Published in final edited form as:
Alcohol Clin Exp Res. 2014 October ; 38(10): 2509–2516. doi:10.1111/acer.12531.

Age-Related Effects of Alcohol from Adolescent, Adult, and Aged Populations Using Human and Animal Models

Lindsay M. Squeglia,
Department of Psychiatry, University of California San Diego, San Diego, California

Jeff Boissoneault,
Department of Psychiatry, University of Florida, Gainesville, Florida

Candice E. Van Skike,
Department of Psychology & Neuroscience, Baylor University, Waco, Texas

Sara Jo Nixon, and
Department of Psychiatry, University of Florida, Gainesville, Florida

Douglas B. Matthews
Department of Psychology & Neuroscience, Baylor University, Waco, Texas; Division of Psychology (DBM), Nanyang Technological University, Singapore City, Singapore

Abstract

Background—This review incorporates current research examining alcohol's differential effects on adolescents, adults, and aged populations in both animal and clinical models.

Methods—The studies presented range from cognitive, behavioral, molecular, and neuroimaging techniques, leading to a more comprehensive understanding of how acute and chronic alcohol use affects the brain throughout the life span.

Results—Age of life is a significant factor in determining the effect of alcohol on brain functioning. Adolescents and aged populations may be more negatively affected by heavy alcohol use when compared to adults.

Conclusions—Investigations limiting alcohol effects to a single age group constrains understanding of differential trajectories and outcomes following acute and chronic use. To meaningfully address the sequencing and interaction effects of alcohol and age, the field must incorporate collaborative and integrated research efforts focused on interdisciplinary questions facilitated by engaging basic and applied scientists with expertise in a range of disciplines including alcohol, neurodevelopment, and aging.

Keywords

Alcohol; Animal Model; Development; Cognition; Neuroimaging

Reprint requests: Lindsay M. Squeglia, PhD, Department of Psychiatry, University of California San Diego, 8950 Villa La Jolla Drive, San Diego, CA 920037; Tel.: 858-822-2306; Fax: 858-822-3933; lsquegli@ucsd.edu.

Present address: Douglas B. Matthews, Department of Psychology, University of Wisconsin – Eau Claire, Eau Claire, WI.

Alcohol is the most commonly used substance across the life span, with alcohol use typically initiated during adolescence, escalating and peaking during early adulthood, and abating through later life (National Epidemiologic Survey on Alcohol and Related Conditions, 2010). Over this same period of time, the brain undergoes significant structural and functional changes, with substantial neurodevelopment occurring between adolescence and the third decade of life, followed by neural restructuring and atrophy beginning in older age (Simpkins and Simpkins, 2013). For the purpose of this review, human adolescence is defined as 12 to 18 years, which corresponds to an animal age of postnatal 28 to 42 days; adulthood refers to human ages 25 to 54 years, which corresponds to an animal age of 70 days to 15 months; and aged adults refers to humans 55+ years, which corresponds to an animal age of 18+ months (Spear, 2000). Not surprisingly, the effects of alcohol on brain functioning differ based on the developmental period when alcohol use was initiated, as well as the ages over which drinking persists. This mini-review expands on existing studies (Welch et al., 2013) by incorporating the most current research examining alcohol's differential effects on adolescents, adults, and aged populations in both animal and clinical models. While prenatal alcohol exposure is an important developmental concern (Riley et al., 2011), this review focuses on alcohol exposure between the ages when alcohol is most commonly used (i.e., adolescence to older adulthood). The overall goal is to present areas of similarity regardless of experimental system and highlight areas of needed research.

The first section of the review focuses on recent adolescent clinical findings. Studies suggest aberrations that exist in human adolescent brain structure and function before initiating heavy substance use are predictive of future substance use, while subsequent alcohol use is related to worsening brain function. The second section reviews the adolescent animal literature, suggesting behavioral and preexisting neurobiological factors might explain heavy alcohol use in adolescents. The third section reviews neurocognitive and neuroimaging findings from human older adults, which suggest that acute alcohol use in aged populations is related to worse cognitive functioning and aberrations in neural response patterns that differ from younger adults. Finally, the last section describes recent findings in aged rats that provide the beginnings of an animal model to study impaired cognitive processing produced by alcohol in the aged population.

The effects of alcohol are complex. However, if these effects are to ever be understood, research must integrate age with clinical and preclinical research into a unified framework. We hope this mini-review is a step in that direction.

The effect of alcohol on human adolescent brain development: *Lindsay M. Squeglia*

Alcohol use is typically initiated during adolescence (Johnston et al., 2014), a stage when the brain undergoes significant neurodevelopment (Giedd and Rapoport, 2010; Somerville and Casey, 2010). Previous research suggests alcohol use is related to poorer cognitive functioning in human adolescents (Squeglia et al., 2009a); but due to the cross-sectional nature of these studies, it is unclear whether brain differences predate alcohol use or were a consequence of drinking.

Recent longitudinal neuropsychological studies have shown that cognitive differences both predate and precede heavy alcohol use. One prospective study examined neurocognitive functioning in 175 substance naïve healthy 12- to 14-year-olds, and assessed participants' alcohol use each year into late adolescence. By ages 17 to 18, 105 participants transitioned into heavy alcohol use, which was defined as typically having 4 or more drinks on an occasion several times per month (for exact classification coding, see Squeglia et al., in press). Findings suggest that compromised inhibitory functioning during early adolescence, prior to the onset of substance use, was related to greater subsequent alcohol use by age 18, and sex did not moderate effects (Squeglia et al., in press). In another prospective study, substance naïve adolescents performed neuropsychological testing at baseline and a 3-year follow-up, at which time approximately half of the sample transitioned to heavy or moderate drinking. For girls, more drinking days over the follow-up interval predicted worsening visuospatial performance; for boys, greater hangover symptoms were associated with declining sustained attention (Squeglia et al., 2009b). These cognitive disadvantages appear to persist into young adulthood (approximately age 24), particularly in regard to attention, visuospatial, and memory abilities (Hanson et al., 2011; Tapert et al., 2002). Taken together, these findings suggest that compromised inhibition, perhaps due to preexisting neurobiological differences, precedes heavy alcohol use, while alcohol use itself is associated with worsening cognitive functioning, particularly in regard to spatial and attentional processing, with deficits persisting into young adulthood.

Imaging studies have begun to elucidate the neurobiological underpinnings of the cognitive differences observed both pre- and postsubstance use initiation. Recent prospective studies have shown preexisting differences in neural activation prior to adolescent engagement in substance use. Specifically, brain activation patterns have been able to predict future alcohol use, episodes of memory loss during drinking (“blackouts”), and substance use disorder symptomatology (Jacobus and Tapert, 2013). In a prospective study of 12- to 14-year-old adolescents who underwent functional magnetic resonance imaging before initiation of alcohol use, adolescents who transitioned into heavy alcohol use by age 18 had lower brain activation at baseline in frontal, temporal, and parietal cortices in response to a go/no-go task of response inhibition than matched controls (Norman et al., 2011). In a separate longitudinal study, 12- to 16-year-old adolescents were scanned before they ever used any alcohol or drugs and then were rescanned approximately 3 years later (Squeglia et al., 2012). Adolescents who transitioned into heavy drinking by late adolescence (approximately age 18) showed less brain activation during a visual working memory task at baseline in frontal and parietal regions than demographically matched controls; this local brain response increased after the initiation of heavy alcohol use. Lower baseline activation predicted future alcohol use above and beyond common predictors of substance use, consistent with previous findings suggesting neural abnormalities predate initiation of heavy substance use (Norman et al., 2011). Taken together, these studies suggest that neural differences both predate and precede heavy drinking, mirroring the behavioral findings from neuropsychological studies (Squeglia et al., 2009b, in press).

White matter abnormalities have also been shown to contribute to risky behaviors such as substance use. In a prospective study of 96 adolescents, poorer frontolimbic white matter integrity at age 16 to 18 was linked to more risk-taking behaviors, including substance use

frequency and externalizing behaviors (e.g., fighting, truancy, driving dangerously) at an 18-month follow-up (Jacobus et al., 2013). In a longitudinal follow-up, 91 adolescents were followed for 18 months and given another diffusion tensor imaging scan. Alcohol use during the 18-month follow-up related to worsening white matter integrity in frontal association fiber tracts (Bava et al., 2013). In sum, lower white matter integrity may precede and follow substance use during adolescence. Taken together with the functional imaging findings, these results suggest that neural response patterns may be risk factors for future initiation of substance use, and that heavy drinking during adolescence is associated with subtle alterations in brain functioning.

In sum, neurocognitive abnormalities both precede *and* follow heavy substance use in clinical populations, an important point that was not established until very recently. Further work with larger populations is needed to increase statistical power to observe moderating effects of other variables (e.g., sex) and help advance the understanding of the relationship between alcohol exposure and brain functioning. Recent cross-sectional findings suggest binge drinking (i.e., 4 or more drinks on an occasion for females, 5 or more for males) affects neurobiology in emerging adult populations (Doallo et al., 2014; Mashhoon et al., 2014; Silveri et al., 2014). The studies presented are following the youth into early adulthood (ages 18 to 24) to further clarify how changing drinking patterns affect neural development over time. Despite the advances in human clinical work, the specific nature of the neurocognitive and neurobiological abnormalities will be difficult to completely determine in clinical populations (particularly given the variability in adolescents' frequency and quantity of alcohol use), and therefore there is a strong need for animal studies to further identify preexisting brain states that may result in altered alcohol responses.

Biological correlates of age-dependent alcohol-induced impairments in rats: *Candice E. Van Skike*

Animal models have demonstrated that adolescents respond uniquely to alcohol compared to adults. Similar to findings from human adolescents (see Squeglia section), these age-dependent differences in alcohol administration suggest that adolescents who consume alcohol have a neurobiological predisposition toward excessive drinking.

In humans, alcohol-induced motor impairments and sedative effects often serve as feedback cues to attenuate alcohol consumption (Spear and Varlinskaya, 2005). However, adolescents and adult rats exhibit differing degrees of behavioral sensitivity to acute alcohol administration. Data suggest that these differences may be due to preexisting age-dependent neurobiological differences in brain electrophysiology, protein kinase activity, and pharmacokinetics (Van Skike et al., 2010). For instance, 20 minutes postacute alcohol challenge, adolescent rats have significantly higher blood alcohol levels and display reduced motor impairments compared to adults. Based on a variety of work, including preclinical work demonstrating that preexisting neurobiological differences in adolescence predict alcohol responsiveness, we identified a particular neurological correlate that may underlie this age-dependent difference in alcohol-induced motor impairments. Specifically, the in vivo firing rate of adolescent rat cerebellar Purkinje neurons was insensitive to acute ethanol (EtOH)-induced suppression, while the basal firing rate from adult Purkinje neurons was

significantly reduced (Van Skike et al., 2010). The differential electrophysiological effects of alcohol due to age are reminiscent of the preexisting neurological differences in human adolescents and adults. Furthermore, adolescent rats have significantly reduced protein kinase C gamma (PKCγ) expression, a protein that phosphorylates gamma-aminobutyric acid type A ($GABA_A$) receptors and increases the effect of alcohol in the cerebellum and whole cortex compared to adult rats (Van Skike et al., 2010). PKCγ-null mice display decreased sensitivity to acute EtOH-induced motor impairments (Harris et al., 1995), which resembles the behavioral profile of the adolescent rat. The preexisting differences in cerebellar electrophysiology and molecular composition appear to lay a biological foundation for excessive drinking (as reviewed in Squeglia) where the physiological feedback cues to attenuate EtOH consumption are reduced, permitting the high incidence of binge-like drinking seen during human adolescence and young adulthood.

Similar age-dependent biological differences likely underlie the increased propensity toward future alcohol use disorders among adolescents compared to adults, as alcohol exposure during adolescence produces long-lasting alterations in brain and behavior. Mounting evidence suggests human adolescents are especially vulnerable to alcohol-induced neurotoxicity (Squeglia et al., 2009a). Animal models indicate chronic intermittent alcohol exposure during adolescence yields persistent reductions in hippocampal volume lasting into adulthood, even after 10 weeks of abstinence (Ehlers et al., 2013b). This long-lasting alteration in hippocampal morphology produced by chronic intermittent alcohol exposure during adolescence is likely due to reduced cell proliferation and increased cell death, which are also present after nearly 7 weeks of abstinence (Ehlers et al., 2013a). This same study revealed that these changes are correlated with persistent increases in disinhibitory behavior in the open field conflict test. Thus, these findings indicate that chronic intermittent alcohol exposure restricted to peri-adolescence produces long-lasting alterations of brain and behavior that persist into adulthood. Given the clinical work showing that alcohol exposure during adolescence leads to altered attentional processing (Squeglia et al., 2009b), future animal work needs to identify brain changes underlying these behavioral changes.

Some research has begun to address subunit alterations involved in addiction neurocircuitry specific to adolescence that may contribute to the persistent behavioral changes produced by adolescent alcohol exposure. Preliminary data from our laboratory has found age-dependent alterations in both NMDA and $GABA_A$ receptor subunits in the whole cortex and hippocampus. These age- and brain-region-specific receptor subunit alterations were accompanied by a prolonged increase in anxiety-like behavior on the elevated plus maze in adolescent and adult rats both 24 hours and 12 days postwithdrawal from the final chronic intermittent alcohol exposure. This study, along with others (Pian et al., 2010), suggests that persistent age-dependent changes in receptor subunits may alter future responsiveness to EtOH.

In addition to the persistent brain changes produced by alcohol use during adolescence, recent research indicates certain epigenetic factors may also contribute to alterations in future alcohol sensitivity. For instance, alcohol exposure during adolescence produces age-dependent alterations of histone acetylation and methylation in the frontal cortex, which are associated with persistent alterations in acquisition, extinction, and reinstatement of place

conditioning, especially during adolescence (Pascual et al., 2012). These modifications appear to alter gene expression related to alcohol-induced behavioral and neural plasticity of the adolescent brain to produce long-term behavioral consequences that may mediate the progression toward future alcohol use disorders.

These recent animal studies support and extend human work showing that adolescents have preexisting neurobiological factors that predispose them to increased alcohol intake through reduced behavioral responses such as ataxia. Given most people who consume alcohol do so throughout the life span, it is important to determine to what extent other periods of the life span, such as older adulthood and the aged, also demonstrate altered responses to alcohol.

Acute Moderate Alcohol Effects on Neurobehavioral Function in Older and Younger Social Drinkers: *Jeff Boissoneault*

Alcohol use is common among older adults, with 53% of adults 55 to 64 years of age and 41 % over the age of 65 reporting having consumed at least 1 drink in the past 30 days. In contrast to adolescent typical drinking patterns, the majority of older drinkers (65 to 80%) are moderate in their alcohol consumption (Substance Abuse and Mental Health Services Administration, 2013). Thus, a thorough understanding of the acute cognitive and behavioral effects of moderate alcohol use in older adults is needed, especially given the recent focus on potential benefits of a moderate drinking lifestyle (Djoussé et al.,2009).

Unfortunately, little attention has been directed to the acute effects of moderate alcohol consumption in older adults (i.e., those ≥55 years of age). However, a large literature focused primarily on young adult drinkers (approximately 18 to 35) demonstrates breath alcohol concentrations (BrACs) of <0.08 g/dl produce a range of performance deficits observed most consistently in tasks with strong attentional demands (for review, see Fillmore, 2007). Given alcohol consumption rates in the aged population and the dearth of research in this stage of the life span, it is critical to investigate whether such performance impairments also exist in older adults.

Gradual, subclinical cognitive decline is a recognized consequence of normal aging. Indeed, both structural (e.g., ventricular expansion) and functional (e.g., increased bilateral activation of the prefrontal cortices during effortful processing) changes in the brains of older adults are well documented (for review, see Drag and Bieliauskas, 2010). Combined with age-related declines in lean muscle mass and increased body fat (Davies and Bowen, 1999), older adults may be especially vulnerable to alcohol-induced cognitive and behavioral alteration. The few studies examining this possibility have largely utilized legally intoxicating doses and task modalities relatively insensitive to potentially subtle effects of age and alcohol. Consequently, these studies have produced an inconsistent pattern of results (for review, see Sklar et al., 2014). Critically, both aging and acute alcohol administration are associated with speed–accuracy tradeoffs; evidence from the aging literature suggests older adults tend to sacrifice speed to maintain accuracy (Carriere et al., 2010). In contrast, acute alcohol administration is associated with the trading of accuracy for speed (Acons et al., 2006). Thus, cognitive efficiency, or the ability to work quickly and accurately at the

same time, represents a critical component process upon which age and acute alcohol may interact.

Recently, several analyses from a double blind, placebo controlled study directly compared the neurobehavioral consequences of moderate alcohol doses (peak BrACs of 0.04 g/dl; approximately 2 standard drinks) between healthy older (55 to 74 years of age) and younger (25 to 35 years of age) adults. Importantly, the dosing strategy employed accounted for age, height, weight, and sex, ameliorating concerns regarding age-related changes in alcohol distribution and metabolic rate as potential confounds. In initial analyses, alcohol-related performance deficits in a working memory and set-shifting task were identified in older, but not younger, adults (Gilbertson et al., 2009). Older adults showed poorer awareness of their behavioral impairment, with lower ratings of perceived impairment than younger adults on the ascending limb when their performance was impaired, but greater perceived impairment on the descending limb when their performance was equivalent (Gilbertson et al., 2009). The mechanism for this effect is unclear, but may reflect age-related declines in the strength of alcohol expectancies (Satre and Knight, 2001). Considering profiles of expectancies, versus simply the magnitude of positive and negative expectancies, may be especially important for understanding drinking behaviors in older adults (Nicolai et al., 2012). Of particular note, expectation of impairment declined less with age than any other expectancy (Nicolai et al., 2012). The potential application of this finding to explaining older adults' dissociation of perceived and measured impairment following moderate alcohol administration should be investigated.

The cohort's performance subsequent to alcohol administration was also examined using an adaptation of Posner's covert attention task (Luck et al., 1994). This task has been shown to be sensitive to changes in cognitive efficiency due to both acute alcohol (Tiplady et al., 2001) and age (Salthouse, 1979). Results revealed a speed–accuracy trade-off in older adults receiving an active alcohol dose (Sklar et al., 2012). This trade-off was not found in older adults receiving placebo or in either group of younger adults. However, further analysis revealed older adults given placebo, who believed they had received alcohol, displayed trade-offs similar to those given the active dose (Gilbertson et al., 2010).

In further analyses, the effects of age, alcohol, and their interaction on the event-related potential evoked by target presentation in the covert attention task were investigated (Lewis et al., 2013). The P300 (P3) component was of particular interest because it reflects higher order working memory and attentional processes; alteration of P3 amplitude and latency may reflect disruption of processes not apparent in behavioral measures. Results indicated that peak BrACs of 0.04 g/dl produced large reductions in P3 amplitude in older, but not younger adults. Furthermore, alcohol was associated with a moderate increase in P3 latency for older adults, whereas younger adults showed a moderate decrease.

Taken together, these reports provide initial evidence of older adults' differential susceptibility compared to young adults to a moderate alcohol-related impairment. This susceptibility, particularly with regard to speed–accuracy tradeoffs, may represent active coping in response to expectation of moderate alcohol-related impairment. Evidence of older adults' altered profile of expectancies provides support for this idea.

These studies are limited by the narrow set of tasks utilized, use of a single active dose level (0.04 g/dl), reliance on a single cohort of participants, and the inability to identify specific neurobiological mechanisms underlying impairments. The results of a larger follow-up study partially address these limitations, providing further evidence of older adults' increased sensitivity to the effects of low alcohol doses (i.e., 0.04 g/dl) and extending previous studies by demonstrating that a higher but still subintoxicating dose level (0.065 g/dl) produces differential effects for older adults. The nature of these effects depends on task type (e.g., psychomotor, set-shifting, or working memory) and whether behavioral end point measures or component processes like cognitive efficiency are assessed (Boissoneault et al., in press). For example, older adults' behavioral efficiency and accuracy, but not reaction time, were improved at the low dose, but only for a specific stimulus type (hits). Importantly, data from this project also reveal age and acute alcohol interactions on simulated driving performance, with older adults showing impaired performance on several measures related to driving ability (Sklar et al., 2014). Data from this study will help to better inform social drinkers and policy makers of the potential neurobehavioral consequences of moderate alcohol consumption and how they may change with increasing age. Notably, few studies have addressed potential interactions of sex with age and acute alcohol on neurobehavioral function. Additional studies addressing this gap in the literature would be beneficial.

The effects of alcohol are exacerbated in aged rats; implications for aged humans: *Douglas B. Matthews*

As previously reviewed by Squeglia and Van Skike, preexisting neurocognitive and neurobiological conditions are important factors influencing the various effects of alcohol across the life span. Specifically, prenatal or early postnatal EtOH exposure produces long-term changes in a variety of measures and adolescents can be more or less sensitive to the effects of alcohol compared to adults (for review, see Chin et al., 2010). Generally, this research has replicated and extended the clinical work by providing potential neurobiological mechanisms by which alcohol produces effects that are age dependent.

In addition to the developing framework for alcohol's effects in prenatal and adolescent subjects, the clinical literature as reviewed by Boissoneault has demonstrated that aged individuals show greater responsiveness to alcohol, including the effects of acute alcohol. Given the unprecedented increase in the aged population worldwide (Kinsella and He, 2009) and the increase in alcohol consumption in this age group (Blazer and Wu, 2009), understanding potential neurobiological factors by which alcohol affects this targeted population is critical.

Previous work has demonstrated that aged rats are more sensitive to high-dose alcohol-induced hypnosis compared to adult rats (Ott et al., 1985). However, little research has been conducted that investigates the effects of acute alcohol on motor impairments and cognition in aged animals. In humans, research using cognitive tasks such as working memory and set shifting have shown that these tasks are more profoundly affected by alcohol in aged subjects compared to adult subjects (Gilbertson et al., 2009). Therefore, to better understand the neurobiological mechanisms by which alcohol produces greater cognitive impairments in aged populations, the development of appropriate animal models are needed.

Recently we have begun investigating if acute alcohol produces greater cognitive impairments in aged rats compared to adult rats. In addition, we have also been investigating if alcohol produces greater motor impairments in aged rats compared to adult rats. Initially we determined the effect of a single moderate 2.0 g/kg alcohol dose on the aerial righting reflex (ARR) in rats across 4 different ages (preadolescents, adolescents, adults, and aged; Van Skike et al., 2010). As expected based on previous research (Spear and Varlinskaya, 2005) peri-adolescent and adolescent rats displayed less ARR impairment (e.g., required less height to right themselves) than adult rats and aged rats. Furthermore, aged rats were slightly more impaired than adult rats indicating that age-related changes in the motor impairments produced by alcohol extend across the entire life span. However, this study was not designed to specifically address the difference between aged rats and adult rats, even though we noticed a trend suggesting aged rats were more impaired than adult rats. Therefore, we directly tested the hypothesis that aged animals are more sensitive to alcohol-induced motor impairments using 2 different behavioral procedures. The previous work from our laboratory was replicated and extended by demonstrating that aged rats show profound alcohol-induced motor impairments in both the ARR and accelerating rotarod tasks compared to adult rats, and that this effect is dose dependent (Novier et al., 2013). We also investigated if aged rats show greater cognitive impairments compared to adult rats by using the spatial version of the Morris water maze. As predicted, based on reports showing greater cognitive impairments in aged humans versus adult human subjects following alcohol (Gilbertson et al., 2009), we found that acute alcohol produces a greater impairment in the cognitive performance of aged rats compared to adult rats. The cognitive results are in general agreement with the human literature reviewed by Boissoneault and coupled with the motor impairment results provide the foundation of developing an animal model to explore the deleterious effects of alcohol in aged populations.

One significant limitation of the previously reviewed work is that humans typically do not experience alcohol intoxication for the first time when they are elderly. Consequently, an animal model that only exposes subjects to alcohol when they are aged could produce data that does not have explanatory validity as it relates to the human alcoholic condition. For instance, it is possible which developmental stage (adult or aged) that animals are exposed to acute alcohol is not a critical factor producing the increased motor impairing and increased spatial memory impairments in aged rats, but, instead the differences are due to the lack of long-term chronic alcohol exposure. While there is some previous research demonstrating that 14 days of chronic EtOH exposure leads to greater EtOH withdrawal in mice (Wood et al., 1982) and that long-term EtOH consumption (approximately 18 months) can cause impaired cognitive learning in rats (Baird et al., 1998), there is little research in rodents investigating if persistent changes in alcohol responsiveness across the life span occur due to alcohol exposure during adolescence. To address this knowledge gap and build upon the adolescent work reviewed by Squeglia and Van Skike, we have an ongoing research project where male rats are administered alcohol in a binge-like fashion during adolescence, and then receive a battery of motor and cognitive tests every 4 months throughout their life span following an acute EtOH challenge. Preliminary data (through the first 9 months of life) indicate that alcohol exposure during adolescence can produce profound motor and

cognitive impairments immediately following treatment and subtle motor and cognitive alterations that can last into adulthood.

Age is a significant factor for determining the impact that alcohol has on an individual, whether it is during adolescence, adulthood, or aging. Clinical research with elderly populations has shown that alcohol can exacerbate motor impairments and increase cognitive deficits associated with normal aging. Recently, research in animals has also provided viable models to begin to explore both the short-term consequences of alcohol use in aged populations and the long-term consequences of alcohol use during adolescence. In the next several years, research needs to focus on developing a translational focus on the effect of alcohol in aged populations.

Discussion: Sara *Jo Nixon*

In constructing the symposium guiding this mini-review, we noted that most research investigating alcohol effects and age retained an age-specific focus and many were restricted to either preclinical or clinical investigations. There are practical and scientific reasons for this approach. Focusing on 1age group facilitates a more complete understanding of the neurobiological and psychosocial factors that may affect that specific group. In turn, such findings can be particularly useful in directing policy recommendations and clinical developments concerning the defined group. However, continuing to examine alcohol effects only within defined groups prohibits the ability to consider sequencing effects and interactions; that is, it constrains understanding of differential trajectories and outcomes.

There are also practical and conceptual reasons for conducting preclinical or clinical work. Sustaining both preclinical and clinical laboratories relevant to any scientific question is complicated by varying training and oversight requirements, animal/participant costs, the availability of trained personnel, and, often, the absence of a shared scientific vocabulary. As scientists in the field, we have yet to solve these challenges.

There is exceptional alcohol-related clinical and preclinical work being conducted in the areas of prenatal exposure, adolescence, emerging adults, adults, and even aging adults. In this review, we focused on only a subset of areas. The presentations provided critical information regarding specific development issues, exposure concerns, and neurobehavioral outcomes. Taken together, it is clear that programmatic animal and human work directed to common questions and using parallel methods is a prerequisite for efficient scientific progression. As a mini-review, we are unable to provide an integrated summary. However, the presentations illustrated several key findings (see Table 1), which in turn, lead to additional questions and concerns. Here, we briefly explore 4 conclusions and potential research implications.

> Conclusion 1: Adolescent drinking is not necessarily a benign activity marking a developmental transition. This finding reflects a need for further understanding of (i) genetic risk and resiliency for binge drinking in adolescence, (ii) individual differences in neurodevelopment, (iii) use trajectories from initial exposure to problematic use, and (iv) psychosocial factors which may modulate initial exposure and use trajectories.

Conclusion 2: Directing questions to whether negative outcomes are due to alcohol exposure or to whether they result from preexisting aberrations (which may then be associated with alcohol misuse) are likely to provide only partial and potentially misleading answers. If we are to better characterize this bidirectional relationship, we must consider not only issues noted in Conclusion 1, but also epigenetic influences which would be predicted to be particularly relevant during adolescence and aging. An essential step is the iterative process of defining the most appropriate variables for study.

Conclusion 3: Age-related differences in response to alcohol exposure are neither uniform nor linear. There is insufficient data to direct the construction of a catalog of "appropriate" tests or to define all the factors which influence nonlinear effects. However, there are clues regarding the types of neurobehavioral systems that might be most sensitive.

Conclusion 4: Age-related differences in response to alcohol are not necessarily related to differential pharmacokinetics. We include this point to illustrate that relying on historical interpretations may not be effective. In short, we must question conventional conclusions as research initiatives expand.

In light of the intent of the symposium, we now ask, "What next"? Is it sufficient that scientists might periodically exchange preclinical and clinical age-related data? Alternatively, given the potential scientific, clinical, and policy implications of clarifying the effects of alcohol exposure from adolescence to older adulthood, might more formal initiatives be appropriate and if so, how would they be structured? We believe that continuing the dialogue is a necessary first step. However, if sequencing and interaction effects are to be meaningfully addressed, we must move toward collaborative and integrated efforts. These efforts will require an effective infrastructure and the potential for interdisciplinary progress facilitated by engaging basic and applied scientists with expertise in a range of disciplines including alcohol, neurodevelopment, and aging. We recognize that the proposed collaborations would require substantial fiscal support. However, we believe this investment would be justified; alcohol use from adolescence to older adulthood is more than a matter of scientific curiosity; it is a matter of individual and public health.

Acknowledgments

Grants F32 AA021610 (PI: LMS); F31AA019862 (PI: JB); R03 AA14039, R01 AA019802, R01 AA022456 (PI: SJN).

References

Acons K, Chan LS, Drummond G, Tiplady B. Effects of ethanol and promethazine on awareness of errors and judgements of performance. J Psychopharmacol. 2006; 20:661–669. [PubMed: 16401655]

Baird TJ, Vanecek SA, Briscoe RJ, Vallett M, Carl KL, Gauvin DV. Moderate, long-term, alcohol consumption potentiates normal, age-related spatial memory deficits in rats. Alcohol Clin Exp Res. 1998; 22:628–636. [PubMed: 9622443]

Bava S, Jacobus J, Thayer RE, Tapert SF. Longitudinal changes in white matter integrity among adolescent substance users. Alcohol Clin Exp Res. 2013; 37:E181–E189. [PubMed: 23240741]

Blazer DG, Wu LT. The epidemiology of at-risk and binge drinking among middle-aged and elderly community adults: national survey on drug use and health. Am J Psychiatry. 2009; 166:1162–1169. [PubMed: 19687131]

Boissoneault J, Sklar AL, Prather R, Nixon SJ. Acute effects of moderate alcohol on psychomotor, set shifting, and working memory function in older and younger social drinkers. J Stud Alcohol Drugs. in press.

Carriere JSA, Cheyne JA, Solman GJF, Smilek D. Age trends for failures of sustained attention. Psychol Aging. 2010; 25:569–574. [PubMed: 20677878]

Chin VS, Van Skike CE, Matthews DB. Effects of ethanol on hippocampal function during adolescence: a look at the past and thoughts on the future. Alcohol. 2010; 44:3–14. [PubMed: 20113870]

Davies BT, Bowen CK. Total body water and peak alcohol concentration: a comparative study of young, middle-age, and older females. Alcohol Clin Exp Res. 1999; 23:969–975. [PubMed: 10397280]

Djoussé L, Lee IM, Buring JE, Gaziano JM. Alcohol consumption and risk of cardiovascular disease and death in women: potential mediating mechanisms. Circulation. 2009; 120:237–244. [PubMed: 19597054]

Doallo S, Cadaveira F, Corral M, Mota N, López-Caneda E, Holguín SR. Larger mid-dorsolateral prefrontal gray matter volume in young binge drinkers revealed by voxel-based morphometry. PLoS One. 2014; 9:e96380. [PubMed: 24789323]

Drag LL, Bieliauskas LA. Contemporary review 2009: cognitive aging. J Geriatr Psychiatry Neurol. 2010; 23:75–93. [PubMed: 20101069]

Ehlers CL, Liu W, Wills DN, Crews FT. Periadolescent ethanol vapor exposure persistently reduces measures of hippocampal neurogenesis that are associated with behavioral outcomes in adulthood. Neuroscience. 2013a; 244:1–15. [PubMed: 23567812]

Ehlers CL, Oguz I, Budin F, Wills DN, Crews FT. Peri-adolescent ethanol vapor exposure produces reductions in hippocampal volume that are correlated with deficits in prepulse inhibition of the startle. Alcohol Clin Exp Res. 2013b; 37:1466–1475. [PubMed: 23578102]

Fillmore MT. Acute alcohol-induced impairment of cognitive functions: past and present findings. Int J Disabil Hum Devel. 2007; 6:115–126.

Giedd JN, Rapoport JL. Structural MRI of pediatric brain development: what have we learned and where are we going? Neuron. 2010; 67:728–734. [PubMed: 20826305]

Gilbertson R, Ceballos NA, Prather R, Nixon SJ. Effects of acute alcohol consumption in older and younger adults: perceived impairment versus psychomotor performance. J Stud Alcohol Drugs. 2009; 70:242–252. [PubMed: 19261236]

Gilbertson R, Prather R, Nixon SJ. Acute alcohol administration and placebo effectiveness in older moderate drinkers: influences on cognitive performance. J Stud Alcohol Drugs. 2010; 71:345–350. [PubMed: 20409427]

Hanson KL, Cummins K, Tapert SF, Brown SA. Changes in neuropsychological functioning over 10 years following adolescent substance abuse treatment. Psychol Addict Behav. 2011; 25:127–142. [PubMed: 21443308]

Harris RA, McQuilkin SJ, Paylor R, Abeliovich A, Tonegawa S, Wehner JM. Mutant mice lacking the gamma isoform of protein kinase C show decreased behavioral actions of ethanol and altered function of gamma-aminobutyrate type A receptors. Proc Natl Acad Sci USA. 1995; 92:3658–3662. [PubMed: 7731960]

Jacobus J, Tapert SF. Neurotoxic effects of alcohol in adolescence. Annu Rev Clin Psychol. 2013; 9:703–721. [PubMed: 23245341]

Jacobus J, Thayer RE, Trim RS, Bava S, Frank LR, Tapert SF. White matter integrity, substance use, and risk taking in adolescence. Psychol Addict Behav. 2013; 27:431–442. [PubMed: 22564204]

Johnston, LD.; O'Malley, PM.; Miech, RA.; Bachman, JG.; Schulenberg, JE. Monitoring the Future national survey results on drug use: 1975-2013 Overview, key findings on adolescent drug use. Institute for Social Research, The University of Michigan; Ann Arbor: 2014.

Kinsella, K.; He, W. An Aging World: 2008 (International Population Reports, P95/09-1). U.S. Government Printing Office; Washington, DC: 2009.

Lewis B, Boissoneault J, Gilbertson R, Prather R, Nixon SJ. Neurophysiological correlates of moderate alcohol consumption in older and younger social drinkers. Alcohol Clin Exp Res. 2013; 37:941–951. [PubMed: 23278355]

Luck SJ, Hillyard SA, Mouloua M, Woldorff MG, Clark VP, Hawkins HL. Effects of spatial cuing on luminance detectability: psychophysical and electrophysiological evidence for early selection. J Exp Psychol Hum Percept Perform. 1994; 20:887–904. [PubMed: 8083642]

Mashhoon Y, Czerkawski C, Crowley DJ, Cohen-Gilbert JE, Sneider JT, Silveri MM. Binge alcohol consumption in emerging adults: anterior cingulate cortical “thinness” is associated with alcohol use patterns. Alcohol Clin Exp Res. 2014; 38:1955–1964. [PubMed: 24961871]

National Epidemiologic Survey on Alcohol and Related Conditions. NIH Publications No. 10-7677. NIAAA; Rockville, MD: 2010. Alcohol Use and Alcohol Use Disorders in the United States, A 3-Year Follow-Up: Main Findings from the 2004-2005 Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), Alcohol Epidemiologic Data Reference Manual.

Nicolai J, Moshagen M, Demmel R. Patterns of alcohol expectancies and alcohol use across age and gender. Drug Alcohol Depend. 2012; 126:347–353. [PubMed: 22748519]

Norman AL, Pulido C, Squeglia LM, Spadoni AD, Paulus MP, Tapert SF. Neural activation during inhibition predicts initiation of substance use in adolescence. Drug Alcohol Depend. 2011; 119:216–223. [PubMed: 21782354]

Novier A, Van Skike CE, Diaz-Granados JL, Mittleman G, Matthews DB. Acute alcohol produces ataxia and cognitive impairments in aged animals: a comparison between young adult and aged rats. Alcohol Clin Exp Res. 2013; 37:1317–1324. [PubMed: 23550918]

Ott JF, Hunter BE, Walker DW. The effect of age on ethanol metabolism and on the hypothermic and hypnotic responses to ethanol in the Fischer 344 rat. Alcohol Clin Exp Res. 1985; 9:59–65. [PubMed: 3887970]

Pascual M, Do Couto BR, Alfonso-Loeches S, Aguilar MA, Rodriguez-Arias M, Guerri C. Changes in histone acetylation in the prefrontal cortex of ethanol-exposed adolescent rats are associated with ethanol-induced place conditioning. Neuropharmacology. 2012; 62:2309–2319. [PubMed: 22349397]

Pian JP, Criado JR, Milner R, Ehlers CL. N-methyl-D-aspartate receptor subunit expression in adult and adolescent brain following chronic ethanol exposure. Neuroscience. 2010; 170:645–654. [PubMed: 20603193]

Riley EP, Infante MA, Warren KR. Fetal alcohol spectrum disorders: an overview. Neuropsychol Rev. 2011; 21:73–80. [PubMed: 21499711]

Salthouse TA. Adult age and the speed-accuracy trade-off. Ergonomics. 1979; 22:811–821. [PubMed: 488072]

Satre DD, Knight BG. Alcohol expectancies and their relationship to alcohol use: age and sex differences. Aging Ment Health. 2001; 2001:73–83. [PubMed: 11513017]

Silveri MM, Cohen-Gilbert J, Crowley DJ, Rosso IM, Jensen JE, Sneider JT. Altered anterior cingulate neurochemistry in emerging adult binge drinkers with a history of alcohol-induced blackouts. Alcohol Clin Exp Res. 2014; 38:969–979. [PubMed: 24512596]

Simpkins, CA.; Simpkins, AM. Brain development through the life span. In Neuroscience for Clinicians: Evidence, Models, and Practice. Springer; New York: 2013. p. 151-164.

Sklar AL, Boissoneault J, Fillmore MT, Nixon SJ. Interactions between age and moderate alcohol effects on simulated driving performance. Psychopharmacology. 2014; 231:557–566. [PubMed: 24030469]

Sklar AL, Gilbertson R, Boissoneault J, Prather R, Nixon SJ. Differential effects of moderate alcohol consumption on performance among older and younger adults. Alcohol Clin Exp Res. 2012; 36:2150–2156. [PubMed: 22591190]

Somerville LH, Casey BJ. Developmental neurobiology of cognitive control and motivational systems. Curr Opin Neurobiol. 2010; 20:236–241. [PubMed: 20167473]

Spear LP. The adolescent brain and age-related behavioral manifestations. Neurosci Biobehav Rev. 2000; 24:417–463. [PubMed: 10817843]

Spear LP, Varlinskaya EI. Adolescence: alcohol sensitivity, tolerance, and intake. Recent Dev Alcohol. 2005; 17:143–159. [PubMed: 15789864]

Squeglia LM, Jacobus J, Nguyen-Louie TT, Tapert SF. Inhibition during early adolescence predicts alcohol and marijuana use by late adolescence. Neuropsychology. in press. Epub ahead of print.

Squeglia LM, Jacobus J, Tapert SF. The influence of substance use on adolescent brain development. J Clin EEG Neurosci. 2009a; 40:31–38.

Squeglia LM, Pulido C, Wetherill RR, Jacobus J, Brown GG, Tapert SF. Brain response to working memory over three years of adolescence: influence of initiating heavy drinking. J Stud Alcohol Drugs. 2012; 73:749–760. [PubMed: 22846239]

Squeglia LM, Spadoni AD, Infante MA, Myers MG, Tapert SF. Initiating moderate to heavy alcohol use predicts changes in neuropsychological functioning for adolescent girls and boys. Psychol Addict Behav. 2009b; 23:715–722. [PubMed: 20025379]

Substance Abuse and Mental Health Services Administration. Results from the 2012 National Survey on Drug Use and Health: Mental Health Findings, NSDUH Series H-47, HHS Publication No. (SMA) 13-4805. Substance Abuse and Mental Health Services Administration; Rockville, MD: 2013.

Tapert SF, Granholm E, Leedy NG, Brown SA. Substance use and withdrawal: neuropsychological functioning over 8 years in youth. J Int Neuropsychol Soc. 2002; 8:873–883. [PubMed: 12405538]

Tiplady B, Drummond GB, Cameron E, Gray E, Hendry J, Sinclair W, Wright P. Ethanol, errors, and the speed-accuracy trade-off. Pharmacol Biochem Behav. 2001; 69:635–641. [PubMed: 11509226]

Van Skike CE, Botta P, Chin VS, Tokunaga S, McDaniel JM, Venard J, Diaz-Granados JL, Valenzuela CF, Matthews DB. Behavioral effects of ethanol in cerebellum are age dependent: potential system and molecular mechanisms. Alcohol Clin Exp Res. 2010; 34:2070–2080. [PubMed: 20860615]

Welch KA, Carson A, Lawrie SM. Brain structure in adolescents and young adults with alcohol problems: systematic review of imaging studies. Alcohol Alcohol. 2013; 48:433–444. [PubMed: 23632805]

Wood WG, Armbrecht HJ, Wise RW. Ethanol intoxication and withdrawal among three age groups of C57BL/6NNIA mice. Pharmacol Biochem Behav. 1982; 17:1037–1041. [PubMed: 6891067]

Table 1
Preliminary Data from this Review are Presented Below

Adolescence	
Human (12–18 years)	**Animal (28–42 days)**
Preexisting differences:	Initiation of heavy alcohol use:
↓Cognitive inhibition	↓ Motor impairment
↓ Neural response	↓ Purkinje neuron response
Initiation of heavy alcohol use:	↓ Hippocampal volume
↓ Attention, visuospatial functioning	Age-specific alterations of protein expression in different brain regions
↑ Neural response in frontal regions	
↓ White matter integrity	
Adulthood (comparison group for older adulthood studies)	
Human (25–54 years)	Animal (70 days to ∼15 months)
Older Adulthood	
Human (>55 years)	Animal (> 18 months)
Acute moderate alcohol:	Acute alcohol:
*Set-shifting performance	↑ Motor impairment
*Cognitive efficiency	↓ Cognitive performance
↓ P3 amplitude	↑ Hypnotic effect
↑ P3 latency	↓ Hypothermia

*Preliminary evidence suggests the directionality and/or presence of these effects depends on both task and dose.

According to these studies, alcohol use in adolescence and aging is related to the following consequences. The table necessarily simplifies the complexity of reported findings and does not reflect the range of possible effects, especially regarding acute effects in older humans for whom the literature is scant. Further research and replication of results, as well as studies integrating human and animal models for more direct comparison, are warranted.