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Introduction to the special issue: Substance use and the adolescent brain: Developmental impacts, interventions, and longitudinal outcomes

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ABSTRACT

Adolescent substance abuse is a major public health problem, particularly given the negative brain and behavioral consequences that often occur during and following acute intoxication. Negative outcomes appear to be especially pronounced when substance use is initiated in the early adolescent years, perhaps due to neural adaptations that increase risk for substance use disorders into adulthood. Recent models to explain these epidemiological trends have focused on brain-based vulnerabilities to use as well as neurodevelopmental aberrations associated with initiation of use in substance naïve samples or through the description of case-control differences between heavy users and controls. Within this research, adolescent alcohol and marijuana users have shown relative decreases in regional gray matter volumes, substance-specific alterations in white matter volumes, deviations in microstructural integrity in white matter tracts that regulate communication between subcortical areas and higher level regulatory control regions, and deficits in functional connectivity. How these brain anomalies map onto other types of youth risk behavior and later vulnerabilities represent major questions for continued research. This special issue addresses these compelling and timely questions by introducing new methodologies, empirical relationships, and perspectives from major leaders in this field.

Aberrant patterns of substance use have long been recognized as a significant clinical and public health problem. Among adults, substance use problems are quite common (Kessler et al., 2005; Merikangas and McClair, 2012). Recent surveys indicate that 7.8% of U.S. adults over the age of 18 had one or more substance use disorders in the past year (http://www.samhsa.gov/data/sites/default/files/NSDUH-DR-N2MentalDis-2014-1/Web/NSDUH-DR-N2MentalDis-2014.htm), largely driven by alcohol use problems. It is broadly perceived that substance use, as a privileged behavior, can readily escalate out of one's control in the absence of appropriate behavioral boundaries. Indeed, a large percentage of the world population has struggled with substance use disorders at some point within their lifetime (Whiteford et al., 2015). Data from the *Monitoring the Future* study (Johnston et al., 2013), funded by the U.S. National Institute on Drug Abuse, consistently indicate that marijuana is the most commonly used illicit substance, a pattern that reflects worldwide trends (http://www.who.int/substance_abuse/facts/psychoactives/en/). Within the United States, substances such as alcohol and nicotine can be legally purchased and ingested in public places at the age of 21; in most of Europe and the UK, the legal drinking age is 18. The legalization of recreational marijuana use is much more recent, and within the United States, highly controversial. At the time of this writing, four States (Oregon, Washington, Colorado, Alaska) and the District of Columbia have legalized recreational marijuana use and 23 States plus the District of Columbia have legalized use for medical purposes (https://www.whitehouse.gov/ondcp/state-laws-related-to-marijuana). Importantly, however, legalization is not yet recognized at the federal level, subsequently resulting in some degree of conflict around the "acceptability" of this substance use behavior. More importantly, in the interim, it is feared that increasing access to this drug for many individuals, including adolescents, may represent an unforeseen consequence of legalized medical use (Cerdá et al., 2012; Harper et al., 2012). In other Western countries, such as the United Kingdom and European Union, the age at which one can legally use alcohol, nicotine, and marijuana varies. In the Netherlands, for example, cannabis can be legally purchased only in designated coffeeshops whereas alcohol can be legally used at any age but can be purchased at age 18.

Within the scientific community, the manner in which these standards that regulate access are adopted and enforced inspires debate, because while it is recognized that experimentation with such substances is highly typical for many adolescents and often time-limited (naturally remitting by mid-adulthood, concurrent with youths' adoption of more "adult" responsibilities; Shedler and Block, 1990), earlier first-time users of alcohol and marijuana show elevated risks of developing substance use disorders in adulthood (Johnston et al., 2013). Moreover, recent reviews have shown that

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even modest levels of alcohol use can be linked to differences in neural structure and function during adolescence (e.g., Bava et al., 2013; Elofson et al., 2013; Feldstein Ewing et al., 2014), and similar trends are evident for marijuana (Batalla et al., 2013; Battistella et al., 2014). Moreover, the use of alcohol and marijuana in large quantities has been associated with cognitive problems, particularly in the areas of learning and memory, attention, and executive function (Becker et al., 2014; Bossong et al., 2014; Crean et al., 2011; Dougherty et al., 2013). At least one longitudinal study suggests that chronic marijuana use, particularly when use begins in adolescence, leads to later declines in general intellectual function (Meier et al., 2012), and similar findings are reported in relation to more specific domains of cognition (Fontes et al., 2011). Negative outcomes are particularly salient in the contexts of earlier use onset (<age 16 years; Gruber et al., 2012, 2014) as well as heavier and more frequent use (Bolla et al., 2002; Filbey et al., 2014; Solowij and Grenyer, 2002). Binging behavior, most often studied in relation to alcohol use, may be one of the most pernicious contributors to persistent structural and functional abnormalities across preclinical (Crabbe et al., 2011; Risher et al., 2015) and human studies (George et al., 2012; Squeglia et al., 2011).

Despite such findings, the "chicken versus egg" question still remains one of the most vexing in this field. It may be that individuals carry genetic liabilities for substance misuse and related difficulties (Kendler et al., 2003). Such liabilities may lead to an increased risk of substance use initiation and escalation as well as associated problems. Alternatively, negative outcomes associated with substance misuse may be directly caused by the impact of substances on developing neural systems and the downstream behavioral impacts of this type of impaired neural activity (Koob and Volkow, 2010). Further, it is possible, if not highly likely, that there is some degree of interaction. For example, it might be the case that substance use disorders represent diathesis/stress associations or gene/environment correlations, wherein certain individuals have a greater risk of developing SUDs based on genetic vulnerabilities (e.g., family history of substance use; risky "reward" neural structure/circuitry) that are "activated" or "exacerbated" by the introduction of substance use during the developing adolescent years (cf., Cadoret et al., 1986; Hayatbakhsh et al., 2012; Iacono et al., 2008). Alternately, what we are observing could be an epigenetic phenomenon, such that substance use during adolescence might not change genetic hardwiring, but may instead alter gene expression (e.g., methylation) in critical regions, consequently changing neural structure/function, and youths' capacity for decision-making around risk contexts, including those that bring opportunities for substance use (Nestler, 2014). Most likely, each of these processes are relevant wherein biologically vulnerable individuals, already distinct in measurable ways prior to use onset, engage in substance use and are then further impacted by toxic effects of the substances. It is thus important to ascertain which traits, characteristics and contextual factors render individuals vulnerable to use prior to initiation, the specific avenues through which each substance exerts its effects on the brain, and when and within which neural circuits substance exposure has the maximum negative impacts. Developmental cognitive and affective neuroscientific investigations are uniquely situated to examine these issues.

One of the more critical contextual influences at hand is the availability and prevalence of substances of abuse, increasing the likelihood that individuals will select substance use as a risk behavior of choice. For example, in the United States, by age 18, 75.6% of adolescents have used alcohol, 48.6% have used cannabis, and 48.1% have used tobacco (with increasing percentages using electronic cigarettes, up to 20.6%) (Kann et al., 2014). Subsequently, if commonly-used substances such as alcohol, nicotine, and marijuana are toxic to developing neural tissues, then we can readily anticipate that such effects could cause the most disruption during periods of pronounced and rapid neural development. Fetal alcohol syndrome provides a compelling illustration of this phenomenon wherein alcohol exposure to the developing fetus has significant, long-standing, negative health sequelae that impede a young person across physical, cognitive, and behavioral domains throughout the lifespan (Stratton et al., 1996; Wozniak et al., 2006). Similarly, there is evidence that heavy substance use, including use of alcohol (Oscar-Berman and Marinkovic, 2007) and cocaine (Ersche et al., 2012) accelerates the human aging process. Heavy users exhibit atrophy of cortical tissue at a rate that exceeds that of non-users (Ersche et al., 2012; Fortier et al., 2011). Whether such associations are evident in other periods such as adolescence, when the brain is actively developing in more subtle ways (Lebel and Beaulieu, 2011; Lebel et al., 2012; Gogtay and Thompson, 2010; Urosevic et al., 2012), or the degree to which normative, smaller (quantity) or shorter (duration) experimental levels of use confer deficits is far from fully understood. However, recent findings (Bava et al., 2013; Filbey et al., 2014; Luciana et al., 2013) as well as the papers in this issue support that heavy substance use during adolescent neurodevelopment has long-range consequences.

Certainly, from a public health standpoint, there is an impetus to find and report deficits associated with adolescent substance use. Substance use is strongly linked to a panoply of other risk behaviors including, other and heavier types of substance use initiation, other types of risk behaviors, externalizing disorders, and disruptions in school, family, and social functioning (Feldstein and Miller, 2006; Feldstein Ewing et al., 2015a,b). Moreover, alcohol use is one the main contributors to the incidence of accidents and injuries during adolescence (Miller et al., 2007), which represents the leading cause of morbidity and mortality in this age group (American Academy of Pediatrics, 2010). Yet, while it seems intuitive that substance use may be the vehicle driving the connections among risk-taking propensity, disruptions in cortical function/structure, and future risk for substance use disorder, these associations and their temporal trajectories are far from established. Instead, the notion that addiction emerges through the impact of substances on the brain remains quite controversial (Volkow and Koob, 2015).

One reason for the lack of certainty in this area is that historically, studies of substance-using populations have been plagued by methodological shortcomings that render objective interpretation of existing findings difficult and call extant findings and potential contributing factors into question. For example, in the absence of prospective studies, it is virtually impossible to identify and disentangle individual differences in cognition and affect that may have existed prior to onset of substance use. Further, even within the psychosocial literature, large-scale, long-term (7 year) longitudinal studies of high-risk individuals are still trying to determine which factors (e.g., peers, family factors, neuropsychology) have the most impact in predicting who is most likely to continue using alcohol and marijuana (Feldstein Ewing et al., 2015b). We also have very little information about how, when, and why youth *begin* to use (e.g., D'Amico and McCarthy, 2006), and even less data on how very early use (prior to age 16) impacts developing brain and behavior. Anecdotally, many former users (now adults) question whether their teenage indiscretions have consequences into middle and older age. Few studies (but see Hanson et al., 2010) address functional improvements that may evolve with abstinence.

Ultimately, at this time, the broader body of literature highlights predominantly cross-sectional studies of single-aspects of substance use or related correlates that suggest substance use is "bad" for brain and broader health. Most of these compare users versus non-users, without considering how users might have already been a distinct subgroup (e.g., significant differences across behavior and/or brain structure/function that existed prior to substance

use initiation). Second, even in longitudinal work, it can be difficult in the absence of sophisticated modeling techniques and very large samples to quantitatively determine the relative contribution of genetic vs. environmental factors on brain structure/function, and related behavioral outcomes. The field is only beginning to use more sophisticated methodological approaches to incorporate simultaneous consideration of multi-dimensional traits or features of behavior, such as elevated levels of impulsivity, high sensation-seeking, and poor executive function. This more collective, holistic approach, particularly with methods from developmental neuroscience, is likely to give us a better sense of who is most impacted by problem substance use, and who is most likely to continue use into adulthood. Capturing nuances of neurodevelopment and function prior to substance use onset is essential. Once an individual reaches the point of a diagnosable substance use disorder, it is much more difficult to disentangle co-occurring other psychopathology, as it is highly typical for other major psychological problems (e.g., externalizing disorders) to be present by adulthood (Iacono et al., 2008). The impact of comorbid conditions on observed neurodevelopmental outcomes is not well-characterized in the current developmental neuroscience literature. Third, we are far from understanding whether brain-based anomalies observed in users are true differences attributable to substance use, predisposing factors, and/or artifacts of a particular study design. Lack of replicability is a major issue (Baker, 2015). Further, we have little sense of the behavioral significance of observed anomalies. For example, among substance users, certain brain differences might, in fact, represent compensatory strategies (Schweinsburg et al., 2005, 2011); the degree to which these compensatory strategies might be *adaptive* is not yet known (Giedd, 2015). Broader looks across the literature have confirmed the need for full context. In a recent study and meta-analytic review, Weiland et al. (2015) concluded, in fact, that daily marijuana use was not associated with morphometric brain changes in adolescents or adults. In their report, it was noted that among published studies, half report findings of increases in regional brain volumes in daily cannabis users while the other half report decreases; overall the mean effect size appears to be minimal.

Overall, recognition of these interpretive dilemmas challenges us, as a field, to improve methodology and remain cognizant of the impact of relevant limitations on our interpretations of the extant data. Without a full picture of how substance using youth are functioning in the broader domains of peers, school, and family, it can be tempting to infer that any observed difference between substance users and non-users represents a negative outcome. Assessment of these real-world behavioral anchors is requisite to fully understand how neural adaptations relate to not only risk, but also function, across the contexts of use and in longer term neurobehavioral development.

Our goal in organizing this special issue is to present cutting edge research in this area. The twenty papers published here present new empirical research, incorporating cognitive and affective neuroscientific methods, from leading laboratories where brain-based outcomes associated with adolescent substance use are a focus of inquiry. Among these papers, 8 present data from longitudinal studies, and two of these (Serlin et al.; Saalfield et al.) present data from animal models. Longitudinal data are important in addressing the longer-term neurodevelopmental consequences associated with substance misuse. The paper by Wilson et al. is notable for its use of a cutting edge behavior genetic approach (the co-twin control design) to disentangle toxic effects of alcohol from genetic predispositions. A large number of the empirical papers in the issue (8 of 20) concentrate on marijuana and its effects on brain structure, function, and connectivity. Many are notable for their attempts to assess the influence of risk factors on salient outcomes, including age of substance use onset (Becker et al.; Filbey et al.; Gruber et al.; Lopez-Larson et al.), binge use patterns (Cservenka et al.), family history (Cohen-Gilbert et al.), polysubstance use (Karoly et al.), histories of prenatal exposure (Gautam et al.), and executive dysfunction (Peeters et al.). As a comprehensive body of work, the sum of these data underscore the salient impact of adolescent substance use on the brain's reward system as a compelling area of inquiry (cf., Karoly et al.; Weissman et al.), along with the assessment of how threat-based motivation is impacted by use (Spechler et al.; Heitzig et al.). These papers call attention to the need to incorporate more basic translational science into this area of inquiry. Our commentators, Boyce, Brown and Giedd, bring unique perspectives from clinical, public health, and developmental standpoints to the findings.

Overall, the issue offers a timely collection of papers that address the empirical connections between adolescent substance use and developing brain structure/volume by leaders in the field. Strengths include the large number of longitudinal studies, the use of methods from the cognitive and affective neuroscientific literatures guiding inquiry into specific brain circuits and processes impacted by use, consideration of neurochemical as well as structural brain outcomes (cf., Cohen-Gilbert et al.), and the examination of both premorbid risk factors as well as substance-specific "toxic" outcomes. As noted by several authors (cf., Becker et al., 2014), the search for behavioral correlates remains challenging outside of the realm of substance use-related behavioral patterns such as age of substance use onset.

We hope that this collection will be a critical resource at this pivotal time as policy-makers within larger-scale organizations (government agencies) render decisions about how to implement legal policy related to this privileged behavior, monitor outcomes, and evaluate patterns of substance use in young adults as well as adolescents.

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