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ADOLESCENT ALCOHOL EXPOSURE: ARE THERE SEPARABLE VULNERABLE PERIODS WITHIN ADOLESCENCE?

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Abstract

There are two key alcohol use patterns among human adolescents that confer increased vulnerability for later alcohol abuse/dependence, along with neurocognitive alterations: (a) early initiation of use during adolescence, and (b) high rates of binge drinking that are particularly prevalent late in adolescence. The central thesis of this review is that lasting neurobehavioral outcomes of these two adolescent exposure patterns may differ. Although it is difficult to disentangle consequences of early use from later binge drinking in human studies given the substantial overlap between groups, these two types of problematic adolescent use are differentially heritable and hence separable to some extent. Although few studies using animal models have manipulated alcohol exposure age, those studies that have have typically observed timing-specific exposure effects, with more marked (or at least different patterns of) lasting consequences evident after exposures during early-mid adolescence than late-adolescence/emerging adulthood, and effects often restricted to male rats in those few instances where sex differences have been explored. As one example, adult male rats exposed to ethanol during early-mid adolescence (postnatal days [P] 25-45) were found to be socially anxious and to retain adolescent-typical ethanol-induced social facilitation into adulthood, effects that were not evident after exposure during late-adolescence/emerging adulthood (P45-65); exposure at the later interval, however, induced lasting tolerance to ethanol's social inhibitory effects that was not evident after exposure early in adolescence. Females, in contrast, were little influenced by ethanol exposure at either interval. Exposure timing effects have likewise been reported following social isolation as well as after repeated exposure to other drugs such as nicotine (and cannabinoids), with effects often, although not always, more pronounced in males where studied. Consistent with these timing-specific exposure effects, notable maturational changes in brain have been observed from early to late adolescence that could provide differential neural substrates for exposure timing-related consequences, with for instance exposure during early adolescence perhaps more likely to impact later self-administration and social/affective behaviors, whereas exposures later in adolescence may be more likely to influence cognitive tasks whose neural substrates (such as the prefrontal cortex [PFC]) are still undergoing maturation at that time. Substantial more work is

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needed, however to characterize timing-specific effects of adolescent ethanol exposures and their sex dependency, determine their neural substrates, and assess their comparability to and interactions with adolescent exposure to other drugs and stressors. Such information could prove critical for informing intervention/prevention strategies regarding the potential efficacy of efforts directed toward delaying onset of alcohol use versus toward reducing high levels of use and risks associated with that use later in adolescence.

Keywords

adolescence; ethanol; nicotine; lasting effects; stressors; neurobehavioral consequences; puberty; timing-specific effects

1. Introduction

Research assessing potential long-term consequences of adolescent alcohol exposure has begun relatively recently in both humans and laboratory animals, driven in part by the increasing recognition of developmental transformations in the brain during adolescence that could provide a period of vulnerability to lasting effects of alcohol exposure on later neuropsychological function and abuse propensity. Two key alcohol use patterns among human adolescents that are thought to confer vulnerability for later alcohol abuse/dependence are: (a) early initiation of use, and (b) high rates of binge drinking during late adolescence (e.g., high school and college age individuals) (e.g., see Windle & Zucker, 2010, for review). The central thesis of this mini-review is that neurobehavioral consequences of these two adolescent exposure patterns may differ, based in part on evidence of notable differences in the developmental alterations occurring in the brain across the broad span of adolescence, as well as emerging data in laboratory animals showing notable dissimilarities in the consequences of alcohol/drug exposures early versus later in adolescence. Data to be reviewed include studies examining adolescent-timing relevant consequences following exposure to alcohol as well as nicotine, cannabinoids and stressors, followed by a brief discussion of timing-related brain changes within adolescence.

2. Human studies

Alcohol use typically is initiated during adolescence, with alcohol use becoming normative in the United States by about 15 years of age (e.g., Masten et al, 2009). Monitoring the Future data have shown that >25% of 8th grades (~13 yrs.), 50% of 10th graders, and ~ 2/3rds of 12th graders used alcohol in the past year. Some of this use is extensive, particularly among older individuals within this group, with 25% of 12th graders reporting having been drunk within the past month, and 22% reporting that they had engaged in binge drinking (consumption of 5+ drinks on a given occasion) within the past two weeks, with a majority of the latter group reporting that they had done so on multiple occasions (Patrick et al, 2013). Prevalence rates for alcohol dependence are highest among 18-20 year old individuals, followed by 21-24 year olds, with rates declining into adulthood (US Department of Health and Human Services, Surgeon General's Report, 2007; cited by Hingson & Zha, 2009).

2.1 Early exposure effect

In 1997, Grant and Dawson reported that rates of alcohol dependence among those individuals that began drinking prior to the age of 14 were over 4 fold greater than those who did not initiate alcohol use until after 20 years of age. Hazards associated with age of first alcohol use (defined as the age when an individual begins to drink, excluding small tastes or sips of alcohol) are non-linear, with markedly elevated risks for the development of alcohol-related problems between 11-14 years that peak at 11-12 years. For instance, DeWit and colleagues (2000) report eventual diagnoses of dependence in 15.9% of those first using alcohol at 11-12 years, dropping to 9% of those beginning use at 13-14 years, and declining rapidly there thereafter to reach an incidence rate of 1% among individuals first using alcohol when they were 19 or older (DeWit et al, 2000).

Although age of first alcohol is a reliable and robust risk factor for later alcohol abuse and dependence (e.g., York et al, 2004; Sartor et al, 2006), factors contributing to this effect are less clear. One possibility is that that this use increases the probability of interacting with environmental factors (e.g., older alcohol-using peers) that favor escalation of use, although it is not obvious why this effect would be restricted to pre-/early-adolescence. It is also possible that early use merely represents a marker for some other problem (e.g., externalizing disorders) or neural vulnerability that elevates the probability of later abuse/dependence, although if this were the case, it would be expected that risk might be elevated at even younger ages (<11 years) rather than peaking at 11-12 years. It is also possible that there is a direct causal relationship, with early use altering normal brain development that is occurring at that time to increase the probability of later abuse/dependence (e.g., see Jacobus & Taper, 2013). Genetic contributors may vary with age to enhance vulnerabilities for alcohol use disorders, with perhaps pre-/early-adolescence representing a window of vulnerability to consequences of alcohol consumption on neurophysiological function (e.g., Chorlian et al, 2013).

2.2 Adolescent binge drinking characteristic of later adolescent period

Adolescents, particularly older adolescents, typically consume more alcohol per occasion than adults (Masten et al, 2009). These elevated consumption levels develop over the course of adolescence, as does the emergence of sex differences. Prevalence rates of early alcohol use are similar in boys and girls, but rates of problem drinking and alcohol use disorders escalate more rapidly into young adulthood in males than females (Young et al, 2002). The rise in the incidence of alcohol problems over adolescence is likely associated with consumption level increases over this age span: whereas the percentage of youth reporting past 30 day alcohol use increases ~3 fold between 8^{th} to 12^{th} grades in the United States, the percentage of student reporting having been drunk over the same time interval increases 5-6 fold (see WIndle & Zucker, 2010). Indeed, rates of binge drinking, when defined as consumption of 5 or more drinks on an occasion, asymptote at around 18-23 years of age at rates higher than among younger or older individuals; this time period is also when rates of past-year DSM-IV alcohol dependence reach their maximum (at ~11-12%) in the United States (see Masden et al, 2009). Extreme binge drinking is of particular concern: whereas >20% of 12^{th} graders report consumption of 5+ drinks/occasions within the past 2 weeks, 10.5% report consumption of 10+ drinks and 5.6% report consuming 15+ drinks (Patrick et

al, 2013). Indeed, more 12th graders report drinking to get drunk as a motivation for their drinking behavior than do young adults (Patrick & Schulenberg, 2011). Among college students, roughly 65% of them drink in a given month (White & Hingson, 2014), yet most of the total amount of alcohol consumed by college students is consumed by binge drinkers, with >2/3rds of the alcohol consumed by the ~20% of college students that are frequent binge drinkers (Wechsler et al, 2002; Weschler & Nelson, 2008).

Although many individuals "mature out" of heavy alcohol use during adolescence, high school substance use is one of the strongest predictors of later substance abuse. For example, binge drinking rates in 12th grade predict alcohol use and dependence at 35 years of age (e.g., Merline et al, 2008) as well as other adverse behaviors (e.g., elevated HIV-related risk behaviors). Interestingly, binge drinking in high school (but not in college) is predictive of dropping out of college (See Patrick & Schulenberg, 2013, for more discussion and references).

2.3 Consequences of adolescent alcohol use: beyond later use disorders and dependence

Consequences of adolescent alcohol exposure may extend beyond the increased propensity for use disorders and dependence on alcohol (or other drugs). There is mounting evidence that adolescents with a history of alcohol use differ on a variety of cognitive and neural measures from their non-alcohol-using peers (see Jacobus & Tapert, 2013; Lisdahl et al, 2013, for recent reviews). These consequences include poor performance on a variety of cognitive measures ranging from deficits in attention, memory and visuospatial function to impaired executive functions, along with neural consequences that include cortical gray and white matter alterations as well as differences in patterns of brain activation during performance of a variety of cognitive tasks (assessed via functional magnetic resonance imaging [fMRI]). Consistent with the adult literature where females are often (e.g., Jacobson, 1986; Hommer et al, 2001) although not always (e.g., Pfefferbaum et al, 2001) more vulnerable than males to ethanol-associated brain damage, several studies have found that heavy drinking female adolescents may likewise be more impaired on certain cognitive tasks and exhibit reduced brain activation during task performance than their male counterparts (Squeglia et al, 2009, 2011). Most of the studies reporting age and sex differences in effects of ethanol exposure have been based on cross-sectional studies that make it difficult to determine whether observed alterations are a cause, consequence or coincidence of prior alcohol use. Emerging longitudinal studies that begin prior to initiation of use, however, are beginning to identify certain neurocognitive characteristics that predate alcohol use and could serve as risk factors for that use whereas other alterations appear to be a consequence of that use (see Jacobus & Tapert, 2013, for discussion).

2.4 Alcohol use early in adolescence vs. binge drinking in late adolescence: different consequences?

In studies with humans, it is difficult to disentangle consequences of early alcohol use from those of binge drinking given the substantial overlap between groups, with early onset individuals often among those engaging in binge drinking during the high school and college years (Hingson & Zha, 2009). Those who begin drinking by the age of 13 are over 3 times more likely than their peers to report binge levels of ethanol consumption at least 6 times/

month by 17 years of age (Youth Risk Behavior Survey; Youth Online, 2008, cited by Hingson et al, 2009), and are more likely to report not only an increased incidence of binge drinking but also extreme drinking (>10 drinks/occasion) 3-4 years later (Hingson & Zha, 2009). Yet, these two types of problematic adolescent alcohol use are separable. Data from twin studies, for instance, suggest that they may differ in genetic and environmental contributors, with environmental influences (such as drug availability) observed to exert a greater influence on early use than on the persistence and escalation of use for both alcohol and other drugs (e.g., see Rhee et al, 2003; Kendler et al, 2011). In contrast, heritability rates have been generally reported to be lower for initiation of alcohol use (~0-25%) than for amount drunk per drinking episode (~55-65%) (Rose, 1998; Fowler et al, 2008), although see also discussion of data from the Collaborative Studies on the Genetics of Alcoholism (COGA) for a somewhat different perspective (e.g., Chorlian et al, 2013). Initiation of use has also been reported to be less heritable than problem use for other drugs as well (e.g., Rhee et al, 2003). Initiation vs. persistence of use not only differ in the strength of heritability, but in the nature of the genetic influences, with genetic factors contributing to use initiation reported to be partially, albeit not completely independent from genetic contributors to the persistence and escalation of use (see True et al, 1997, for an example with smoking). Thus, at least in terms of genetic underpinnings and environmental influences, early use and later problematic use are partially dissociable.

There has been little focus to date on assessing the relative consequences of early use versus later adolescent binge use. One intriguing hint, however, emerges from comparing two studies published byTapert and colleagues. In one study of 15-17 year old adolescents with about a 2 year history of heavy alcohol use (i.e., heavy use beginning at ~ 13-15 years, increased activation was evident in the parietal lobe during a spatial working memory task when these adolescents were compared to their light drinking control counterparts (Tapert et al, 2004); in contrast, attenuated activation in parietal lobe was seen during this task in an older group of 18-25 year old women with alcohol dependence (Tapert et al, 2001). Similar ontogenetic reversals in brain activation patterns have been reported when examining adolescent marijuana users early versus later in adolescence (Lisdahl et al, 2013). In both instances, the early increased activation was interpreted as reflecting inefficient neural activation during the initial use period, with continued use inducing diminished capacity (decreased activation) (Jacobus & Tapert, 2013; Lisdahl et al, 2013). Yet, another potential interpretation of these data is that consequences of the alcohol/marijuana use may vary with exposure age. Indeed, it is interesting that research examining adolescent marijuana use has found that onset of use before 16-18 years of age is associated with more severe cognitive and neural consequences than onset occurring after that time (see Lisdahl et al, 2013, for review and references). There has been little focus to date on similar exposure age studies with alcohol. Yet, assessment of relative vulnerabilities for adverse outcomes of early use vs. later binge drinking is more than of just academic interest. Such information could be critical for informing intervention/prevention efforts – e.g., whether efforts would be more effectively directed towards delaying onset of use, or to reducing the high levels of use or consequences of that use that are particularly prevalent late in adolescence.

3. Animal studies

With the increasing recognition over the past decade and a half of considerable maturational changes in brain during adolescence – a time during which use of alcohol (and other drugs) is often initiated and escalates – attention has recently turned to assessment of the consequences of such exposure in studies with laboratory animals, most typically using rat models of adolescence. In such studies, lasting consequences of adolescent exposure to alcohol (as well as other drugs such as nicotine and cannabinoids) have been observed, including alterations in later cognitive and socioemotional functioning, as well as increases in drug self-administration under some circumstances (e.g., see Spear, in press, for review). In this emerging research area, the work to date has not always manipulated exposure age to determine whether adolescence represents an especially vulnerable period for inducing long-lasting neurobehavioral consequences, let alone to assess whether there are different vulnerable periods within the broad age-span of adolescence. As outlined below, however, various recent studies have reported timing-specific effects of exposure within adolescence to ethanol, other drugs such as nicotine and cannabinoids, as well as social isolation and other stressors.

3.1 Adolescent timing in rats

To set the stage for discussion of age-specific adolescent exposure effects in rats, let's first consider the timing of adolescence in rats. The absolute boundaries of adolescence are as imprecise in rats as they are in human youth, although the duration of adolescence is of course much shorter in the rat with its brief life span. The length of adolescence in the rat has been suggested to subsume somewhere from a conservative 2 weeks (e.g., postnatal days [P] 28-42; see Spear, 2000) to a broader 6 or so weeks (e.g., P25-65)(See Vetter-O'Hagen & Spear, 2012). The latter age span is thought to encompass the range from early adolescence through late adolescence/emerging adulthood and has been parsed into subgroups in various ways (e.g., Vetter-O'Hagen & Spear, 2012; Burke & Miczek, 2014; for mice, see Adriani et al, 2004). For example the P25-42 interval in rats may be roughly analogous to the 10-18 year, early-mid adolescent period in humans, with the ages from P43 to P55 or P65 approximating the 18-25 year old period of late adolescence/emerging adulthood in humans (e.g., Vetter-O'Hagen & Spear, 2012).

At some point within the broad adolescent period the process of puberty occurs – i.e., the physiological and hormonal changes associated reproductive maturation. The peak velocity of these pubertal changes often occurs in early through mid-adolescence in humans as well as rodents. For instance, when pubertal maturation in rats is indexed via development of genitalia (balano preputial skinfold separation and sperm presence in the seminiferous tubules in males; vaginal opening in females), signs of pubertal development are evident in some males by P36, with genitalia maturation in a majority of males by P40 and in almost all males by P44. As in humans, female rats mature on average more quickly than their male counterparts, with the processes of genitalia development generally occurring ~4-8 days more rapidly in females than males (Vetter-O'Hagen & Spear, 2012). Consequently, the pubertal period typically occurs within the early-mid adolescent period in rats as in humans, with females undergoing this transition earlier than males. Interestingly, as we shall see,

alcohol/drug and stressor exposures occurring at this time in laboratory animals often have different consequences than analogous exposures occurring later in adolescence or at maturity.

3.2 Adolescent exposure timing effects with ethanol

Most studies assessing the effects of repeated exposure to ethanol during adolescence in rats have used a single adolescent exposure period, often without including another aged comparator group, even in adulthood. However, in those instances where timing of ethanol exposure during adolescence has been varied, observed effects have often differed with exposure timing. For instance, when indexed via electrophysiological alterations in hippocampus following ethanol vapor exposure, consequences were more marked with a P30-40 than a P35-40 exposure period (Slawecki et al, 2001). While these effects could be related to either exposure timing or duration, in other studies where adolescent exposure timing was varied while holding duration of exposure constant, timing-dependent effects have also emerged. For instance, in work where ethanol was administered intraperitoneally intermittently to rats from P30-43 or P45-57, only the earlier exposure period resulted in elevated ethanol consumption relative to control animals in adulthood (Alaux-Cantin et al, 2013). In a study conducted in mice, C57BL/6J mice exposed to ethanol in early (P30-45) but not late adolescence (P45-60) observed increases in risk choice behavior whereas the late (but not early) adolescent exposure decreased attention and increased waiting impulsivity (Sanchez-Roige et al, 2014). A double dissociation was also seen in the consequences of early (P28-48) versus late (P35-55) adolescent exposure administered intragastrically (i.g.) to rats on assessments of context fear retention and extinction in adulthood. Exposure beginning at P28 (but not at P35) resulted in context retention deficits whereas exposure beginning at P35 (but not at P28) was associated with a context extinction deficit that was comparable to that seen with ethanol exposure in adulthood (Broadwater & Spear, 2013). Thus, even when there is some overlap in the exposure periods, a week of exposure prior to 35 days of age produced a notably different pattern of effects than exposure beginning at that time or at maturity.

When effects of intermittent i.g. ethanol exposure during early-mid adolescence (P25-45) versus late adolescence/emerging adulthood (P45-65) were assessed, adult male rats that had been exposed to ethanol during early-mid adolescence were found to exhibit long-lasting social anxiety that was not evident in their adult male counterparts that had been exposed to ethanol during the late adolescent exposure period (Varlinskaya et al, 2014). As adults, the early adolescent-exposed male rats also continued to exhibit adolescent-like responding to ethanol, showing social facilitation to low doses of ethanol that is normally evident during adolescence but not in adulthood; such retention of adolescent-typical ethanol sensitivities into adulthood following adolescent ethanol exposure has been reported in a number of studies (see Spear & Swartzwelder, 2014, for review). Preservation of adolescent-typical social facilitation to low doses of ethanol was not evident in adults exposed to alcohol during late adolescence (P45-65), although exposure at this time did induce lasting tolerance to the social suppression that emerges at higher ethanol doses (Varlinskaya et al, 2014). This insensitivity to ethanol's social suppressing effects is reminiscent of the normal attenuated sensitivity that adolescents exhibit relative to adults to the social suppressing effects of

ethanol; hence, this effect, too, may also represent retention of adolescent-typical ethanol sensitivities into adulthood. No such evidence of tolerance was seen following ethanol exposure during early-mid adolescence. Interestingly, both males and females were tested in this study, and both the social anxiety and retention of adolescent-typical social facilitation into adulthood evident after early ethanol exposure as well as the lasting tolerance to ethanol-induced social suppression seen after late adolescent exposure were evident only in males. These findings contrast with human studies where females have been often found to be more susceptible than males for developing negative consequences from extensive alcohol use, a gender imbalance most studied in adult alcoholics (e.g., Nolen-Hoeksema, 2004) but evident in late adolescence as well (Schulte et al, 2009). Few other basic science studies have assessed consequences of adolescent ethanol exposure in females and hence the extent to which these effects may be generally sex dependent is not known.

Taken together, these studies suggest that ethanol exposures beginning pre-pubertally and extending into puberty often produce a different pattern of consequences than those beginning later in adolescence. Early/mid adolescent exposure has been associated with increases in later ethanol exposure and retention of adolescent-typical social facilitatory effects of ethanol into adulthood, along with context fear retention deficits, increase in risky choice behavior, and more pronounced electrophysiological alterations in hippocampus. These effects are specific to early exposure, with exposure later in adolescence inducing instead lasting tolerance to ethanol's social inhibitory effects, attentional deficits, as well as adult-typical context extinction deficits. Whether the seemingly more pronounced consequences to date of early adolescent exposures are representative or just a function of the specific response measures investigated to date is unclear at this point. Nor is it clear whether the timing-related sensitivity of early-mid adolescent exposures reflects vulnerabilities in neural systems undergoing pubertal change or are related to other developmental changes in brain that also occur around that time.

3.3 Adolescent-exposure timing effects: other insults

Exposure timing-related effects during adolescence occasionally have been examined with other drugs as well as stressors. Particularly well explored has been the developmental timing of social isolation effects. Some studies of exposure timing effects have also been reported following repeated nicotine exposure at different points during adolescence. Findings in these areas will be briefly highlighted to comparison and contrast with the alcohol timing data.

3.3a Timing effects of social stress—Studies in humans and laboratory animals have revealed that the adolescent period is associated with increases in hormonal stress reactivity, with stressors at this time thought to play a critical role in influencing later reactivity to stressors (e.g., see Romeo, 2010; Klein & Romeo, 2013). Social isolation may be a particularly sensitive stressor early in adolescence. This is, whereas housing animals in social isolation (i.e., isolate housing with minimal handling or enrichment) has consequences for social species such as the rat at any age, effects are generally most pronounced when this isolation is initiated early in adolescence (or even the late juvenile (pre-adolescent) period). For instance, Einon and Morgan (1976) observed that isolate

housing increased object contact in an open field when the isolation occurred from P16-25, P25-45, or P45-90; this effect was reversed by subsequent social housing in the youngest and oldest isolation age groups, whereas this effect was irreversible in the animals that were socially isolated during early-mid adolescence (i.e., from P25-45). Social isolation from P21-42 followed by social housing thereafter resulted in enhanced conditioned place preferences for EtOH and amphetamine, whereas social isolation from P21-28 or P42-63 had no effect on these measures (Whitaker et al, 2013). The critical period for social isolation to increase later social behaviors in male rats was found to be when social isolation was *initiated* at P21 or 30 and continued thereafter for at least several weeks during adolescence, with effects generally more evident with earlier than later isolation (Ferdman et al, 2007). The P21-28 day period was also reported to be critical period for*initiation* of social isolation to increase later anxiety in male rats, with isolation periods that did not begin until P28 or later inducing either anxiolysis or having no effect on later anxiety (Lukkes et al, 2009). Thus, the critical period for social isolation effects appears to begin somewhat earlier than that associated with adolescent ethanol exposure, with isolation effects most evident with exposures that begin around the time of conventional weaning in the rat (P21) and that continue for several weeks through early/mid-adolescence. Likewise, using an alternating series of physical stressors (elevated platform, water immersion or footshock on different days) instead of social isolation, stressor exposure from P22-33 was observed to increase anxiety-like behavior in the elevated plus maze and probe burying task; these effects were more pronounced in males and were not evident with stressor exposure from P35-46 (Wilkin et al, 2012). Exposure to two variable stressors (fox odor; exposure to an elevated platform) from P28-42 was reported to induce deficits in sociability, increased aggression and novelty reactivity, and to alter expression of genes influencing excitatory-inhibitory balance in the amygdala (Tranoulinou et al, 2014). These effects were not evident when the stressor period was from P28-30 or P40-42; whether these differences reflect stressor timing versus duration of the stressor period is unclear.

Snyder and colleagues (2014) used a somewhat different social stressor – 5 days of resident-intruder stress – and tested male rats shortly or several weeks later on an operant strategy-shifting task. Performance on the strategy-shifting, medial PFC-mediated portion of the task was impaired in adults that had been exposed to the stressor during late adolescence (P42-46) but not in rats exposed early in adolescence (P28-32) or adulthood (P70-74), although the early adolescent exposure induced a more general impairment in performance evident across all phases of the test. The authors suggested that the late adolescent exposure period may have been a particular vulnerable period for disruption of performance on the medial PFC-critical strategy-shifting task because on ongoing developmental changes in this brain region during late adolescence. Thus, it was argued that age dependency of exposure timing may depend partly on the nature of the dependent measure and the timing of development of its neural substrates, a point to which we will return later.

3.3b Adolescent timing effects: nicotine—Several studies have reported adolescent timing effects on later consequences of nicotine administration. Rats exposed to experimenter-administered nicotine during early adolescence (P28-31) were found to subsequently exhibit increased cocaine self-administration, an effect not evident with

exposure later in adolescence (P38-41) or in adulthood (P86-89)(Dao et al, 2011). In contrast, adolescent-onset nicotine self-administration was not observed to alter later cocaine self-administration, although females allowed to self-administer nicotine from 4-8 weeks of age self-administered more nicotine after a week of abstinence than females given the opportunity to self-administer nicotine from 8-12 weeks of age; this effect was not evident in males (Levin et al, 2011). In mice, nicotine exposure during early adolescence (P24-35) was reported to increase later oral self-administration and stimulant effects of nicotine relative to control animals, whereas mid- and late-adolescent exposures (P37-48; P50-61) did not (Adriani et al, 2002). In contrast, in other work by this same group (Adriani et al, 2004), mid-adolescent exposure (P36-48), but not early and late adolescent exposures, was found to disrupt habituation of locomotor activity and to downregulate AMPA receptors in striatum and hippocampus. As illustrated by these findings, effects on later self-administration were generally more pronounced with exposure during early adolescence, although with some measures, exposure later in adolescence may produce more alterations. In one of the few studies examining sex differences in vulnerability, effects after early adolescent nicotine exposure were found to be more pronounced in females.

3.4 Summary: Adolescent timing effects

There are data with alcohol, nicotine and stressors that timing of exposure during adolescence can profoundly influence the nature the consequences observed. Exposure timing effects are specific to the dependent measure, with double dissociations evident – i.e., early exposure may influence measure X but not Y, whereas later adolescent exposure may impact measure Y but not X. Timing effects and resultant consequences may well depend on the nature of the insult, although relevant data available to date are limited. However, even when looking across the limited timing-relevant data with these three insults, it is interesting that exposures that include the early adolescent period appear to be more likely to impact later self-administration and social/affective behaviors, whereas there is some hint that exposures later in adolescence may be more likely to influence cognitive tasks whose neural substrates are still undergoing maturation at that time. This may extend to other insults as well with, for instance, chronic treatment with a cannabinoid agonist altering sensorimotor gating and recognition memory after exposure during late adolescence/emerging adulthood (P40-65) but not from P15-40 (see Schneider, 2008, for discussion and references). Of course, the available data at this point are limited and hence conclusions about timing-specific neural and behavioral consequences of adolescent exposures are speculative, but ripe for further confirmation or disconfirmation. The design of such studies may be aided by emerging findings that the brain of the early adolescent differs notably from that of late adolescents, with both differing from the mature brain, as discussed briefly in the next section.

4. Maturational changes in the brain during adolescence

4.1 Human imaging studies

With rapid advances in human brain imaging technology, substantial evidence for notable maturational changes in the brain over the course of adolescence has accumulated over the past decade and a half, as have numerous excellent reviews focusing on specific aspects of

this emerging literature (e.g., Luna et al, 2010; Somerville & Casey, 2010; Tau & Peterson, 2010; Sturman & Moghaddam, 2011). Very briefly, among the notable neural alterations of adolescence are considerable declines in the number of excitatory synapses in some brain regions (see Tau & Peterson, 2010, for review) as well as in gray matter volume within the cortex and some subcortical regions (e.g., reviewed in Paus, 2005). In contrast, continued maturation of axons and the development of myelin around axons interconnecting different brain areas continues through adolescence (see Paus, 2005), speeding electrical transmission and hence information flow across these regions. Perhaps related in part to the increase in speed of communication across regions, there are important changes in the neurocircuitry of brain activation – from patterns favoring more local processing to broader networks of connectivity across distributed regions throughout the brain (e.g., Luna et al, 2010). These maturational changes are regionally-, age-, and sex-dependent, and occur in different brain regions at different times, with prefrontal regions being among the last to mature and develop adult-typical patterns of neural processing and functional connectivity (e.g., Luna et al, 2010). There has been substantial interest in relating developmental alterations in brain activation to cognitive and behavioral change during adolescence. For instance, in general subcortical limbic systems (critical for responding to motivational, rewarding, and emotional cues) are thought to be especially sensitive to activation early in adolescence and perhaps related to early- to mid-adolescent rises in sensation seeking, with more slowly developing prefrontal systems providing cognitive control thought to be associated with post-peak declines in sensation seeking and increases in impulse control which continue through adolescence (e.g., see Steinberg et al, 2008; Ernst & Fudge, 2009; Casey et al, 2011). Such regional dissociations in propensity for neural activation from early to late adolescence could provide differential neural substrates for timing-specific consequences of developmental perturbations.

4.2 Animal studies

While much exciting progress has been made examining structural and functional connectivity of the adolescent brain, the level of analysis permitted in human imaging studies is far more global that the more fine-grained neuroanatomical and molecular analyses that can be conducted in laboratory animals. Studies of brain development using animal models, however, have rarely assessed more than a single adolescent time point – if that. Indeed, many initial developmental studies tended to emphasize assessments during the preweanling period, skipping then to an adult endpoint for comparison (see Spear & Brake, 1983). However, studies examining time points within adolescence have reported a diversity of neurodevelopmental differences between early/mid-adolescence (P25-45) vs. late adolescence/emerging adulthood (P45-65). These will be illustrated here using several better studied examples, leaving discussion of interesting ontogenetic differences between adolescents (more broadly defined) and adults to prior excellent reviews (e.g., McCutcheon & Marinelli, 2009; Brenhouse & Andersen, 2011).

4.2a Dopamine—Across a variety of measures, numerous alterations in the dopamine (DA) system have been reported to occur within adolescence. For instance, basal DA levels in dialysates of the nucleus accumbens (nAc) have been found to peak in late adolescence (P45) at levels levels higher than in pre/early/mid-adolescence (P25, P35) or emerging

adulthood (P60) (Badanich et al, 2006; Philpot et al, 2009). In general DA receptors tend to peak in striatum during early/mid-adolescence and to decrease thereafter to reach adult levels by ~P60, although developmental patterns often differ for specific DA receptor subtypes (e.g., Andersen et al, 2000; Tarazi & Baldessarini, 2000). Indeed, using MRI, evidence of DA D1 receptor hypofunction was evident in striatal areas of juvenile and early adolescent rats, with a functional predominance of D2 over D1 DA receptors observed from approximately P20-P35 (Chen et al, 2010). In contrast to the generally early/mid-adolescent peak in DA receptors in striatal regions, DA receptors in PFC typically rise until adolescence/emerging adulthood, peaking at ~ P60 and declining thereafter to reach adult levels by ~ P80 (Andersen et al, 2000). Changes across adolescence are also evident in PFC in terms of electrophysiological responsiveness to DA receptor stimulation, with responsiveness of non-fast spiking GABA neurons to both D1 and D2 stimulation emerging during the late adolescent period. Intriguingly, while fast-spiking GABA interneurons in PFC are also responsive to both D1 and D2 excitation in late adolescence/adulthood, these fast-spiking interneurons are only are responsive to D1 (and not D2) stimulation during early/mid-adolescence – a converse ontogenetic pattern of relative D1 vs. D2 responsiveness to that observed in striatum (Tseng & O'Donnell, 2007).

Based on a variety of neurochemical measures such as developmental increases in DA tissue content, and developmental declines in DA turnover rates (estimated by the ratio of the DA metabolites HVA and DOPAC to DA), Naneix and colleagues (2012) concluded that the mesocortical DA pathway matures more slowly than the mesolimbic and nigrostriatal DA projection systems, an opposite suggestion from that postulated earlier by Spear (2000). Based on review of the human and laboratory animal data, Luciana and colleagues (e.g., Whalstrom et al, 2010) suggested that elevated PFC DA activity might lead to a functional DA “overdose” there during adolescence and hence a preponderance of subcortical DA activity, although they did not detail when during adolescence such changes might take place.

While the exact functional relationship between mesocritical and mesolimbic DA systems during adolescence is still under investigation, what is clear is that there are often different, and sometimes opposite patterns that emerge in a variety of DA measures across adolescence. Given these differences it would be surprising if drugs, stressors or other perturbations early in adolescence did not produce different consequences on DA-related mesolimbic and mesocortical regions than when such exposure occurs later in adolescence. Indeed, work by Philpot et al (2009) has shown that there is a “key developmental transition in the ability of rats to adapt to the effects of repeated ethanol exposure” that emerges between P35 and P45 in the nAc. During early/mid adolescence, repeated ethanol exposure was found to result in greater increases in tonic DAergic activity than was evident after ethanol exposure during late adolescence and to attenuate the normal increases in DA efflux induced by a challenge dose of ethanol. Such age-dependent DA adaptations to repeated ethanol in the nAc, perhaps in association with concomitant alterations in DA regulation in other interrelated mesocortical and mesolimbic DA terminal regions, would likely differentially influence motivational and rewarding properties of alcohol and other stimuli, influencing later vulnerability for alcohol use/abuse. There are many possibilities for further work in this area.

4.2b Connectivity changes—Reminiscent of human imaging findings, studies in laboratory animals using retrograde and anterograde tracers to examine connectivity across brain regions have observed notable differences in connectivity among mesolimbic and mesocortical regions across adolescence. On the one hand, medial PFC connectivity to the basolateral (BLA) nucleus of the amygdala is more extensive during early adolescence than late adolescence and adulthood, decreasing by 50% between P45 and P90 (Cressman et al, 2010). In contrast, glutaminergic projections from the amygdala to the medial PFC (Cunningham et al, 2012) show curvilinear increases during development, with fewer projections to these regions during early/mid adolescence than later in adolescence and into adulthood. Likewise, there are fewer projection neurons to the ventral tegmental area (VTA) from regions such as the nAc, ventromedial PFC, anterior cingulate cortex, insula, etc. during mid-adolescence (P39) than in late adolescence/emerging adulthood (P56-63) (Yetnikeff et al, 2014). Thus, although in general connectivity among these regions increases from early to late adolescence, there is a notable exception of an early/mid-adolescent peak in the medial PFC → amgydala projection system, with declines thereafter.

4.2c Pubertally-associated sexual dimorphism—The early/mid-adolescence period also differs from later in adolescence in terms of pubertal-related changes in the developing brain. For both male and (slightly earlier maturing) female rats, pubertal maturation largely occurs during early/mid-adolescence, as discussed earlier. Hence, exposure to alcohol, other drugs, and environmental challenges early vs. late in puberty would intercept brain development at different points either in the midst of puberty or post-pubertally, respectively. Evidence is mounting that some of the pubertally-associated rises in gonadal hormones induce expression of certain sexual dimorphisms in the brain; thus, puberty is now thought to be a second “organizational” period that serves to further elaborate the sexual differentiation of the brain begun during the prenatal and neonatal period (e.g., Juraska et al, 2013). Such brain sexual dimorphism is not only critical for the emergence of sex-appropriate reproductive behavior, but also likely for the expression of other sex-typical differences in cognition, anxiety-like behaviors, and social behavior (Schultz et al, 2009). The timing of when rising gonadal hormone levels intercept the developing brain matters, with early pubertal timing postulated to generally increase expression of these sex-typical behaviors relative to more delayed pubertal timing (see Schultz et al, 2009, for review). To the extent that drugs or environmental insults influence the timing of puberty, such a perturbation during early/mid-adolescence might have a long-term impact on measures as diverse as sexual behaviors, affect and social behavior – effects that would not be evident with later exposures.

There has been little emphasis to date on examining potential consequences of stressors, alcohol or other drugs of abuse on pubertal timing. Yet, there is evidence that stimulation of glutamate NMDA receptors speeds pubertal timing, whereas NMDA antagonists delay puberty (Brann & Mahesh, 1997; Ojeda & Terasawa, 2002). These findings are of particular interest given that among ethanol's critical neural effects is its action as an NMDA antagonist (see Eckardt et al, 1998, for review and references). Thus, it would appear plausible that an insult such as alcohol exposure during early/mid-adolescence could delay puberty, altering the timing of pubertally-associated organizational influences on the brain

and thereby potentially influencing functions ranging from sexual behavior to cognition, anxiety and social behavior. The same insult later in adolescence would interact with a post-pubertal brain that is much less sensitive to the organizational influence of gonadal hormones – and hence would be expected to have little impact on these functions.

4.2d Summary and further comments—The focal systems discussed above are not the only ones showing age-related alterations within adolescence, with scattered reports of alterations in other neural systems as well. Cannabinoid systems exhibit notable developmental transitions during adolescence with, for instance, cannabinoid receptor binding peaking in early/mid-adolescence (between P30-40), a developmental inflection particularly dramatic in striatum (Rodriguez de Fonseca et al, 1993). Levels of the endocannabinoid anandamide has been also reported to show an inverted U-shaped function, peaking at P38 in nAc at levels higher than at P29 or P40, whereas levels of 2-arachidonoylglycerol (2-AG) in PFC exhibited an opposite ontogenetic pattern, with levels at P38 lower than at younger or older ages (Ellgren et al, 2008). Little explored is also the possibility that differences may emerge in the molecular signature of signaling pathways across adolescence. For instance, during early/mid-adolescence, protein-kinase A (PKA) is not required for induction of long-term potentiation (LTP) in the hippocampus, whereas PKA is required for LTP induction in late adolescents/emerging adults (and also in very young rats), data supporting the suggestion that different molecular mechanisms underlying synaptic strengthening at these ages (Lu et al, 2007).

5. Summary and conclusions: a look to the future

Although pertinent studies are limited, timing-specific consequences of adolescent insults have nevertheless emerged with exposures ranging from ethanol, nicotine and cannabinoids to stressors. While the evidence to date is spread across various insults rather than thoroughly characterized within a given type of insult, where exposure age within adolescence has been manipulated, timing-specific exposure effects have frequently emerged. Various examples of double dissociations in exposure timing effects are evident, with early/mid-adolescent exposures often affecting one outcome and not another, and late exposure inducing the converse. Extrapolating from the limited data to date, it appears that exposure to various insults during the early/mid-adolescent period may be especially likely to affect social behavior, reward sensitivity, and affective measures that rely particularly strongly on subcortical limbic areas and that may be sensitive to pubertal timing. In contrast, late adolescent exposures may be more likely to disrupt cognitive tasks dependent on more slowly developing PFC systems. Of course, there are many other possible neurobiological mechanisms underlying timing-related differences in consequences of repeated ethanol exposure during adolescence. As but one example, ethanol-induced neuroinflammation has been shown to contribute to neurotoxic effects produced by intermittent ethanol exposure during time periods that include early-mid adolescence (e.g., P3-43: Pascual et al, 2007; Guerri & Pascual, 2010; P25-55: Vetreno & Crews, 2012). These effects are more pronounced than those seen after comparable exposure in adulthood (see Guerri & Pascual, 2010, for review), although it has yet to be explored whether differential timing-related vulnerabilities extend to exposures during early/mid vs. late adolescence. It should also be noted that to date, most basic science studies have been conducted only in males; when both

sexes have been studied, sex-dependent effects have often emerged, with greater vulnerability sometimes evident in males. Studies that have included both sexes, however, are rare and insufficient to assess the generality of these findings.

Returning to the question asked at in the title: are there timing-specific vulnerabilities of ethanol exposure within adolescence, the data to date suggest that the answer is “yes”. Substantial more work is needed, however, to characterize the consequences of alcohol exposure during separable vulnerable periods during adolescence and their sex dependency, uncover the mechanisms underlying timing-specific effects, and determine whether such timing-dependency extends to other drugs and stressors, and to human adolescents. Another important area for further inquiry is the extent to which prenatal exposure to alcohol or other drugs, and exposure to stressors prenatally or during the early postnatal period, alters neural development in ways that may promote early initiation, exacerbate escalation of use, and intensify consequences of such exposures (e.g., see Spear, 2013).

Ultimately, such studies could prove critical for informing prevention and intervention efforts to minimize adverse lasting consequences of adolescent exposure to ethanol and other drugs. For example, if studies reveal that early adolescence is an especially vulnerable period, enhanced prevention efforts to delay use would appear warranted, using means to restrict access, increase both community and parental awareness of the hazards of early initiation, and bolster the scaffolding provided for early adolescents in this area. If binge levels of alcohol exposure later in adolescence exert particular vulnerabilities, increased efforts could be directed within colleges, universities and the armed forces to encourage moderation in alcohol consumption and promote drinking contexts and circumstances designed to mitigate short- and long-term harm. Adolescent alcohol use is often accepted as inevitable and a right-of-passage; publicizing established findings of age-related neural, behavioral and cognitive consequences of binge exposure may help unravel this acceptance and lead to changes within communities, schools and families that serve to effectively delay alcohol initiation and moderate levels of use in youth.

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Highlights

Consequences of early vs. late adolescent alcohol exposure may differ.

Timing-specific effects of adolescent insults may extend to other drugs/stressors.

Brain ontogeny imparts changing landscape of possible timing-related vulnerabilities.