulnerability (Tomie et al, 2008), we assessed whether adolescent exposure to EtOH would alter later incentive drive in adulthood, and whether equivalent EtOH exposure in adulthood would have a similar effect (McClory & Spear, 2013). In separate studies, male rats were given 0 (water) or 4 g/kg i.g. EtOH every other day or left non-manipulated as adolescents (P28–48) or as adults (P70–90). Subjects were then examined beginning >3 weeks later using a Pavlovian conditioned approach “autoshaping” procedure. Each day animals were given 25 trials, each consisting of an 8 sec presentation of a lighted response lever, immediately followed by a response-independent delivery of food reward. Under these circumstances, some animals begin to focus attention on the location where the food will be delivered, called “goal tracking”, whereas others excessively approach and interact with the lighted lever -- a behavior termed “sign tracking” that is thought to reflect incentive salience. We found that adult rats repeatedly exposed to EtOH as adolescents exhibited a significant increase in sign tracking behavior relative to both chronic water intubated and non-manipulated control animals, whereas no alterations from control animals were seen in adults whose EtOH exposure was delayed until adulthood. Given that high levels of sign tracking are thought to serve as a marker for drug abuse vulnerability (Tomie et al, 2008), these results suggest the possibility that repeated exposure to EtOH in adolescence, but not when that exposure is delayed into adulthood, could potentially elevate the later risk for drug abuse.

4.4 Relationship to the broader literature

The examples above from our laboratory illustrate replicable and persisting alterations induced by adolescent exposure to EtOH. These recent findings join an emerging literature in this area that has likewise reported a number of other persisting behavioral consequences of EtOH exposure during adolescence that include reversal learning deficits (Coleman et al, 2011), alterations in tests that may reflect increased impulsivity (Gilpin et al, 2012; Ehlers et al, 2013), decreases in aversive effects of EtOH indexed via CTA (Diaz-Granados & Graham, 2007; Alaux-Cantin et al, 2013), and retention of adolescent-typical responses to EtOH into adulthood that is evident with some (White et al, 2002; Matthews et al, 2008; Fleming et al, 2012) but not all (Broadwater & Spear, 2013b) response measures. Consequences of adolescent EtOH exposure on later drinking behavior are mixed and may vary with the nature of the adolescent exposure (self-administered vs. experimenter-administered; vapor vs. i.g. vs. intraperitoneal exposure routes) and the model used to examine EtOH drinking (home cage or limited access; operant self-administration; relapse-drinking, etc.) (e.g., see McBride et al, 2005; Pascual et al, 2009; Gilpin et al, 2012; Broadwater et al, 2013; Alaux-Cantin et al, 2013). Compelling data are emerging from a variety of laboratories demonstrating long-lasting neural alterations following adolescent EtOH exposure that include, for example, disruptions in mesolimbic dopaminergic and glutaminergic systems (Pascual et al, 2009), basal forebrain cholinergic systems (Coleman et al, 2011; Ehlers et al, 2011), and CRF neurons in the central amygdala (Gilpin et al, 2012), along with the induction of inflammatory brain damage (Pascual et al, 2007).

In most studies to date, only males have been tested. Yet, at least in the case of social anxiety, there is evidence for notable sex differences in the effect of adolescent ethanol exposure (Varlinskaya et al, submitted), and hence more investigation of sex differences would appear warranted. Moreover, in a majority of cases it is not yet known if the effects observed are adolescent-specific given that consequences of comparable exposure in mature animals have often not been examined. In the instances where adult exposure groups were included, effects are often exposure-age specific, with some observed effects generally found to be specific to adolescent exposure (e.g., White et al, 2002; Diaz-Granados & Graham, 2007; Pascual et al, 2009; Fleming et al, 2012) or early adolescence in particular (see Alaux-Cantin et al, 2013; Broadwater & Spear, 2013b; Varlinskaya et al, submitted), whereas other effects may characterize later exposures (e.g., see Broadwater & Spear, 2013b). It is intriguing that during adolescence (especially early adolescence), an age when animals are more resistant than adults to many acute intoxicating effects of EtOH and to the body weight suppression induced by repeated EtOH exposure, persisting effects of this exposure may be more pronounced than after comparable EtOH exposures in adulthood. Thus, adolescence joins the fetal period as being times of developmental vulnerability to long-lasting neurotoxicity and behavioral and cognitive alterations as a result of EtOH exposure (e.g., Driscoll et al, 1990). Indeed, these exposures may often be interrelated, with children exposed prenatally to EtOH being particularly likely to use EtOH as young adolescents, and both exposures increasing EtOH use and the probability of developing alcohol use disorders lasting into adulthood (see Miller & Spear, 2006).

Clearly, though, research in this area is in its early stages, and much work remains to determine the specificity and extent of lasting neurocognitive and behavioral consequences of adolescent EtOH exposure, and the degree to which adolescence is an especially vulnerable period for these effects.

5. Summary and conclusions

- Adolescence is an evolutionarily conserved period that is characterized by numerous brain and behavioral similarities across species.

- Due in part to age differences in brain function and in the expression of acute tolerance, adolescents exhibit:
 - An attenuated sensitivity to intoxicating and aversive effects of EtOH that likely serve as cues to moderate drinking, that contrast with
 - Greater sensitivity to EtOH-induced social stimulation and disruption in brain plasticity and memory.
- Although by necessity, these findings with EtOH are based on work in laboratory animals, to the extent that these findings are relevant to human adolescents, this pattern of adolescent-typical EtOH sensitivities could promote relatively high levels of EtOH intake during adolescence, particularly among individuals that have further insensitivities to EtOH intoxication based on genetic or environmentally-induced vulnerabilities, with these high intakes potentially leading to various adverse consequences during and outlasting adolescence.
- Indeed, evidence is emerging for replicable, specific, and timing-dependent effects of adolescent EtOH exposure on later neurobehavioral function, including a long-lasting suppression of neurogenesis in adulthood that is not evident following comparable EtOH exposure later in life.
- Adolescent EtOH research, especially research assessing long-lasting effects of EtOH exposure during adolescence, is still at its early stages. Given the recent acceleration of research in this area, continued rapid progress is likely – findings that will be important for informing effective prevention and intervention programs.

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Highlights

Adolescent-typical brain and behavior is evolutionarily conserved across species.

Adolescents differ from adults in their sensitivity to different ethanol effects.

Adolescent-typical ethanol sensitivities may permit high intake levels.

Adolescent ethanol exposure exerts specific long-lasting neurobehavioral effects.