Neuroscience and Biobehavioral Reviews 70 (2016) 244–259

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

# Neurobiological signatures associated with alcohol and drug use in the human adolescent brain

Marisa M. Silveri[a,b,c,*], Alecia D. Dager[d,e], Julia E. Cohen-Gilbert[a,b,c], Jennifer T. Sneider[a,b,c]

[a] Neurodevelopmental Laboratory on Addictions and Mental Health, McLean Hospital, Belmont, MA, USA
[b] McLean Imaging Center, McLean Hospital, Belmont, MA, USA
[c] Department of Psychiatry, Harvard Medical School, Boston, MA, USA
[d] Olin Neuropsychiatry Research Center, Hartford, CT, USA
[e] Department of Psychiatry, Yale University, New Haven, CT, USA

ARTICLE INFO

*Article history:*
Received 15 March 2016
Received in revised form 17 June 2016
Accepted 30 June 2016
Available online 1 July 2016

*Keywords:*
Adolescence
MRI
DTI
fMRI
MRS
Resting state
Alcohol
Marijuana
Nicotine
Substance abuse
Addiction
Development
Frontal lobe
Hippocampus
Reward sensitivity
Impulsivity

ABSTRACT

Magnetic resonance (MR) techniques provide opportunities to non-invasively characterize neurobiological milestones of adolescent brain development. Juxtaposed to the critical finalization of brain development is initiation of alcohol and substance use, and increased frequency and quantity of use, patterns that can lead to abuse and addiction. This review provides a comprehensive overview of existing MR studies of adolescent alcohol and drug users. The most common alterations reported across substance used and MR modalities are in the frontal lobe (63% of published studies). This is not surprising, given that this is the last region to reach neurobiological adulthood. Comparatively, evidence is less consistent regarding alterations in regions that mature earlier (e.g., amygdala, hippocampus), however newer techniques now permit investigations beyond regional approaches that are uncovering network-level vulnerabilities. Regardless of whether neurobiological signatures exist prior to the initiation of use, this body of work provides important direction for ongoing prospective investigations of adolescent brain development, and the significant impact of alcohol and substance use on the brain during the second decade of life.



**Contents**



* Corresponding author at: McLean Imaging Center, McLean Hospital, 115 Mill St., Mailstop 204, Belmont, MA 02478, USA.
*E-mail address:* msilveri@mclean.harvard.edu (M.M. Silveri).

http://dx.doi.org/10.1016/j.neubiorev.2016.06.042
0149-7634/

## 1. Introduction

Adolescence is an age period, typically spanning the second decade of life, characterized by physiological and social maturation that occurs along with significant structural, functional and neurochemical brain changes (Paus, 2005; Spear, 2000). This special issue provides a comprehensive set of reviews of preclinical and clinical studies detailing adolescent brain maturation across multiple domains: neurobiological development, cognition, affect, motivation, reward sensitivity, puberty and sex differences, stress and adversity, sleep physiology, the social brain, genetic influences and the emergence of psychopathology. The purpose of this review is to provide an evaluation of the existing human data, obtained using non-invasive magnetic resonance (MR) neuroimaging methods that document alcohol- and drug-related neurobiological consequences in currently using adolescents.

Over the past decade, MR techniques have dramatically improved the ability to characterize adolescent-related brain changes, due in part to the evolution and availability of higher field-strength scanners, hardware and software innovations, and advanced MR sequences. As a result, MR studies have been able to significantly advance the field in our understanding of neuromaturational changes from childhood through adolescence (Casey et al., 2008; Dahl, 2004; Ernst and Mueller, 2008; Giedd and Rapoport, 2010; Gogtay et al., 2004; Luciana, 2013; Pfefferbaum et al., 1994; Sowell et al., 2004; Steinberg, 2010), and into late adolescence/emerging adulthood (Bennett and Baird, 2006; Sullivan et al., 2011). Adolescent brain reorganization, refinements and functional improvements map onto enhanced cognitive abilities (Casey et al., 2005; Paus, 2005), with the most prominent changes occurring in frontally-based regions and functionally connected subcortical structures (Anderson, 2001; Casey et al., 2000; Giedd et al., 1999; Klenberg et al., 2001; Pfefferbaum et al., 1994; Rosso et al., 2004; Sowell et al., 2001; Sowell et al., 2004; Williams et al., 1999), including age-related increases in frontal lobe gamma-Amino butyric acid (GABA) levels (Silveri et al., 2013). While such changes make adolescence a time of neurobiological opportunity, increased propensity to seek out novel stimulation and engage in risk-taking behaviors, such as using alcohol and drugs, enhance the potential vulnerabilities of this age period. Characterizing the neurobiology underlying immature cognitive and behavioral responses, which result in suboptimal self-regulatory control, have been areas of extensive investigation (Casey et al., 2000; Casey and Jones, 2010; Dempster, 1992; Durston et al., 2006; Schweinsburg et al., 2004; Silveri et al., 2011). Accordingly, the frontal lobes, and limbic/hippocampal circuitries, have been identified as regions particularly vulnerable to early and escalating alcohol and substance use. Due to ethical considerations prohibiting administration of alcohol and drugs to human youth, animal studies have proven invaluable in initiatives to identify consequences of alcohol and drug use on the brain and behavior in adolescents, under controlled laboratory conditions. The companion preclinical review on alcohol and drug effects in this issue (c.f., Spear this issue), as well as a wealth of past studies, demonstrate strong evidence for age-specific alcohol and drug effects, which in humans could influence the initiation, escalation of use, and risk for abuse during the adolescent period.

Age of initiation and escalation of alcohol and drug use, as well as a high prevalence of substance use disorders (SUDs), overlap with the critical period of adolescent brain re-organization. The Monitoring the Future (MTF) survey has been an essential resource for understanding changing rates of and attitudes towards alcohol and drug use since 1975. In addition to alcohol, drugs assessed include tobacco/nicotine (cigarette smoking, hookah use and e-cigarettes), marijuana, synthetic cannabinoids (K2/Spice), prescription and over-the-counter drugs (including non-medical opioid and stimulant use, cough/cold medicines), ecstasy ("Molly"), other amphetamine-type stimulants (methamphetamine), synthetic stimulants (bath salts), hallucinogens (e.g., salvia), and inhalants. A summary of lifetime prevalence of alcohol and selected drug use, from 44,900 students in grades 8, 10 and 12, from the 2015 MTF survey (Johnston et al., 2016) are presented in Table 1.

Alcohol continues to be the most commonly used substance among adolescents; however, marijuana use has been increasing over time. Recent surveys have also considered new drugs and modes of drug use, including use of e-cigarettes and synthetic cannabinoids. This review focuses specifically on adolescent MR studies of the most frequently used substances, alcohol and marijuana, and selected other drugs when available (nicotine, stimulants, ecstasy, inhalants, and poly-drug use). Studies included were limited to those conducted in current alcohol- and/or drug-using adolescents that were age 10 and older, excluding studies that began at age 18, or that were specific to emerging adulthood (age 18–25+ years). Although limited to adolescents, this review notably highlights the rapidly growing data available, obtained using multiple imaging modalities that permit comparison of regions and networks affected across multiple substances. While the collection of results presented in this review may reflect drug use in general, regardless of age, longitudinal studies currently in progress will be instrumental in characterizing adolescence as a unique period of neurobiological vulnerability to alcohol and drugs. Fulfilling the inclusion criteria were, to our knowledge, 103 published structural, functional and spectroscopy studies, together comprising data from thousands of alcohol- and substance-using adolescents and healthy, non-using comparison subjects.

## 2. Magnetic resonance technologies

Structural magnetic resonance imaging (MRI) provides quantitative information regarding brain tissue and volume, by using