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Adolescent alcohol exposure and persistence of adolescent-typical phenotypes into adulthood: a mini-review

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Abstract

Alcohol use is typically initiated during adolescence, which, along with young adulthood, is a vulnerable period for the onset of high-risk drinking and alcohol abuse. Given across-species commonalities in certain fundamental neurobehavioral characteristics of adolescence, studies in laboratory animals such as the rat have proved useful to assess persisting consequences of repeated alcohol exposure. Despite limited research to date, reports of long-lasting effects of adolescent ethanol exposure are emerging, along with certain common themes. One repeated finding is that adolescent exposure to ethanol sometimes results in the persistence of adolescent-typical phenotypes into adulthood. Instances of adolescent -like persistence have been seen in terms of baseline behavioral, cognitive, electrophysiological and neuroanatomical characteristics, along with the retention of adolescent-typical sensitivities to acute ethanol challenge. These effects are generally not observed after comparable ethanol exposure in adulthood. Persistence of adolescent-typical phenotypes is not always evident, and may be related to regionally-specific ethanol influences on the interplay between CNS excitation and inhibition critical for the timing of neuroplasticity.

Keywords

Adolescent; Ethanol; Persisting effects; Cognitive; Behavior; Electrophysiological; Neural

1. Introduction

Alcohol is the most widely used recreational drug, and most people in the U.S. begin to use alcohol during adolescence or young adulthood. According to nationwide surveys, by approximately 14 years of age, alcohol use has become normative among youth in the

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United States, with about 75% of 12th graders and 85% of college students reporting that they have tried alcohol. Some of this consumption reaches high levels, with 10% of 8th graders, 25% of 12th graders and >40% of college students reporting that they had consumed five or more drinks in a row during the last two weeks (Johnston et al, 2006). This prevalence of high risk drinking occurs at a developmental period when the brain is undergoing rapid changes in structure and function that could make it especially vulnerable to negative consequences of alcohol exposure (Dahl, 2004; Monti et al., 2005). Epidemiological studies have shown that adolescence and young adulthood are the periods of greatest risk for the onset of alcohol abuse and that adult abuse of alcohol is strongly (although not necessarily causally) associated with young age at drinking onset (Dawson et al., 2008; Sher and Gotham, 1999). Thus, evaluating the acute and chronic effects of ethanol on the adolescent brain and behavior may be of great value in understanding the development of alcohol abuse disorders. Studies with laboratory animals such as the rat have proved particularly useful in this regard given ethical constraints limiting experimental investigation of ethanol effects in youth, and the seeming number of neurobehavioral characteristics shared among adolescents across mammalian species (see Spear, 2010; Brenhouse & Andersen, 2011, for review). Reminiscent of human adolescents, adolescent rats also often exhibit elevated ethanol intake relative to their adult counterparts (e.g., Doremus et al, 2005; Vetter et al, 2007).

During the past several decades, it has become clear that significant development and remodeling occurs in the brain throughout adolescence and into early adulthood, with this developmental interval characterized by various neural and behavioral phenotypes that differ notably from those seen at other ages (see Spear, 2000, 2010; Brenhouse & Andersen, 2011). Among the notable alterations in neurobehavioral function seen during adolescence relative to younger and older ages are alterations in responsiveness to a variety of drugs (e.g., see Adriani and Laviola, 2004). One particularly well-investigated drug is alcohol (ethanol), with substantial research demonstrating that acute ethanol induces different effects on both neural and behavioral function during adolescence than are evident at maturity. For example, adolescent rats show greater ethanol-induced memory impairment in the Morris water maze and in a discrimination task than do adults (Land and Spear, 2004; Markwiese et al., 1998). Similarly, humans in their early 20's are more sensitive to the effects of ethanol on both semantic and figural memory tasks than those in their late 20's (Acheson et al., 1998). Acute ethanol has been shown to more potently suppress both NMDA receptor-mediated synaptic activity (Swartzwelder et al., 1995b) and the induction of long-term potentiation (LTP)(Swartzwelder et al., 1995a) in hippocampal slices from adolescent animals compared to those from adults. Adolescents are also uniquely sensitive to the social facilitation effects of ethanol relative to their adult counterparts (e.g. Varlinskaya & Spear, 2002). Conversely, adolescent rats are less affected than are adult rats to most other ethanol effects. These include ethanol's sedative (Little et al., 1996; Silveri & Spear, 1998), motor impairing (Little et al, 1996; White et al., 2002a, b), social inhibitory (Varlinskaya & Spear, 2002) and aversive (Anderson et al, 2010) effects, as well as ethanol's impact on γ-aminobutyric acid (GABA) type A ($GABA_A$) receptor-mediated inhibition (Li et al., 2003; Li et al., 2006; Yan et al., 2010; but see Yan et al., 2009). Therefore, it is now clear that acute ethanol affects both behavioral and neural function differently in adolescents than

adults, although whether ethanol sensitivity is augmented or attenuated during adolescence is dependent on the specific function being tested.

Although such studies have provided crucial information about age differences in the acute effects of ethanol between adolescents and adults, a perhaps even more pressing question is whether the adolescent is at greater or lesser risk for long-term changes in neurobehavioral function after repeated ethanol exposure. Studies of spatial learning in the radial arm maze have shown that adolescent intermittent ethanol (AIE) exposure but not chronic intermittent ethanol (CIE) exposure in adulthood, results in greater long-term sensitivity to the memory-impairing effects of acute ethanol in the absence of any evidence of changes in baseline learning ability (Risher et al., 2013; White et al., 2000). In contrast, Silvers and colleagues showed that AIE exposure across the 20-day period of adolescence in the rat markedly reduced the efficacy of ethanol to impair spatial learning in the Morris water maze 24 hours after the last in the series of chronic ethanol doses (Silvers et al., 2003; Silvers et al., 2006), though it is likely that those outcomes were related to withdrawal, tolerance, or both, rather than reflecting an enduring change in ethanol sensitivity. Sircar and Sircar (2005) reported that five consecutive days of ethanol exposure during adolescence resulted in spatial learning deficits in the Morris water maze up to 25 days after the last ethanol treatment, independent of subsequent ethanol challenge. Fear retention deficits have also been observed 25 days following AIE but not the same length of time following CIE exposure (Broadwater & Spear, 2013a). Outside the domain of learning, AIE but not CIE has been shown to produce a long lasting decrease in the sensitivity of rats to the sedative/motor-impairing effects of acute ethanol (White et al., 2002b) and, when administered early in adolescence, to increase ethanol consumption in adulthood and enhance motivation for ethanol (Alaux-Cantin et al, 2013). At the cellular level, AIE (but not comparable ethanol exposure in adulthood) was found to produce an enduring decrease in the magnitude of GABA receptor-mediated tonic current in dentate granule cells (Fleming et al., 2012; Fleming et al., 2013) which is critical for maintaining the balance of excitation and inhibition within hippocampal circuits. Moreover, although both AIE and CIE decreased A-type potassium current (I_A) in GABAergic hippocampal interneurons, this effect was notably more pronounced after AIE (Li et al., 2013).

Despite the relatively limited amount of work to date assessing later effects of repeated exposure to ethanol during adolescence, a few common themes have begun to emerge. The emphasis of this mini-review is on one such theme: emerging across-study commonalities in AIE effects characterized by the persistence of adolescent-typical phenotypes into adulthood. That is, after adolescent exposure to ethanol, certain characteristics of adolescence continue to be expressed developed after their normal ontogenetic decline, and are evident in adulthood, weeks after termination of the adolescent exposure period. Persisting adolescent phenotypes after AIE prominently include retention of adolescent-typical sensitivities to ethanol. These effects can be manifest as either increases or decreases in responsiveness to ethanol challenge in adulthood, so it is important to distinguish persistence of an adolescent-typical response to ethanol from ethanol tolerance *per se*. As outlined in the sections below, examples of persisting adolescent phenotypes have emerged with behavioral and cognitive measures as well as electrophysiological and other neural

characteristics, although it is important to point out that certainly not all consequences of AIE reflect the persistence of an adolescent phenotype. For some measures, particularly those that require extensive amounts of training, it may not be possible to assess similarity of the AIE effect to an adolescent phenotype because temporal constraints may limit the ability to assess the adolescent-typical phenotype within the short time-span of adolescence in rodents (i.e., the 2 week period from roughly postnatal day [P] 28–42 as early/mid adolescence, and ~ the next 2 weeks [P43–55] as late adolescent/emerging adulthood – see Spear, 2000; Vetter-O'Hagen & Spear, 2012). Without clear characterization of the adolescent phenotype, it is of course not possible to determine whether this phenotype is retained into adulthood after AIE. The notion that AIE results in the retention of certain adolescent phenotypes into adulthood also seemingly implies that similar findings would not emerge from ethanol exposure at a time when the adolescent phenotype was no longer evident (i.e. after CIE). Only a subgroup of adolescent exposure studies to date have included comparison groups of animals given comparable exposure in adulthood, but in those studies that have, the expression of adolescent-like phenotypes has principally been found to be specific to AIE, and not evident following comparable CIE (see Table 1).

It is important to note that no one adolescent exposure regimen is necessary to produce these persisting adolescent-like phenotypes, with evidence for such effects reported across a number of different ethanol exposure regimens and strains of rats. For instance, adolescent-like phenotypes have emerged after intragastric (ig) AIE exposure regimens of every other day administration of 3.5 or 4 g/kg ethanol in Sprague-Dawley rats (e.g., Broadwater & Spear, 2013a, b e.g., Broadwater & Spear, 2014a, b; Varlinskaya et al, 2014) as well as a two day on, two day off, exposure regimen to 5 g/kg ethanol in Sprague-Dawley rats (e.g., Fleming et al, 2007, 2012, 2013). Persistence of adolescent typical phenotypes have also been reported after AIE using every other day intraperitoneal injections of 3.0 g/kg ethanol in Sprague-Dawley rats (e.g., Alaux-Cantin et al, 2013) as well as when using intermittent (14 hrs. on; 10 hr. off) ethanol vapor exposure with Wistar rats (e.g., Ehlers et al, 2013; 2014). Timing of the exposure has also varied across studies. As can be seen in Figure 1, some exposures have extended throughout a broad period subsuming adolescence in the rat (e.g., ~ postnatal days (P) 25–65), and with other exposures centered more typically around the early-mid-adolescent exposure period (P28–45 or so), with some exposures continuing into, or restricted to periods thought to represent late adolescence/emerging adulthood (e.g., P45–65). In cases where different exposure periods have been examined in the same study, AIE effects have often been found to vary with exposure period within this broad adolescent period (e.g., Alaux-Cantin et al, 2013; Broadwater & Spear, 2013a; Varlinskaya et al, 2014). Effective adolescent exposure regimens commonly have included periods of ethanol exposure separated by intervals during which ethanol has cleared the body. The intermittency of this exposure may be important: although little studied, where investigated AIE effects have been found to be more pronounced with intermittent than continuous exposures (e.g. Diaz-Granados & Graham, 2007; Sánchez et al, 2014). Peak blood alcohol levels (BALs) produced with the AIE exposure regimens reviewed here are typically above those seen with binge level use (>90 mg% as defined by the National Institute on Alcoholism and Alcohol Abuse) but in a pharmacologically relevant range to that seen among drinking youth (e.g., BALS up to ~300 mg% – e.g., see Day et al, 2013).

2. Retention of adolescent-typical phenotypes after AIE: Cognitive/ Behavioral

Response to Ethanol Challenge

Adolescents are less sensitive than adults to many ethanol effects, including ethanol-induced motor impairment and sedation (Little et al, 1996; Silveri & Spear, 1998; White et al, 2002a), ethanol-induced anxiolysis (Varlinskaya & Spear, 2002), ethanol-precipitated conditioned taste aversions (CTA)(Anderson et al, 2010) and the social inhibition that emerges at moderate or higher doses of ethanol (Varlinskaya & Spear, 2002). Adolescent animals have also been found to be less likely than adults to exhibit anxiety during withdrawal from ethanol (Doremus et al, 2003). Adults given AIE retain the adolescent-typical attenuation in sensitivity to ethanol's effects on motor performance and sedation, exhibiting an attenuated response to the motor impairing and sedative effects of ethanol when compared with adult control animals (Little et al, 1996; White et al, 2002a, b; Matthews et al., 2008; Quoilin et al, 2012); similar attenuations in ethanol-induced motor impairment were not evident after CIE (White et al, 2002b). Likewise, reminiscent of the attenuated sensitivity of adolescents to ethanol CTA, adults previously given AIE exhibited attenuated CTAs to ethanol relative to age-mates who had not previously been exposed to ethanol (Diaz-Granados & Graham, 2007; Alaux-Cantin et al, 2013). Adult male rats given AIE exposure during late adolescence have also been found to be less sensitive than their control counterparts to the social impairing effects of moderate or higher doses of ethanol, an insensitivity analogous to that exhibited typically during adolescence (Varlinskaya et al, 2014). Again similar to that seen normally during adolescence, adults given AIE do not exhibit signs of anxiety during ethanol withdrawal that was evident in adult controls and in adults given CIE (Mejia-Toiber et al, 2014). Findings of altered ethanol sensitivities after AIE are not ubiquitous, however, with a report of no differences in sensitivity to ethanol's sedative and motor impairing effects between adults previously given AIE and their controls (Alaux-Cantin et al, 2013) and evidence that the attenuated disruptive influences of ethanol on context fear retention seen in adolescents relative to adults were not evident after AIE (Broadwater & Spear, 2014b). When conducting psychopharmacological studies, of course it is difficult to tell whether the absence of differences reflects a true null effect or is merely a function of the specific dose(s) chosen for testing, given that group differences often are manifest as shifts in dose-response curves, and hence are most likely to emerge at doses representing critical points of inflection on the curves.

Although as discussed above, adolescents are less sensitive than are adults to various intoxicating and impairing effects of ethanol, they are conversely notably *more* sensitive than adults to a few critical cognitive/behavioral effects of ethanol, the two best studied of which are ethanol-induced learning impairments and ethanol-induced social facilitation. There is emerging evidence that both of these types of ethanol sensitivities are retained into adulthood after AIE. Turning first to the ethanol influence on learning, acute ethanol exposure has been shown to disrupt learning more potently in adolescent rats than in adults (Markweise et al, 1998). Adults exposed to AIE likewise show an enhanced sensitivity to the disruption of learning induced by acute ethanol than their control counterparts; this effect is specific to adolescent exposure in that it is not evident after CIE (White et al, 2000; Risher

et al, 2013). Adolescents also differ from adults in ethanol's effects on social behavior, with adolescents showing a notable facilitation of social behavior by low doses of ethanol that is not typically evident in adulthood (e.g., see Varlinskaya & Spear, 2002). Yet, after AIE exposure during early/mid adolescence, adult males were found to exhibit atypical expression of this facilitation, showing pronounced ethanol-induced social facilitation that is reminiscent of that seen normally during adolescence, whereas adult control males only showed an age-typical inhibition of social behavior (Varlinskaya et al, 2014).

Although the data are somewhat more mixed, there are several reports that adolescents are more sensitive to the rewarding effects of ethanol than are adults (e.g., Pautassi et al, 2008; Ristuccia & Spear, 2008; but see also Dickinson et al, 2009). AIE may induce the persistence of this adolescent-typical ethanol effect, with AIE reported to enhance some, although not all, measures of ethanol's rewarding effects when AIE and control animals were tested in adulthood (Alaux-Cantin et al, 2013). Although the measures used vary somewhat from those that have been used to assess ethanol effects on reward processing during adolescence, in recent work assessing sensitivity to ethanol challenge-induced reward enhancements and deficits, AIE also was found to decrease the sensitivity of adults to the reward-impairing effects of ethanol and precipitate in a sub-set of the animals atypical ethanol-induced reward enhancement (Boutros et al, 2014). Effects of AIE on later consumption of ethanol in adulthood are mixed, with adolescent-typical elevations in ethanol consumption (e.g., Doremus et al, 2005) reported under some but not all circumstances after AIE (e.g., see McBride et al, 2005; Gilpin et al, 2012; Alaux-Cantin et al, 2013; Broadwater et al, 2013b); critical variables influencing the impact of AIE on later ethanol intake may be related to the mode of ethanol exposure during adolescence (e.g., experimenter administered vs. self-administered; route of exposure) as well as how intake was assessed in adulthood (home cage or limited access; operant self-administration, etc.).

Non-drug challenge

Maintenance of an immature behavioral phenotype after AIE is not necessarily restricted to ethanol challenge effects, although work assessing baseline behavioral consequences is limited to date. Adolescents often exhibit higher levels of risk-taking and novelty-seeking than do adults (e.g., Adriani et al, 1998; Laviola et al, 2003). Similarly, adults after AIE have been observed to exhibit greater disinhibition in a modified open-field conflict task than adult rats (Ehlers et al, 2013) and elevations in impulsive-like behaviors (Gilpin et al, 2012). During fear conditioning, typical adult animals show overshadowing of context conditioning by the presence of a tone conditioned stimulus (CS+) that is paired with footshock in that context during conditioning – i.e., they do not develop as strong a fear to a context when conditioned in that context in the presence of a more predictive tone CS+. Immature animals, in contrast, show the opposite, displaying potentiation of context conditioning when footshock is paired with a tone CS+ in that context during conditioning. After AIE, adults exhibited this immature potentiation effect, a consequence specific to ethanol exposure during adolescence, with adults showing the normal, adult-typical pattern of overshadowing when tested at the same period of time after CIE (Broadwater & Spear, 2014a). Clearly, more work is needed to determine the relative pervasiveness of AIE-

associated retention of adolescent-typical baseline behavior and cognitive function into adulthood beyond the limited findings reported to date.

3. Retention of adolescent-typical phenotypes after AIE: Electrophysiological

Baseline

Long-term potentiation (LTP) in the hippocampal formation is a manifestation of synaptic plasticity that has been linked to learning (Grant et al, 1992) and is potently inhibited by acute ethanol exposure (Sinclair & Lo, 1986; Morrisett & Swartzwelder, 1993). Using hippocampal slices from both adolescent and adult rats, slices from adolescents reliably exhibited more robust induction of LTP, with this LTP being inhibited more potently by ethanol than the LTP induced in slices from adults (Swartzwelder et al, 1995a; Pyapali et al, 1999). The greater capacity for LTP in hippocampal circuits in adolescent animals is consistent with other observations of enhanced excitability in the developing brain such as enhanced susceptibility to ethanol withdrawal seizures (Chung et al, 2008), hippocampal epileptogenesis (Swann and Gomez-Di Cesare, 1994), and susceptibility to excitotoxicity (Johnston, 1995). Recently, AIE was found to reduce the stimulus intensity threshold for LTP induction in area CA1 of hippocampal slices in adulthood (Risher et al, 2013b). This greater network excitability after AIE is consistent with the enhanced induction of LTP observed in hippocampal slices from control adolescent rats relative to those from adults (Swartzwelder et al, 1995a). Thus it appears AIE induces the retention of adolescent-like hippocampal network excitability with respect to the induction of LTP.

Ongoing hippocampal excitability is powerfully modulated by GABA-mediated tonic inhibition. Consistent with the generally more excitable network profile of the developing hippocampal formation, tonic inhibition in the dentate gyrus of the adolescent has been shown to be less prominent than in the adult, and also more efficaciously promoted by acute ethanol (Fleming et al, 2007). Type-A GABA ($GABA_A$) receptors can be divided into two broad classes, synaptic and extrasynaptic, based on their function, ligand sensitivity, and location on the neuron (Fritschy and Brunig 2003; Nusser and Mody 2002; Rossi et al. 2003; Yeung et al. 2003). For many years, studies of ethanol focused on synaptic $GABA_A$ receptors. However, it has now become clear that extrasynaptic $GABA_A$ receptors are highly sensitive to ethanol (Eckardt et al. 1998; Wallner et al. 2003) and that one important function of these non-synaptic $GABA_A$ receptors is to maintain tonic inhibition in hippocampal networks. Tonic inhibition recorded in dentate granule cells within hippocampal slices is not only less prominent when recorded in hippocampal slices from adolescent rats than those of adults (Fleming et al, 2007), but is likewise attenuated in adult animals that had been exposed to AIE relative to controls (Fleming et al, 2012). Thus, analogous to the effects of AIE on LTP, it appears that the repeated ethanol exposure during adolescence resulted in the retention of the adolescent-typical, relatively low level of tonic inhibition, into adulthood. This effect was not observed in slices from animals that had received CIE (Fleming et al, 2013), suggesting that adolescence is a period of distinctive vulnerability to the long-term effects of ethanol on hippocampal network function.

Response to Ethanol Challenge

As noted above, $GABA_A$ receptor-mediated tonic current in dentate granule cells from adolescent rats is not only less prominent than in those from adults, but is also potentiated more efficaciously by ethanol (Fleming et al, 2007). This finding has prompted speculation about enhanced tonic inhibition as one possible mechanism underlying the greater sensitivity of adolescent than adult animals to the memory impairing effects of acute ethanol (Markweise et al, 1998). Evidence has emerged that this hypersensitivity is perpetuated into adulthood after AIE exposure. Specifically, AIE (but not CIE) exposure results in greater potentiation of tonic inhibition by acute ethanol in dentate granule cells from adult animals (Fleming et al, 2012; 2013). This increased ethanol sensitivity in adulthood after AIE exposure is reminiscent of the 'naturally' greater sensitivity of tonic inhibition to ethanol during adolescence.

In contrast, adolescents have been shown to be less sensitive than adults to the effects of acute ethanol on certain neocortical EEG frequency bands as well as ethanol's effects on neocortical event-related potentials (ERPs). AIE has been shown to sustain this adolescent-typical phenotype of attenuated ethanol sensitivities into adulthood. For example, Pian et al (2008) reported that EtOH (1.5 g/kg) promoted EEG power in the 4–6 Hz band in the parietal cortex of adult Wistar rats, but not in adolescents. The same acute ethanol dose promoted 4–6 HZ power in the parietal cortex and hippocampus in adult Sprague-Dawley rats who had not received AIE exposure, whereas this ethanol effect was not evident in those exposed to AIE (Slawecki, 2002). Similarly, it is known that ethanol increases the latency of certain neocortical event-related potentials (ERPs), and does so less efficaciously in adolescent than adult rats (Ehlers et al, 2014). Interestingly, in the same study, when animals were exposed intermittently to ethanol vapor throughout adolescence and then tested in adulthood, their ERP latencies were less sensitive to acute ethanol than those of adult control animals. This suggests that the relatively ethanol-insensitive phenotype had been retained into adulthood in animal that received AIE.

Taken together with the effects of AIE exposure on tonic inhibition in adulthood, these findings illustrate the important point that AIE appears to prolong adolescent electrophysiological responsiveness to ethanol into adulthood independent of whether that responsiveness represents greater or lesser ethanol sensitivity in adolescents compared to adults. Thus, AIE does not perpetuate insensitivity or hypersensitivity to ethanol, but, rather, sustains the adolescent characteristic responsiveness of the particular dependent measure.

4. Retention of adolescent-typical phenotypes after AIE: Neural

Immature dendritic spines tend to have longer neck length and lack the "stubby" mushroom-like morphology typically associated with mature and stable spines (Bourne and Harris, 2007; 2008). Recent studies have indicated that AIE alters dendritic spine morphology in CA1 pyramidal cells of the adult hippocampus in a manner that appears to reflect (Risher et al, 2013b) a predominance of immature spine morphology (Risher et al, 2013b). Although AIE did not alter overall spine density, it decreased the number of spines with characteristic mature appearances, increased the number of spines with immature appearance, and increased spine neck length. Thus, these initial results suggest that AIE causes persistence of

an immature dendritic spine phenotype into adulthood. This alteration of spine morphology by AIE may be relevant to findings that the threshold for LTP induction was decreased after AIE in the CA1 area of the hippocampus (Risher et al, 2013b). Although a precise characterization of adolescent hippocampal dendritic spine phenotype has not been conducted, those experiments are currently underway. More work will be required in order to explore the possibility that AIE induces both morphological and physiological characteristics that combine to disrupt adult hippocampal function.

5. Summary, Conclusions, Future directions

Although a relatively recent area of study, assessment of consequences of repeated intermittent adolescent ethanol exposure is beginning to reveal a pattern of specific and long-lasting effects that, where examined, are not evident after comparable ethanol exposure in adulthood. Among these alterations are numerous instances where exposure to ethanol during adolescence seemingly induces the persistence of an adolescent-typical phenotype into adulthood. As described in this review, persisting adolescent phenotypes after AIE have been observed behaviorally, cognitively, electrophysiologically and neurally, and are expressed not only via retention of certain adolescent-typical sensitivities to ethanol, but also as alterations in baseline neurobehavioral function (e.g., baseline levels of tonic inhibition, propensity for induction of LTP, expression of potentiation rather than overshadowing in fear conditioning) as well.

The data available to date clearly demonstrate that the persistence of adolescent-typical responsiveness to ethanol into adulthood after AIE is not merely related to the emergence of ethanol tolerance. AIE has been found to result in the retention of not only adolescent-typical *insensitivities* to ethanol (such as ethanol-induced sedative, anxiolytic, and aversive effects and ethanol effects on certain EEG frequencies and evoked potentials), but also in the persistence of adolescent-typical *accentuated sensitivities* to other acute ethanol effects, including ethanol-induced memory impairments, social facilitation, and potentiation of tonic inhibition. Thus, neither tolerance nor other pharmacokinetic considerations can explain the retention of adolescent-typical responsiveness to ethanol into adulthood.

The balance of excitation and inhibition in neural circuits undergoes dynamic regional changes during adolescence and other critical developmental periods, and is markedly influenced by ethanol. This interplay between excitatory and inhibitory processes during adolescence has been shown to play a critical role in driving the timing and duration of critical periods and the developmental neuroplasticity (see Hensch & Fagiolini, 2004. Hensch, 2005), and has been suggested to be critical for normative cortical development during adolescence (O'Donnell, 2011; Selemon, 2013). Observations that AIE results in the persistence into adulthood of adolescent-typical increases in network excitability and decreases in tonic inhibition in the hippocampus may provide clues as to neural substrates underlying persisting adolescent-typical characteristics after AIE. That is, since acute ethanol prominently alters glutamatergic and GABAergic function, repeated exposure during adolescence may perturb this delicate balance, perhaps promoting the retention of adolescent-typical excitatory/inhibitory balances in specific regions and contributing to the persistence of certain adolescent-typical phenotypes. To date there has been limited

exploration of adolescent exposure effects on neural substrates that might underlie the perseverance of adolescent-typical phenotypic expression in brain regions other than the hippocampus. Clearly more work is needed.

Through highlighting examples of the retention of adolescent-typical phenotypes into adulthood after AIE, this review was designed to serve more as a "call to action" than as a summary of a well-characterized and established phenomenon. While instances of persisting adolescent-typical phenotypes have emerged behaviorally, electrophysiological, neurally, and under both baseline and ethanol challenge conditions, these effects are not always evident, with AIE effects reported in a number of studies that do not resemble adolescent-typical phenotypes (e.g., see Broadwater & Spear, 2014b; Alaux-Cantin et al, 2013; Varlinskaya et al, 2014). Work remains to distinguish the circumstances under which adolescent phenotypic expression does and does not persist after AIE, and determine the mechanisms underlying these differences. To provide information relevant to such studies, investigators must know the ontogeny of the dependent measures under investigation, and that information is not always available or feasible to collect in some cognitive tasks (e.g., in cases involving extended training that might exceed the time constraints of adolescence in rodent models). And when it is possible to collect this information, it may not necessarily be so simple as testing adolescents in a task designed for adults; rather, consideration of the particular ontogenetic niche of the adolescent may lead to necessary modifications of experimental parameters, including size and sensory attributes of the test apparatus, training conditions, physiological constraints, or motivational state. Of course, to conclude that a particular dependent measure represents the retention of an adolescent-typical phenotype after AIE, it is important to determine the specificity of this effect for adolescent exposure *per se* – i.e., to demonstrate that this effect is specific to AIE and not likewise evident after CIE. Timing of the AIE exposure during adolescence may also be critical, with sometimes different consequences observed after AIE during early-mid versus late adolescence (see Varlinskaya et al, 2014).

Ultimately it may be of interest to determine the degree to which these findings are specific to ethanol, or are approximated by other adolescent experiences. The balance of excitation to inhibition is influenced during adolescence not only by ethanol but also under some circumstances by alterations in sensory input, stressors, and drugs other than alcohol (Turrigiano & Nelson, 2004; Romeo & McEwen, 2006; Carpenter-Hyland & Chandler, 2007). Moreover, the retention of adolescent-typical phenotypes into adulthood after adolescent exposure may potentially be evident with some other drugs as well. For example, both "normal" adolescent rats as well as adult rats previously exposed to nicotine during adolescence were found to self-administer more nicotine intravenously (and to be less sensitive to the appetite and weight suppressing effects of nicotine) than adults that were not exposed to nicotine as adolescents (Natividad et al, 2013). The enhancement of nicotine self-administration in adulthood after prior nicotine exposure was found to be specific to adolescent exposure, with rats exposed to nicotine during mid-adolescence (P34–43) but not late-adolescence/early adulthood (P60–69) exhibiting greater nicotine self-administration in adulthood (Adriani et al, 2003). Is it possible that retention of an adolescent-typical phenotype may also emerge after repeated exposure to drugs other than ethanol during

adolescence? Substantially more work is needed to determine the degree to which the maturing brain may be modified by adolescent use of ethanol (and possibly other drugs) to result in the persistence of specific adolescent characteristics into adulthood, and the mechanisms underlying these long-term alterations.

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Highlights

- Some adolescent-like phenotypes persist in adults after adolescent ethanol exposure
- As adults, exposed animals often continue to respond to alcohol like adolescents do
- These persisting phenotypes are seen behaviorally, cognitively, and neurally
- Similar effects are typically not seen when exposure is delayed until adulthood
- These lasting alterations may be related to shifts in excitatory/inhibitory balance

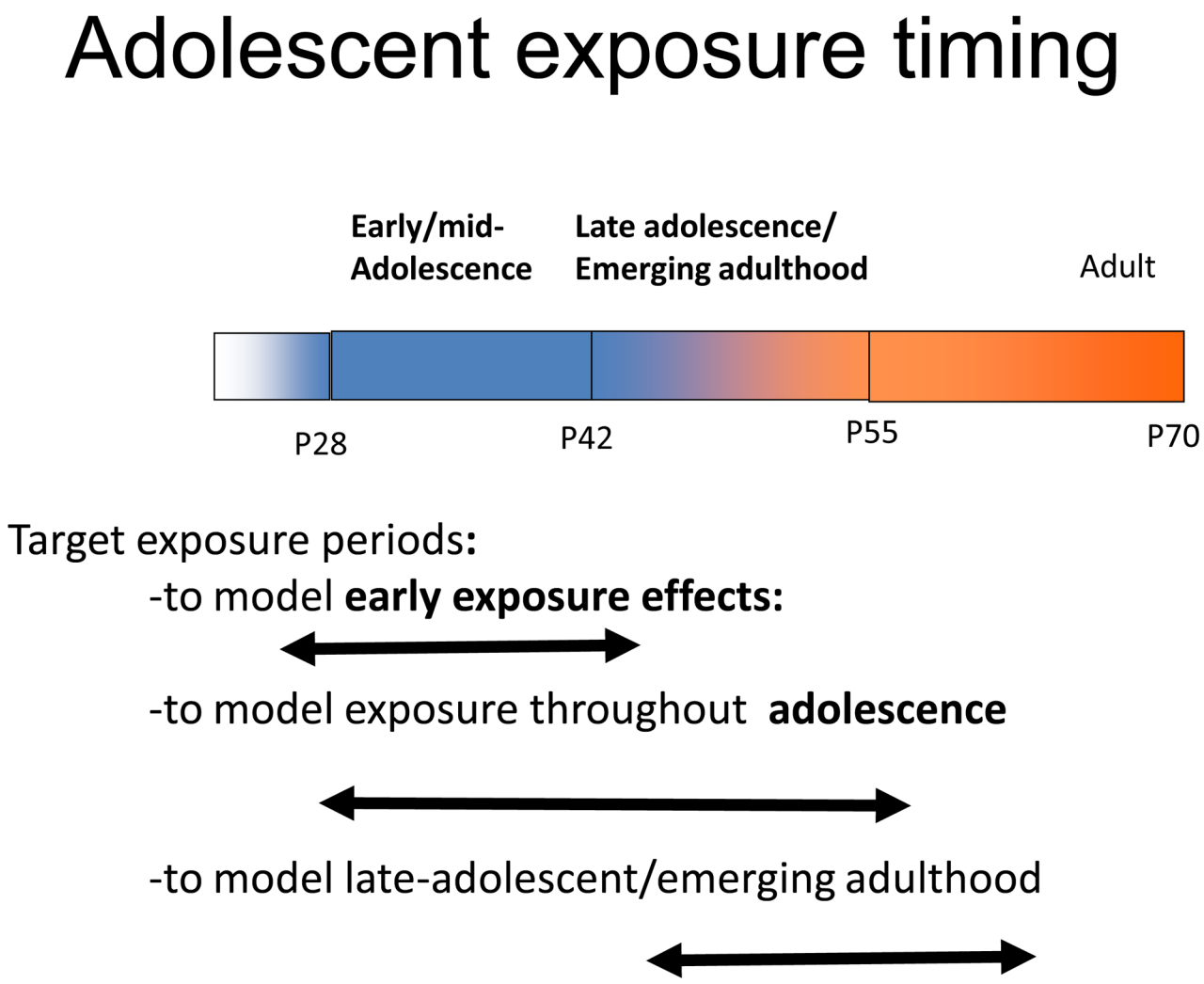

Figure 1.

Illustration of typical exposure periods in studies using laboratory rodents to assess effects of adolescent ethanol exposure either during early adolescence, throughout adolescence, or during the late adolescent/“emerging adulthood” period.

Table 1

Studies showing retention of adolescent-typical phenotypes into adulthood after adolescent intermittent ethanol exposure (AIE)

Study	Timing*	Exposure Pattern	Route (dose)	Strain**	Adolescent-typical phentoype retained into adulthood***
Alaux-Cantin et al (2013)	P30–43 (not evident P45–58)	2 days on; 2 days off	i.p. (3 g/kg)	SD	elevated home cage ethano (EtOH) consumption attenuated EtOH conditioned taste aversion (CTA) increased motivation for EtOH's rewarding effects
Broadwater & Spear (2013b)	P28–42	every other day	30 min. access to sweetened EtOH solution	SD	elevated voluntary EtOH consumption
Broadwater & Spear (2014)	P28–48*	every other day	i.g. (4g/kg)	SD	immature pattern of potentiation of context fear by tone conditioning
Diaz-Granados & Graham (2007)	P28–31 or 32*	contin. for 64 hr. or 16 hr. on/8 hr. off (effects greater w/intermittent) [Blood Alcohol Content (BAC) ~110mg/dl]	vapor	C3H mice	attenuated EtOH CTA
Ehlers et al (2013)	P23–58	14 hr on/10 hr off/day (BAC~165mg/dl)	vapor	W	more "disinhibitory" behavior in open field conflict
Ehlers et al (2014)	P24–59	14 hr on/10 hr off/day (BAC ~ 175mg/dl)	vapor	W	insensitivity of P3 latency to acute EtOH
Fleming et al (2012)	P30–50 [not evident P50–70* (Fleming et al, 2013)]	2 days on; 2 days off	i.g. (5g/kg)	SD	reduced GABAAR-mediated tonic current (TC) enhanced TC EtOH sensitivity
Gilpin et al (2012)	P28–42	every 3 days	4 pds. of 30 min access to sweetened EtOH	W	elevated voluntary EtOH consumption (intermittent access) increased impulsivity (elevated plus maze)
Matthews et al (2008)	P30–50	every other day	i.p.(1,2,3 or 4 g/kg)	SD	attenuated senstivity to EtOH-induced sedation
Quoilin et al (2012)	P28–42	daily	i.p. (2.5,4 g/kg)	Swiss mice	attenuated sensitivity to EtOH-induced sedation