



Alcohol and Its Effect on Adolescent Brain Development and Executive Functioning: Some Results from Neuroimaging

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There exists considerable evidence from both human and experimental animals indicating the central nervous systems' vulnerability to the effects of alcohol exposure. Specifically, alcohol is a known neuroteratogen with especially harmful effect on developing brains. Given many adolescents abuse alcohol and their brains are still developing, this population may be vulnerable to alcohol's neurotoxic effects. In particular, executive functions may be especially vulnerable. The objective of this paper is to summarize what neuroimaging techniques reveal about alcohol's effect on executive functions in adolescence. This review synthesizes structural and functional neuroimaging studies on alcohol and executive functions. Results suggest that alcohol is associated with both acute and long-term impairment in executive functions. Finally, this review suggests that neuroimaging techniques reveal that alcohol is an especially harmful neuroteratogen which compromises executive functions in adolescence.

Defined as the second decade of life, adolescence is perhaps best conceptualized as a period of development marked by changes in physiology, personality, emotionality, and neurobiology that includes ages 8 through 20 in humans [1]. Research concerning brain development has revealed that several aspects of brain maturation may be linked to behavioral, emotional, and cognitive development during adolescence [2]. Although a rich body of research exists concerning adolescent brain development, the following review focuses specifically on alcohol and its effects on adolescent brain development and executive functioning. In particular, the purpose of the present paper is to review whether neuroimaging techniques reveal a relationship between alcohol exposure and compromised executive functioning during adolescent development.

Alcohol is the most commonly used drug during adolescence [3]. Alcohol is also a known neuroteratogen [4] whose deleterious effects on neurodevelopment were first described in the offspring of ethanol-abusing women [5]. Since then, [6] proposed that adolescence is an important developmental stage that is particularly vulnerable to the neurotoxic effects of alcohol. Specifically, functional magnetic resonance imaging (fMRI) has associated alcohol use with brain cell damage such as cell differentiation which can affect synaptic maturation and cell signaling [7,8]. More recently, [9] found that alcohol exposure causes brain cell damage and apoptosis. [10] also reported that alcohol and other drug use during adolescence can disrupt cortical brain development and brain function.

Overall, there exists a substantial literature from both human and experimental animals indicating the central nervous systems' vulnerability to the effects alcohol during brain ontogeny and, in particular, how alcohol exposure can cause irreversible abnormalities in neuroanatomy and physiology [11]. Moreover, alcohol is a neuroteratogen that appears to be especially harmful to developing brains. Given many adolescents abuse alcohol and their brains are still developing, this population may be especially vulnerable to the neurotoxic effects of alcohol. In particular, executive functions may be most vulnerable.

Executive Functions (EF)

Executive functions consist of those abilities which enable individuals to maintain an appropriate problem-solving set for attaining future goals and typically include strategic planning, impulse control, organized search, and flexibility of thought and action [12,13] define EF as a higher-order cognitive construct involved in the planning, initiation, and self-regulation of goal-directed behavior. [14] define EF as a set of cognitive skills that includes attention control, hypothesis generation, previewing, strategic planning, abstract reasoning, temporal response sequencing, cognitive flexibility, set shifting, and the ability to adaptively manipulate and process information in working memory. Others define EF as a set of abilities that includes working memory, inhibition, flexibility, and decision-making [15]. Overall, EF can be defined as a set of high-order cognitive capacities that includes planning, reasoning, flexibility, decision-making, and goal-oriented behavior.

Although EF has been historically used to describe a broad set of skills and abilities, recent research suggests that there are a number of executive sub-components each comprised of distinct anatomy and physiology. Fernandez-Serrano (2009) reviewed lesion research and functional neuroimaging studies and concluded that discrete executive mechanisms are endorsed by differentiated neural systems. For example, they found that the dorsolateral prefrontal cortex has a prominent role in working memory, that the inferior frontal gyrus and supplementary motor area are primarily responsible for response inhibition, and that the lateral orbitofrontal cortex is critical to cognitive flexibility. Of note, research seems to further suggest that different drugs have differential effects on brain structures. Namely, alcohol, nicotine, opioids, and amphetamines seem to have different effects on the brain and its associated functioning. Considered together, it seems alcohol may have differentially powerful effects on different brain structures and its associated functions.

Especially relevant to this review is the fact that executive functions are important early in development and that different developmental competencies develop at different times [20]. That is, although executive functions emerge early, they seem to further develop in

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adolescence. Moreover, the majority of normed, validated, and popular neuropsychological measures of executive functioning (i.e., DKEFS, NEPSY) only begin at 8-years-old. Interestingly, this is the same age [16] delineated adolescence from childhood. That executive functions emerge in early adolescence is important because this is also a time when adolescents first experiment with alcohol. Given this, it seems executive functions may be especially vulnerable given the neurotoxic effects of alcohol exposure on brain development. Indeed, [17] found that substance use has been shown to have an especially powerful effect on higher-order cognitive skills responsible for selection, monitoring and fine-tuning of goal-directed behavior.

Neuroimaging and Adolescent Brain Morphology

Neuroimaging refers to a wide variety of techniques that provide information about brain structure and/or function. The former refers to anatomy while the latter refers to physiology. Some of the commonly used neuroimaging techniques are computed tomography (CT), electroencephalogram (EEG), magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), and positron emission tomography (PET). Although each technique differs with respect to its ability to measure a) cellular activity, b) brain structure, and c) brain function, neuroimaging has led to exponential growth in the past decade in understanding brain functioning [12]. This paper reviews relevant data revealed by a variety of neuroimaging techniques with limitations addressed in a following section.

When considering the effects of alcohol on adolescent brain development and EF, it is important to first consider three critical physiological processes that occur during adolescence: proliferation, myelination, and synaptic pruning. Proliferation refers to the rapid growth of gray matter and the formation of new connections in the brain. Neuroimaging has found that the maximum size in frontal and parietal-lobe gray matter occurs at about 12 years in males and at 10.2-11 years in females and that the maximum size of temporal-lobe gray matter is not reached until 16.5 and 16.7 years for males and females, respectively [18].

Myelination is the process of how myelin, a protective sheath consisting of lipids and proteins, insulates and facilitates the transduction of messages between neurons. Synaptic pruning refers to the selective removal of unused or unnecessary neuronal structures [12]. Although these processes occur throughout development (including prenatally), adolescence has been shown to be a particularly active time. For example, neuroimaging has revealed that synaptic pruning results in the selective removal of approximately 40-50% of the synapses in cortical and subcortical regions during adolescence [19] and that myelination and synaptic pruning both produce dramatic changes in receptor levels and sensitivity [20]. Combined with proliferation, these processes produce faster, more efficient intercellular communication. In addition to these physiological changes, neuroimaging techniques have also revealed considerable growth in particular brain structures.

“The prefrontal cortex is the part of the brain that is active when we are engaged in complicated cognitive activities such as planning, decision-making, goal setting, and metacognition” [21]. Of note, the prefrontal cortex (PFC) is also the last brain region to mature [22]. Interestingly, maturation of the PFC is associated with absolute volume decreases during adolescence (Sowell, 2001). Of particular importance, however, is the development of the dorsolateral and ventrolateral prefrontal cortices [16,23]. The former refers to the outer and upper part of the anterior brain, while the latter refers to the lower and outer part of the anterior brain. Given the well-established relationship

between the PFC and higher-order cognitive processes [20], it is widely accepted the PFC is critical to executive functions.

Neuroimaging, Alcohol, and Executive Functioning

Neuroimaging data suggest that the effects of alcohol are both acute and chronic. Specific to brain development and EF, however, [24] found that as compared to recreational users, executive deficits in individuals with substance dependence are more generalized (i.e., affecting working memory, inhibition, planning, flexibility, and decision-making) and greater in magnitude (i.e., effect sizes ranging 0.5-2.2) than individuals with substance abuse (q.v. appendix A.1 on p. 22 for DSM-IV-TR diagnostic criteria for substance abuse and dependence).

[25] used PET scans to investigate the acute effects of alcohol exposure. Their data added further evidence to the literature which shows alcohol's tendency to decrease brain glucose metabolism, an effect which tends to be most pronounced in the occipital cortex and the cerebellum. However, their data also showed that acute alcohol exposure was also associated with increases in cerebral blood flow (CBF) in multiple brain regions. This latter finding led [26] many years prior to hypothesize that the increase in CBF is linked to alcohol's reinforcing effects. Overall, these data suggest that although alcohol produces acute effects, multiple systems and structures are affected and the precise underlying mechanisms are not well understood.

There is considerable evidence from neuroimaging that links alcohol to long-lasting executive impairments in verbal fluency, working memory, inhibition, flexibility, and decision-making as well as decreases in the prefrontal cortex [27,28]. In fact, neuroimaging data specifically measuring neuropsychological functioning has shown that alcohol produces alterations in visual-spatial functioning as well as alterations in verbal and nonverbal information in youths with alcoholic episodes [29]. Using neuroimaging techniques and neuropsychological tests, [30] found that memory problems are not only among the most common neuropsychological dysfunction in adolescence, but that the effects are responsible for the abnormalities in the brain's response to spatial working memory task. [31] further showed a reduction in blood oxygen level-dependent (BOLD) response in the in the left precentral gyrus and the bilateral cerebellar areas, with a greater response in bilateral parietal cortices. With functional magnetic resonance imaging (fMRI), [32] found alcohol abusing adolescents have bilateral deficits in hippocampal volume as compared to healthy matched controls. Considered together, these data suggest that alcohol impacts brain development and, in particular, executive functions.

In their review, [29,31] also showed how adolescents with AUD (alcohol use disorder) are associated with executive function degradations and reductions in cognitive performance and brain function. Furthermore, they also showed that chronic alcohol use was associated with poor verbal and nonverbal skills as well as problems with working memory and planning. More specifically, alcohol impaired verbal fluency and visuospatial skills as well as the capacities critical to executive functioning (i.e., working memory and planning). Interestingly, one finding from neuroimaging research that sharply contrasts alcohol's effect on adults and adolescents is alcohol's effect on the hippocampus and the motor cortex. Specifically, [33] found that adolescents appear more sensitive to hippocampal-dependent memory impairments and less sensitive to ethanol-induced motor impairments than adults. This suggests that perhaps memory is more resilient in adulthood while motor coordination declines with age.

[34] investigated the acute effects of alcohol on global visuospatial attention. These researchers found alcohol disrupts the fidelity of visuospatial performance. Specifically, participants engaged in a forced-choice tachistoscopic line bisection task in both ethanol challenge and no ethanol control conditions. Mean leftward bisection error in the control condition was 0.238 degrees visual angle and leftward bisection error significantly increased ($p=0.001$) under ethanol challenge. They concluded that bisection precision indicated disruption of visuospatial performance and, more specifically, that exaggerated leftward bisection error implies that ethanol may exert a differential effect on left versus right hemispheric function with regard to global visuospatial function.

Alcohol appears responsible for neuroanatomical and neurophysiological changes associated with impaired executive functions. Specifically, changes in the dorsolateral and ventrolateral prefrontal cortexes as well as the hippocampus appear primarily responsible for the observed changes in executive functions. In addition to the obvious concerns about compromised working memory, judgment, decision-making, planning, and goal-oriented behavior, [35] also found that performance on indices of executive functioning were also strongly associated with treatment retention and drug relapse. Although interesting, this relationship requires further elucidation before any definitive conclusions can be drawn. Nonetheless, these data suggest that alcohol may not only lead to irrevocable damage to executive functions, but that executive functions may also moderate substance abuse treatment retention and outcomes.

Given the continued prominence and importance of executive functioning in adolescence in combination with the prevalence of alcohol and it is known neurotoxic effects, it appears alcohol has an especially pervasive neurotoxin. Specifically, neuroimaging has revealed compelling data which suggests that alcohol use is associated with compromised growth and maturation of several brain structures critical to executive functions. In particular, the prefrontal cortex and the hippocampus seem to be the structures most implicated during adolescence. This is important because damage to these structures is associated with impairment in domains such as memory, planning, judgment, and decision-making; collectively comprising executive functions.

Conclusion

This review has identified several important findings about alcohol exposure and its effect on adolescent brain development and executive functions. First, although there is increased reliance on neuroimaging techniques in this area, the interpretation of these data should be done cautiously. While a thorough review of neuroimaging techniques is beyond the scope of the present task, it is suffice to conclude that many neuroimaging techniques lack adequate baseline information and group norms. Moreover, most neuroimaging studies are based on small samples that generally do not account for demographic factors such as sex, gender, SES, IQ, as well as other important variables such as comorbidity with other substances and psychiatric problems. This is particularly concerning given the high comorbidity between alcohol and nicotine, alcohol and marijuana, as well as alcohol and other psychiatric disorders (e.g., depression). Neuroimaging techniques are also correlational in nature. Therefore, they cannot identify causal relationships. Neuroimaging techniques often have low sensitivity and specificity. Consequently, they tend to have important research implications, but often little clinical utility as they often cannot increase diagnostic accuracy of neuropsychiatric disorders. Despite these limitations, a notable strength of the neuroimaging literature is that it

yields invaluable information on the gross anatomical and underlining physiological processes associated with alcohol and its effects on brain development.

Second, alcohol's deleterious effects on brain development and executive functions seem primarily related to impairment associated with the PFC and the limbic system [27,28,36]; more specifically, the dorsolateral and ventrolateral prefrontal cortexes as well as the hippocampus. In contrast, it appears alcohol does not have as strong an effect on the cerebellum and motor cortex as observed in adulthood [33]. Perhaps this is related to why alcohol appears to affect planning, judgment, decision-making, goal-oriented behavior, working memory and, more generally, executive functions in adolescence [17]. However, these conclusions are all predicated on the assumption that certain brain structures are responsible for particular processes and functions. While it may be the case for some behaviors and functions, it remains entirely unclear as to which specific brain structures, if any, are responsible for more global and complex behavior such as executive functions. In fact, given its complexity, executive functions likely involve the integration of multiple structures and systems including the frontal lobe [37-42]. Moreover, there is also some question about the construct of executive functions itself, in addition to reliable means of measurement. Although these are important philosophy of science and methodological issues, a thorough discussion is beyond the scope of the present review [43-48].

Third, this review suggests that some damage associated with alcohol is irreversible. Namely, there are both acute and long-term effects of alcohol exposure and its use is associated with compromised development and maturation of important brain structures and functions. Although this is obviously troublesome, it becomes particularly concerning when also considering the brain's remarkable capacity to change and adapt to maintain optimal functioning despite insult or injury (i.e., plasticity). That is, alcohol may be an especially harmful neuroteratogen whose deleterious effects on development occur both prenatally and postnatally, and whose damage may be irreversible leading to lifelong consequences throughout adulthood.

Fourth, a notable limitation of the literature is its reliance on animal models. Given the tremendous variability between and among species, it remains unclear how research conducted on experimental animals may or may not generalize to humans [49-52]. To date, the literature does not seem to address these concerns. Additionally, and specific to executive functions, animal models can only provide data that are highly inferential in nature. That is, there is not only serious doubt as to whether other animals have "executive functioning", but also whether they can serve as a model executive functions in humans. Additionally, some have further argued that addiction is a purely human phenomenon and, therefore, data drawn from research animal models are inherently flawed. At present, the current body of literature consists primarily of highly inferential claims drawn from animal models or retrospective, postmortem studies with humans. Despite these limitations, a noteworthy advantage of animal model research is its ability to tightly control for alcohol dose, timing, age, and other salient variables. Specifically, given current legal and ethical issues, research designs investigating dose-response of alcohol and its associated short and long-term sequelae are not feasible with adolescents.

One critical question that remains unexplained from the literature is whether the differences in neuroanatomy and physiology as indicated by neuroimaging techniques are causally related to clinical symptoms? That is, are the differences detected in neuroanatomy and physiology pre-existing or causally due to alcohol exposure? It could be that the

differences were pre-existing, part of normal variation, or the result of something else. Another related question is whether the observed differences are characteristic of individuals who are predisposed either genetically or physiologically to develop substance abuse problems or whether they are characteristic of the general population?

Another question that remains unanswered from neuroimaging studies is whether or not the results revealed by neuroimaging are specific to alcohol and its effect on adolescent brain development and executive functions. For example, hyperperfusion is often found with individuals diagnosed with Alzheimer's disease (AD) which suggests that hyperperfusion is associated with AD. However, hyperperfusion is also associated with other neuropsychiatric disorders such as AD/HD and depression. Therefore, it is quite possible, and perhaps even likely, that neuroimaging results are not specific to particular psychiatric disorders. Furthermore, because the brain is a highly interconnected set of structures and systems and with no function operating in isolation, it is dubious to make strong inferences from research which assumes that specific brain structures are solely, or at least primarily, responsible for specific functions. This point addresses the need for intensive longitudinal and hierarchical models of data analysis.

In the future, it is important that research incorporate large scale, population-based, randomized controlled studies on alcohol-abusing adolescents. Also, given the comorbidity between alcohol with nicotine, other drugs, and other psychiatric disorders (e.g., depression, anxiety) in adolescence, it is also important to establish stringent inclusion and exclusion criteria. Furthermore, in addition to differentiating among abuse, dependence, and comorbidity, it is also important that future research include "healthy" controls. Such improvements in research design and methodology would not only improve efficacy and effectiveness, but also enhance understanding of the specific physiological processes associated with alcohol and its effect on adolescent brain development and executive functions. In particular, future research should integrate neuroimaging data as part of a larger, longitudinal research design and methodology. In doing so, science could begin to accumulate group norms on neuroanatomical structures. This is critical as neuroimaging suggests there is natural variability between and among individuals with regard to neuroanatomy and physiology. Without normative and/or baseline data, all conclusions must be drawn cautiously. Ultimately, neuroimaging techniques should be incorporated as an adjunctive scientific tool, but not relied upon as the sole means of diagnosis or scientific inquiry.

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