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## Hunting for what works: Adolescents in addiction treatment

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## **Abstract**

Although adolescents are developmentally distinct from adults, they often receive addiction treatment based on adult models. This is problematic because adolescents face significantly different conditions in addiction treatment, including distinct basic biological and neurodevelopmental stages, unique sociodevelopmental concerns, distinctive addiction trajectories, and in turn, disparate treatment goals and outcomes. In sum, it can be difficult for even savvy clinicians to know how to approach addiction treatment with this important age group.

In an effort to help clinicians and researchers consider substance use via a neurodevelopmental lens, we approached this review with four goals: (1) characterize the prevalence, and related health and safety implications, of substance use within this age group; (2) identify the nature of the adolescent brain, including characteristic features of this phase of neurodevelopment relevant for adolescent substance use treatment; (3) provide an overview of current adolescent addiction interventions and avenues to improve clinical treatment and clinical research efforts for adolescents; and (4) examine the intersection between the nature of the developing brain and adolescent substance use, and utilize that information to inform alternative routes and directions for substance use treatment in this critical age group.

This review concludes by offering a novel neurodevelopmental model and framework to examine substance use interventions, along with a series of recommendations to optimize adolescent substance use treatment and clinical research.

**Keywords:** adolescent, MRI, treatment, development, addiction

## I. Introduction

Adolescence has been argued to be the only developmental period bookended by highly disparate events (Giedd, 2018). It commences with biology, defined as the onset of puberty, and concludes via social construct, typified by the achievement of “independent functioning” such as obtaining a job, completing training, and beginning a family (Giedd, 2018). While the ages for this window vary widely throughout the globe, most agree that the central work of adolescence largely encapsulates ages 13-18 (Giedd, 2018).

Across cultures and societies, it is during this precise developmental period that substance use is most often initiated (Vega et al., 2002), with peak age of first misuse, and related problems following soon thereafter (Wagner, 2002). Given that adolescents have goals, cognitions, and social contexts distinct from adults, it is critical that clinicians and researchers consider adolescent substance use through a neurodevelopmental lens. In the present review, we engage a developmental neuroscience framework to characterize the prevalence, and related health and safety implications of substance use within this age group; identify the nature of the adolescent brain, including characteristic features of this phase of neurodevelopment relevant for adolescent substance use treatment; and provide an overview of current adolescent addiction interventions and avenues to improve clinical treatment and clinical research efforts for adolescents. We then conclude by examining the intersection between the nature of the developing brain and adolescent substance use, and utilize that information to inform alternative routes and highlight promising future directions for substance use treatment in this critical age group.

Due to the inherently polysubstance-using nature of this age group (Karoly et al., 2015, Clark, 2004), we focus this review primarily on the three most frequently used substances by adolescents: alcohol, cannabis and tobacco (Johnston et al., 2018, CDC, 2016). We have not integrated examination of prescription pain/opioid misuse here due to its relatively recent history within adolescent addiction clinical research and treatment settings, and the related dearth of empirical adolescent opioid treatment research in this area (Dash et al., 2018).

## **Prevalence of adolescent substance use**

The rates and patterns of adolescent substance use have maintained historical consistency throughout the past several decades. Alcohol continues to be the top substance used by adolescents across the globe (Cousijn et al., 2018, Feldstein Ewing et al., 2014). Noted in top United States (U.S.) surveys (Johnston et al., 2018, CDC, 2016), despite the legal age being 21 years, alcohol is highly accessible for American youth, with most accessing alcohol through peers or other individuals (CDC, 2016). In turn, it is no surprise that half of American 14-year-olds have consumed alcohol. This rises to 75% by age 18, with half drinking to intoxication (Johnston et al., 2018, CDC, 2016). Relevant to potential neurotoxicity and health impact (Feldstein Ewing et al., 2014, Lisdahl et al., 2013), 20% of adolescents start drinking by age 13 (prior to initiating high school) (CDC, 2016).

Interestingly, U.S. surveys reflect a current 10-year low in youth drinking. Yet, rates of youth alcohol use and related problems still remain consequential, in terms of safety and health impact (Johnston et al., 2018).

One currently debated reason for the decline in adolescent alcohol use in the U.S. revolves around recent changes in cannabis legislation (Choo et al., 2016, Feldstein Ewing et al., 2017). For example, treatment providers in states where cannabis is medically and/or recreationally legal are observing some degree of youths' increasing preference for cannabis over alcohol (Feldstein Ewing et al., 2017). Presently, one quarter of U.S. youth report cannabis use by age 14, with 8% starting by age 13. Of relevance, rates of cannabis use have recently begun to approximate adolescent alcohol use patterns, with half of U.S. teens now using cannabis by age 18 (Johnston et al., 2018, CDC, 2016). This reflects a 22% rise in adolescent cannabis use during the past decade (Johnston et al., 2018).

These startling trends raise the question of whether increased recreational and medical legalization of cannabis are contributing to observed increases in adolescent use (Feldstein Ewing et al., 2017). Unfortunately, requisite data needed to identify causal relationships between changes in cannabis legislation and adolescent use are not yet

available, and thus far, evidence has been mixed regarding effects on both adolescent consumption and perceived harmfulness. Further, effects may vary substantially across states/contexts (Ingraham, 2017, Schmidt et al., 2016, Cerda et al., 2018, Cerda et al., 2017, Hasin et al., 2015). Active efforts by scientists and practitioners in recreationally and medically legal areas are needed to disaggregate directional impacts between public policy legislation and adolescent use (National.Academy.of.Sciences, 2017, Feldstein Ewing et al., 2017). For example, in 2017, national survey databases indicated adolescents reported significant drops in their estimations of potential harm and disapproval of cannabis use (Johnston et al., 2018); how this aligns with patterns of adolescent cannabis use and intersects with alcohol use is a critical, and increasingly pressing, empirical public health question that has direct implications for addiction treatment providers working with adolescents in this field (Feldstein Ewing et al., 2017).

In terms of tobacco, one quarter of American youth have tried tobacco, with 7% initiating use before age 13; this rises to a third of youth by age 18, with 10% smoking 10+ cigarettes/day (Johnston et al., 2018, CDC, 2016). National data reflect that American adolescents are moving away from tobacco use, as represented by a 71% drop in past 11 year cigarette use (Johnston et al., 2018). Part of this may be due to teens' transition to electronic vapor products ("vaping"), a recent newcomer to the world of adolescent substance use. Adolescents report vaping nicotine (25%) and cannabis (11%), preferring flavor-based cartridges (31%), contentiously marketed toward children (Johnston et al., 2018, Lodrup Carlsen et al., 2018). Surveys reflect 20% of U.S. youth have vaped an e-liquid containing nicotine and/or cannabis by age 14, rising to one third by age 18 (Johnston et al., 2018, CDC, 2016).

### **The ubiquity of adolescent substance use does not equate with its safety**

For many clinicians, the most pressing public health concern around adolescent substance use is not that it represents an entry point into a life-long course of protracted addiction. Rather, the more imminent concern for parents and providers is that adolescents

will make a risky choice while trying to obtain, use, and/or dispose of substances that result in consequences that cannot be undone (e.g., getting a head injury in an accident; being a victim of sexual assault; making a foolish mistake that costs them life or limb), and that render their life trajectory much more difficult (e.g., posting illicit pictures of themselves on social media; getting arrested; losing a scholarship) (Feldstein Ewing et al., 2016a).

One of the central challenges in this area is that experimentation with substance use is so typical among adolescents that for decades it has been interpreted as largely “normative”, and to some degree to-be-anticipated, and some argue, even developmentally-appropriate (Shedler and Block, 1990). While the initial part of this trajectory has been interpreted as largely “harmless” in terms of behavioral impact, conferring a degree of social advantage, for some, during high school (Feldstein Ewing et al., 2016a), the nature of substance use shifts for many during this period.

Specifically, more than half of adolescents have tried at least one substance by age 18, with many using at least one substance in a “harmful way”, such as binge (heavy) use. Due to the inherently illicit behaviors that must be engaged in to access and utilize most substances (with the exception of prescription opioids, see (Dash et al., 2018)), many youth use substances in ways that increase the likelihood of encountering other forms of harm (e.g., using in an unsupervised setting; using with peers or older adolescents that the youth does not know well; having to navigate getting home from a friend’s house while intoxicated; trying to quickly dispose of substances in areas that could cause damage to the youth and/or their surroundings) (Johnston et al., 2018, CDC, 2016).

In terms of health relevance, large-scale data reflect that health sequelae for substance use for adolescents have become much more severe throughout the past three decades. Not only does morbidity and mortality increase 200-300% during this developmental period (Giedd, 2018), but a recent *JAMA* review indicates that alcohol use increased morbidity from 5,800 deaths in 1980 to 9,400 deaths in 2014, with years of life lost doubling (Dwyer-Lindgren et al., 2018). Further, substance-related consequences have

skyrocketed from 3,300 deaths in 1980 to 33,100 deaths in 2014, with years of life lost up by a factor of *nine* (Dwyer-Lindgren et al., 2018).

The relevance of these values is that *adolescent initiation* of substance use plays a key role in this equation. Viner and colleagues (2017) utilize a metric that quantifies impact of adolescent exposure, referred to as adolescent attributable fraction (AAF). This represents the relative impact on mortality that would have occurred in the absence of exposure to the risk (e.g., if no substances had been used during adolescence). In the example of tobacco, this team found that 80% of individuals commence tobacco use during adolescence, contributing to 72% of smoking during the adult years, with a pronounced link particularly for those who initiated smoking *before age 16* (Viner et al., 2017). Additionally, a recent *Lancet* review highlighted that the ages of 15-19 are particularly precarious for adolescents throughout the globe, with accidents and injuries (including road injuries, interpersonal violence, self-harm, drowning, which of relevance, are often intertwined with substance use) as the top cause of death in this age group, and substance use itself a leading cause of disability (Mokdad et al., 2016).

Despite several decades of efforts by experts to identify the best avenues to prevent and reduce adolescent substance use, progress continues to be limited. Given that adolescents have goals, cognitions, and social contexts that are distinct from adults, one avenue that may improve treatment outcomes for this age group is considering substance use via a neurodevelopmental lens (Dwyer-Lindgren et al., 2018).

## **II. The nature of the adolescent brain: characteristic features relevant for the adolescent addiction treatment context**

Despite the rise of scientific interest in the neurodevelopmental period of adolescence (Giedd, 2018), exemplified by recent large-scale research initiatives (e.g., Australian iCATS; European IMAGEN; US NCANDA and ABCD) (Whelan et al., 2014, Jernigan et al., 2018, Simmons et al., 2014, Brown et al., 2015), throughout history contributions of this salient developmental period on health and neural drivers of behavior



have largely been overlooked (Bundy et al., 2018). This is relevant because adolescence is, at this moment, being recognized as a highly unique neurodevelopmental period that can impact lifelong health and wellbeing - the *chrysalis* before adulthood.

While much of the literature tends to focus on adolescents' newly piqued penchant for risk behaviors, fewer clinical and research efforts have been dedicated to the highly adaptive aspects of the adolescent period (Giedd, 2015). Data are now showing that the adolescent brain is, in many ways, pre-programmed for resilience (Cousijn et al., 2018, Blakemore, 2018, Giedd, 2018), with the adolescent brain purposefully transitioning from an overproliferation of neurons, characteristic of childhood, to greater specificity and focus of brain networks, demonstrated by increases in strength and purpose (Nelson et al., 2016). In lay terms, the adolescent brain can be seen as the development of a system of functional highways established within the brain during this developmental stretch. Ultimately, across theoretical perspectives, biology and environment dynamically interact throughout this time to generate an enhanced set of developmental tasks during this window; the outgrowth of which sets the foundation for later adaptive network connectivity, structure/function, and resultant behavior and cognition during adulthood. Central facets likely to drive the primary tasks of this neurodevelopmental period are:

(1) Substantive pubertal changes. Defined as the process by which an individual reaches sexual maturity, puberty is initiated by a series of internal changes that precede external ones; girls often commence ~2 years before boys (Herman-Giddens et al., 2001). The earliest phase includes adrenarche (~age 8). Adrenarche is initiated by the hypothalamic-pituitary-adrenal (HPA) axis, which triggers relevant hormones including dehydro-epiandrosterone (DHEA), dehydroepiandrosterone-sulfate (DHEAS), and testosterone (Barendse et al., 2018). DHEA contributes to axonal and white matter development by stimulating neurogenesis via opposition of the neurotoxic impact of glucocorticoids (Barendse et al., 2018, Nguyen et al., 2017). DHEA plays a central role in cortical plasticity in prefrontal (dorsolateral prefrontal cortex, dlPFC; anterior cingulate, ACC),

parietal (temporal parietal junction, TPJ), and subcortical structures (amygdala, hippocampus) involved in memory and attention (Nguyen et al., 2013, Nguyen et al., 2017).

Subsequently, relevant for the adolescent treatment context, DHEA has cognition-promoting functions during adolescent development, particularly in emotionally “hot” situations (Nguyen et al., 2017, Brumback et al., 2016).

Gonadarche, the maturation of the gonads, follows adrenarche and is characterized by a surge of hormones and rapid physical growth, contributing to sexual dimorphism in the body, face and voice (Crone and Dahl, 2012). Gonadarche begins in the brain, with hypothalamus release of gonadotrophin-releasing hormone (GnRH), in turn activating the resting hypothalamic-pituitary-gonadal (HPG) axis, and pituitary to produce follicle-stimulating hormone (FSH) and luteinizing hormone (LH) (Crone and Dahl, 2012). FSH and LH generate estrogen (via ovaries) and testosterone (via testes), instrumental in movement toward sexual dimorphism in the body and brain (Draganski et al., 2014, Blakemore et al., 2010).

One particularly robust finding, relevant to the adolescent treatment context, is that pubertal maturation, particularly increased testosterone, promotes structural and functional development of the striatum (Braams et al., 2015, Op de Macks et al., 2011, Herting et al., 2014, Goddings et al., 2014). This is salient, as hormonally-mediated striatal development has been implicated as predictive of risk-taking and substance use during adolescence (Marceau et al., 2018, Braams et al., 2016), above and beyond chronological age. This suggests that variability in gonadal hormones may play a crucial role in organizing striatal development and consequential reward-seeking behavior during adolescence; factors relevant in the adolescent addiction treatment context. While such striatal changes have been examined in the context of negative risk-taking, there is reason to believe that striatal changes also serve a vital role in positive risk-taking, including pursuit of goals and movement into more mature social and cognitive challenges (Davidow et al., 2018) (Crone and Dahl, 2012).

While the hormonal cascade has been established, how each element contributes to the nature of cognitive development and its intersection with adolescent mental health, including substance use and its treatment, has been under-examined (Byrne et al., 2017). Here we highlight the central and interactive roles of DHEA and gonadal hormones in neurocognitive development, and indicate their potential role and impact within the adolescent addiction treatment context.

(2) Surge of cognitive skills. Another hallmark of adolescence is the steep improvement in cognitive abilities that allow individuals to set and accomplish high-level goals (Davidow et al., 2018). In addition to the widely recognized role of cognitive control, adolescents show an elegant network of development across an array of cognitive skills during this period. Examples of emergent cognitive skills highly relevant to the treatment context include the inception of abstract reasoning, higher-order reasoning, working memory, self-monitoring, and cognitive flexibility (Luna et al., 2004, De Luca et al., 2003). Of note, this array of cognitive skills matures across a range of timelines throughout adolescence. For example, cognitive flexibility is firmly online by early adolescence, whereas working memory shows strongest effects by late adolescence (Luna et al., 2004, De Luca et al., 2003, Anderson et al., 2018). Developmental neuroscientists propose that the heterogeneous patterns of behavior observed throughout adolescence are subserved by the comparably heterogeneous patterns of brain development; this has direct implications for clinical treatment with adolescents.

A rich collection of functional neuroimaging studies in healthy adults compared with lesion patients reveal the centrality of prefrontal and parietal cortices in cognitive control and related cognitive capacities (Miller, 2000, Miller and Cohen, 2001, Knight, 1990). Structural prefrontal and parietal cortical development is typified by cortical thinning (i.e., pruning) in gray matter, along with linear increases in white matter. Marked regional variability is

observed; medial and ventral prefrontal cortex (PFC) develop notably sooner than lateral and dorsal PFC (Giedd et al., 1999, Gogtay et al., 2004, Shaw et al., 2008, Tamnes et al., 2017).

Further, these patterns do not linearly associate with emerging cognitive skills. For example, cross-sectional studies of working memory and inhibitory control have, somewhat counterintuitively, shown *both* increases (Rubia et al., 2006, Rubia et al., 2013, Jolles et al., 2011) and decreases in activation (Velanova et al., 2008, Velanova et al., 2009) of prefrontal and parietal cortex with age, depending on task demands and the precise adolescent age tested. This mirrors the adolescent substance use neuroimaging literature, which has shown the same pattern of counterintuitive increases and decreases in activation (Feldstein Ewing et al., 2014).

One possibility is that age predicts stronger activation in a smaller, more specialized subset of prefrontal and parietal regions, and less reliance upon more diffuse, and less task-relevant regions (Durstun et al., 2006, Guassi Moreira et al., 2018). Indeed, a growing number of longitudinal studies support “task-positive” activation increases, and in tandem, less task-irrelevant activation, throughout adolescence (Durstun et al., 2006, Simmonds et al., 2017).

Of relevance to the treatment context, these disparate patterns of developmental timing may help explain why developing adolescent cognitive skills like working memory, which is supported by dlPFC (Nee et al., 2013, Moser et al., 2017, Wager and Smith, 2003), along with abstract thinking and reasoning, which rely upon the most rostral portions of dlPFC (Dumontheil, 2014), emerge a bit later in the cognitive skill cascade.

A challenge that stymies succinct characterization of adolescent cognitive development – and likely adolescent substance use treatment as well – is that the same adolescents often show markedly different cognitive skills when placed in different socioemotional contexts. Relative to adults, adolescent performance is more strongly impacted by affectively salient stimuli and by socioemotional contexts (see Section 4 below) (Gardner and Steinberg, 2005, Hare et al., 2008, Somerville et al., 2011, Cohen et al., 2016). This sensitivity to socioemotional contexts is mirrored by the relatively greater responsivity of

subcortical structures (ventral striatum, amygdala) as compared with lateral prefrontal regions during this age period; relevant to the treatment context, these networks serve a crucial role in identifying and behaviorally responding to salient cues (Hare et al., 2008, Somerville et al., 2011, Chein et al., 2011, Cohen et al., 2016). Importantly, turning up the socioemotional dial also impacts functional coupling (i.e., connectivity) in nascent prefrontal-parietal (Cohen et al., 2016) and prefrontal-subcortical networks (Somerville et al., 2011). These adolescent-specific differences in circuit-level communication may be crucial for understanding how and why adolescents identify (and communicate about) emotions, particularly when emotions run hot (Casey, 2015).

Similarly, adolescents differ significantly from adults in their emerging skills in engaging cognitive strategies, including reappraisal and emotional distancing, to regulate emotions (Guassi Moreira and Silvers, 2018). A long history of behavioral research has shown that very young children can utilize cognitive regulatory strategies if provided the appropriate scaffolding, but not necessarily when left to their own devices (Moore et al., 1976, Mischel et al., 1989, Mischel and Mischel, 1983, Garnefski and Kraaij, 2006, Williams and McGillicuddy-De Lisi, 1999). Relevant to the treatment context, one's ability to effectively engage cognitive strategies in the area of self-regulation improves linearly from childhood to adolescence, with performance plateauing at around age 17 (Silvers et al., 2012). The precise age at which adolescents achieve adult-like performance differs for social and non-social stimuli (Silvers et al., 2012), as well as for appetitive and aversive stimuli (Silvers et al., 2017, Silvers et al., 2014).

Adolescents show protracted development, particularly in the context of salient, negative emotions (particularly negative social emotions; see Section 4), and in turn, adolescence is typified by a period of greater experienced negative affect and elevated amygdala response relative to adults (Silvers et al., 2017, Silvers et al., 2012, Silvers et al., 2015). Compared to adolescents, adults show reduced concurrent and sustained amygdala responses to aversive stimuli, and these age-related reductions in amygdala response are mediated by the enhanced role of ventrolateral prefrontal cortex (vlPFC) (Silvers et al., 2017,

Silvers et al., 2015). However, the interaction between vIPFC and amygdala responses requires relatively mature prefrontal-amygdala coupling, suggesting that neurobiological development serves as a relevant potential rate-limiting step in adolescents' ability to navigate certain types of strong emotions, and engage planful behavior in the context of deep negative feelings (Silvers et al., 2017).

Another central hallmark of adolescent cognitive development is the emergence of abstract reasoning (e.g., "formal operations"). Of relevance to the treatment context, abstract reasoning enables an adolescent to generate and systematically evaluate hypotheses (e.g., Erickson et al., 2005) and engage in relational reasoning (Inhelder and Piaget, 1958), which involves the simultaneous consideration of interrelated dimensions and situations necessary to arrive at a conclusion (Osherson and Markman, 1975). Children can solve 0- and 1-relational level problems easily, but only adolescents with sufficient frontal lobe maturation have the capacity to solve 2-relational level problems, wherein two dimensions of variation are simultaneously considered (e.g., Christoff et al., 2001). As behavioral treatment often requires this type of simultaneous processing, the development of this cognitive skill may impact adolescents' capacity to engage and successfully participate in treatment.

Together, the findings above suggest that adolescence is characterized by an array of novel cognitive skills highly relevant to the treatment context, including the emergent capacity to reason abstractly, to experience and react to negative emotions, and in turn, to develop and engage in purposeful and planful behavior.

(3) Sculpting out of self. A core feature of adolescence is a heightened focus on the self, as adolescents increasingly consider who they are and what others might think of them (Pfeifer and Peake, 2012, Sebastian et al., 2008); this shift of focus contributes to the development of cognitive and socio-emotional processes crucial during adulthood, including self-awareness and its impact on increasingly complex decision-making (Blakemore and Robbins, 2012, Pfeifer and Peake, 2012). Increased self-awareness is integral to the formation of self-identity (Pfeifer and Berkman, 2018), including on the level of traits (e.g.,

academic versus social) (Pfeifer et al., 2013) and other dimensions of culture and identity (Telzer et al., 2013b).

Many developing cognitive processes hinge upon the capacity for *meta-cognition*, including the capacity to self-reflect sufficiently in order to effectively self-monitor. This may explain why social and cognitive processes appear to co-develop behaviorally and neurally (Blakemore and Choudhury, 2006, Sebastian et al., 2008, Pfeifer and Peake, 2012). Relative to children, in some of these dimensions, adolescents are more akin to adults in arenas of self-processing (Jankowski et al., 2014, Pfeifer et al., 2009, Debbané et al., 2017, Pfeifer et al., 2007, Pfeifer et al., 2013), subserved by the ventromedial prefrontal cortex (vmPFC) and the ventral striatum (VS) (Denny et al., 2012, Pfeifer and Berkman, 2018, Roy et al., 2012). However, highly relevant to the adolescent treatment context, the vmPFC is uniquely sensitive to evaluating the self-relevance of social information during adolescence (Pfeifer et al., 2013, Dégeilh et al., 2015), while the VS is central to “what other people think about you”, a characteristic cognitive feature heightened during adolescence (Jankowski et al., 2014).

While a heightened sense of self is normative during adolescence, the novel experience of self-reflection and self-monitoring has some unpleasant implications. Adolescents’ growing ability to consider what others think about them can be accompanied by natural elevations in attendant negative affect, including fears about social assessment and self-consciousness, both of which peak during adolescence (Rankin et al., 2004, Michiel Westenberg et al., 2004). The enhanced feelings of others’ scrutiny can be activated even during minimally evaluative circumstances – such as simply telling a study participant that a peer is watching them– and has been linked to adolescent-specific increases in medial prefrontal cortex (mPFC) recruitment and mPFC-VS connectivity (Somerville et al., 2013). Greater self-focus also has a darker side. It can lead to rumination, negative affect, and depression (Moberly and Watkins, 2008, Nolen-Hoeksema, 2000), and can contribute to adolescents’ sense that they need to engage in behaviors to improve their social standing and affect, including substance use (Cousijn et al., 2018, Caouette and Feldstein Ewing, 2017).

Together, relevant for the adolescent addiction treatment context, these data suggest that adolescent-emergence of self-focus is supported by functional changes in regions involved in self-cognition, and to a lesser extent – regions involved in cognitive and affective processing – and that these normative changes likely contribute to the characteristic pronounced self-focus experienced by most adolescents.

(4) Adolescents' changing social landscape. Developmental psychologists have long observed that adolescents' growing sense of self-awareness occurs concurrently with substantive shifts in their social landscapes. Only recently, however, have developmental neuroscientists begun to probe the neural underpinnings that correspond to these social behavioral changes (Foulkes and Blakemore, 2018).

Adolescents' growing sense of self-awareness shifts concurrently with their changing social landscapes. Indeed, adolescents' desire to establish individuality is almost by necessity coupled with their transition away from their caregivers (Crone and Dahl, 2012). At the same time, adolescents' increased self-consciousness reflects not only greater self-awareness, but also concern over how their peers perceive them. Social networks expand dramatically as adolescents spend an increasing time with friends and less with family (Wrzus et al., 2013, Larson and Richards, 1991). Beliefs about what constitutes normative behavior among peers (Knoll et al., 2015, Knoll et al., 2017), and being in the presence of peers (Gardner and Steinberg, 2005), impact adolescent decision-making around perceived risk during this period.

It is during this timeframe that most youth begin to make decisions about whether and when to engage in substance use, and these situations often arise in peer-based contexts (Shedler and Block, 1990, Winters, 1999). Despite the panoply of factors involved in this decision, the proportion of alcohol-using friends continues to be the best predictor of adolescents' decision to engage in substance use (e.g., accounting for 50% of the variance; Chassin et al., 2004). Further, adolescents' perception of peer substance use behavior has been directly related to both their current substance use, as well as their substance use



progressions (e.g., substance use in the following year; D'Amico and McCarthy, 2006, Kilmer et al., 2006)

While neural correlates of peer acceptance and rejection have been evaluated (for a review, see Burnett et al., 2011), few studies have employed ecologically-valid paradigms to evaluate the influence of adolescents' actual peers on their risk-taking behavior. Chein and colleagues found that adolescents (ages 14-18) (Chein et al., 2011), as contrasted with emerging adults and adults, made more risky driving decisions when they were aware that their friends were in the fMRI control room than when they conducted the task on their own (peer vs. alone). The authors also found greater BOLD response in VS and orbitofrontal cortex (OFC) in the peer versus the alone condition.

Overlapping with other neurodevelopmental theories (e.g., Casey et al., 2008, Ernst et al., 2005), In his 2008 model, Steinberg (e.g., Steinberg, 2008) posits the predominance of the social-emotional network (SEN) during adolescence. Critical nodes within the SEN include the dopaminergic (DA)-pathways of the OFC, nucleus accumbens (NAc), VS, and mPFC. These areas are particularly important for adolescents' processing of social (peer) information (e.g., Steinberg, 2008, Guyer et al., 2009, Masten et al., 2009). The greater activation of these regions during the neurodevelopmental period of adolescence may be the result of substantive neurodevelopmental changes (including a redistribution of DA receptor density in the PFC, striatum, and NAc). These changes peak during adolescence, resulting in a relatively greater release of DA during this timeframe (e.g., Paus et al., 2008a).

Practically, this means that risk taking behaviors, which are inherently exciting, frightening, and fun, may indeed feel much more rewarding during middle adolescence (e.g., Dahl, 2011, Galvan et al., 2007)

While it is clear that peers take on newfound significance during adolescence and that this shift has the *potential* to increase risk behaviors, an important body of work is beginning to reveal important caveats to this thesis. First, peer influence is also a powerful motivator for *prosocial behavior* during adolescence (van Hoorn et al., 2016, Foulkes et al., 2018). Relatedly, while neural reward circuits are linked to a variety of risk behaviors during

adolescence, VS and vmPFC reactivity to social cues also portend *positive, prosocial development* (Telzer et al., 2013a) (Pfeifer et al., 2011). Second, while peers become increasingly important during adolescence, this does not render parents as unimportant. Despite spending less time with parents, connectedness with parents can attenuate the impact of the enhanced reward circuit responses typical during adolescence, serving as a protective force insulating adolescents against risk behavior, stress and even depression (Guassi Moreira and Telzer, 2018, Telzer et al., 2015, Guassi Moreira and Telzer, 2015, Doom et al., 2016). In fact, when compared with peers, parents show a significantly greater impact on adolescent decision-making (Welborn et al., 2016, Guassi Moreira et al., in press).

Understanding how adolescents navigate not only risk, but also prosocial peer interactions is one of the ultimate challenges for adolescent addiction treatment developers. We believe that this challenge is not insurmountable (Pfeifer et al., 2011, Paus et al., 2008b). Our task is to determine how best to channel youths' drive and developmentally-unique cognitive systems to help them make more healthy choices.

Summary. These four developmental domains interact dynamically throughout adolescence (Crone and Dahl, 2012), and are highly relevant to the adolescent addiction treatment context. For example, an adolescent's environment can impact the nature and timing of puberty (e.g., family stress and parent conflict can accelerate onset) and vice versa; adolescents who look older may be treated differently than same-age adolescents who appear younger (Ellis and Garber, 2003). These pubertal changes can alter the social spheres that adolescents are introduced to and experience (e.g., more mature girls may find themselves in the company of young men, who are already more advanced in terms of substance use). Moreover, social experiences, in turn, shape adolescents' cognitive opportunities and related development early (e.g., youth who initiate substances – such as alcohol, cannabis, vaping may be altering the capacity and nature of their brain growth) (Lisdahl et al., 2013). Considering the interplay of these factors is crucial for understanding

adolescent development as well as cultivating impactful programs to prevent and treat adolescent substance use.

### **III. How well do existing treatments for adolescent substance use work?**

Throughout the past 3 decades, adolescent addiction treatment has shown some degree of capacity to catalyze and sustain behavior change in adolescents, but overall, results have been underwhelming (Feldstein Ewing et al., 2016a). More specifically, despite several decades of efforts by experts to identify the best avenues to prevent and reduce adolescent substance use, few youth receive treatment (<6%) (SAMHSA, 2014). Of those who do, even when the treatment is grounded in evidence-based approaches and works well for adults, many youth do not show significant long-term changes in their substance use (Jensen et al., 2011, Tripodi et al., 2010), with 86% returning to use within a year of treatment (Winters et al., 2000).

As reviewed in Feldstein Ewing (2016a), this contrasts with the adult addiction literature, wherein a number of psychosocial interventions have much stronger impact in terms of instantiating and sustaining meaningful behavior change (Anton et al., 2006, Project Match Research Group, 1997). For example, meta-analyses examining the efficacy of motivational interviewing (MI) indicate that in the context of addiction treatment, MI's effect sizes are notably less robust for adolescents (mean  $d = 0.17$ ) (Jensen et al., 2011) as compared with their impact with adults (mean  $d = 0.77$ ) (Hettema et al., 2005).

At issue is that most of the interventions clinicians use with adolescents are “borrowed” from adult clinical addiction research (Feldstein Ewing et al., 2016c). Yet the samples and populations utilized in large scale adult addiction studies, such as Projects COMBINE and MATCH (Anton et al., 2006, Project Match Research Group, 1997), included inherently different populations, such as adults who largely self-referred to treatment. As a result, there is a notable gap between the nature of adults from whom these treatments were derived, and the nature of adolescents that we are trying to implement the same interventions with (for more see (Feldstein Ewing et al., 2016a). Ultimately, better targeting

with adolescent neurodevelopment in mind is likely to improve adolescent addiction treatment outcomes.

The poor generalizability of “adult” treatment to adolescents revolves around the significantly different conditions that make interactions within adolescent addiction treatment highly disparate from adults; within treatment sessions, adolescents face inherently different neurodevelopmental issues (Giedd, 2015), disparate sociodevelopmental concerns (Blakemore, 2018), are on a different addiction trajectory (Cousijn et al., 2018), and in turn, have different treatment outcome goals than adults (Feldstein Ewing et al., 2016a).

Here, we include a brief overview of the challenges facing adolescent addiction treatment and its reporting, and our recommendations for avenues to improve best practices for clinicians and clinical research in this critical area of adolescent addiction treatment development.

### **How can adolescent addiction treatment be improved?**

(1) Absence of uniformly-agreed upon outcome in the adolescent addiction treatment literature. The current status of the field renders it quite difficult, if not impossible, to compare adolescent treatment outcomes across different treatment approaches (e.g., Black and Chung, 2014). This is in contrast to the adult literature, wherein there are *common, widely-agreed upon outcome metrics*, such as percent days abstinent (PDA) or drinks per drinking day (DDD) (Anton et al., 2006, Project Match Research Group, 1997). In this brief examination, numerous different categories of outcome variables were reported. The most common included number of substance use days, substance-related consequences, and quantity of substance use.

This range of outcomes is likely to reflect a number of issues; one, as observed throughout the adolescent addiction treatment literature, there may simply be different targets for adolescent treatment response. More likely, this reflects that adolescents often show behavior change within one dimension of substance use (e.g., decrease in alcohol use days), while still retaining high scores on another (e.g., continued alcohol-related problem

scores due to ongoing processing for an alcohol-related arrest that occurred prior to change in drinking) (McCambridge and Strang, 2004, Feldstein Ewing et al., 2013). Of greater concern to adolescent addiction practitioners, variance on outcomes may reflect reporting bias that favors treatment outcomes that withstood the test of statistical significance.

One avenue to improve the field may be to report on commonly-agreed upon adolescent treatment outcome measures (see **Table 1**) and do so regardless of statistical significance. We believe that this recommendation, to move toward a core outcome set in the field of adolescent addiction treatment, is highly important, and follows recent relevant initiatives, including the Scottish National Health System's core outcome work (The.Scottish.Government, 2015), and the Core Outcome Measure in Effectiveness Trials (COMET) Initiative (Gargon et al., 2017, Williamson et al., 2017). Notably, while these examples serve as excellent models, they have thus far been largely implemented with adult, rather than adolescent, clinical research studies. This fact again highlights the need for identifying and rolling out jointly-agreed upon core outcome metrics for adolescents in addiction treatment.

(2) Difficult to determine the degree of clinical relevance and impact in adolescent treatment response. Additionally, even when effect sizes are significant, it is not clear the degree to which reported outcomes are clinically meaningful with adolescent addiction patients. For example, one less drinking day per month may achieve statistical significance, but not a meaningful clinical change in terms of adolescents' overall health, social, cognitive, and academic outcomes. In the adult literature, clinical impact has been defined as a statistically significant reduction in initial rates or problem scores, or a halving of initial symptoms (Miller and Manuel, 2008).

As with many other forms of adolescent health risk behaviors (e.g., HIV risk behavior), a central measurement challenge is that adolescents engage in substance use sporadically and inconsistently (Clark, 2004). This makes treatment outcome measurement quite different from adults, whose use is often characterized by heavy, consistent patterns. For example,

an adolescent may use alcohol very heavily (binge drink 3x/month over the summer), but then not drink at all during the initial months of the school year (Del Boca et al., 2004).

Another avenue to improve the field is to examine pre-to-post changes in interference in functioning for youth; this represents changes in the degree to which alcohol or other substance use disrupts interactions with peers, with family, with school/other academic, and/or other relevant work/extracurricular obligations. To this end, examining reductions in interference in functioning is likely a more meaningful metric (see **Table 1**). Examples of measures that can effectively access and assess this factor include the Rutgers Alcohol Problems Index (White and Labouvie, 1989) and the Marijuana Problems Index (Lisdahl et al., 2018).

(3) Wide variance on examined timing. Adolescent addiction studies continue to reflect the importance, but notable absence, of longitudinal adolescent addiction treatment outcome studies (Larimer and Crouce, 2007). Further, there is substantial variance in the timing of reported outcomes; some studies include end-of-treatment only, while others report data in a variety of windows (e.g., 1 month, 6 weeks, 8 weeks, 3 months).

A third recommendation to improve the field includes examining behavior change, systematically (such as every 3 months; see **Table 1**) for at least the first year following treatment, to begin to generate comparable windows to examine youth change.

(4) Substance substitution? While it is clear that adolescents tend to gravitate toward polysubstance, rather than mono-substance, use (Clark, 2004), many adolescent treatment studies do not report treatment outcomes for non-target substances of abuse. For example, many measured treatment outcomes in alcohol (only), cannabis (only), tobacco (only); some examine 2 substance categories, but include inconsistent pairings across each study (e.g., alcohol+cannabis; alcohol+tobacco). This is relevant, as many contemporary adolescent addiction treatment teams are trying to disaggregate whether or not youth are “swapping”

out one substance for another, particularly in the changing cannabis and opioid landscapes (Choo et al., 2016, Feldstein Ewing et al., 2017, Dash et al., 2018).

Our fourth recommendation to the field is our encouragement to explicitly examine and report outcomes across all types of substance use, to ensure that we can disaggregate the differential impacts and interactions that each substance (and their intersection) might be having with the developing brain (e.g., Whelan et al., 2014, Karoly et al., 2015). This is likely to become an increasingly important issue in the field of addiction treatment as researchers move towards a precision medicine lens for understanding the genetic, lifestyle, psychological, social, and other bio-behavioral markers associated with treatment responsiveness (Volkow, 2018). Of course, it should be noted that this point applies equally to adult studies, and to psychosocial interventions for most kinds of behavior disorders. Sadly, adolescent treatment has continued to lag behind advances made in other age groups in the journey towards precision medicine (Feldstein Ewing et al., 2016c, Feldstein Ewing et al., 2017, Feldstein Ewing et al., 2016a, Bundy et al., 2018).

Summary. Many adolescent addiction treatments appear to have clinically meaningful outcomes, but cross-treatment comparison and interpretation is not truly possible in the literature's current state. At this time, inconsistent targets and timing obscure careful detection of comparative clinically-meaningful treatment gains (Black and Chung, 2014). In turn, it is currently quite difficult to access the driving mechanisms and their intersection with potential developmental cognitive factors, and true treatment success in this age group. In turn, we make these recommendations for the assessment of adolescent treatment outcomes, with examples of how each recommendation maps onto relevant neural targets (**Table 1**). It will be fascinating to continue to see if and how these developmental neuroscience findings translate to the clinic.

#### IV. Promising future directions for substance use treatment in this age group.

While the previous section indicates that existing treatments available to adolescents have had difficulty examining behavior change, it is our position that actively considering the nature of the developing adolescent brain can inform the revision and approach of interventions with this age group. In other words, the developing brain gives us an invaluable perspective regarding what might “work” better in this age group in terms of prevention/intervention.

As summarized in **Figure 1**, we propose four key neurodevelopmental features of adolescence, and encourage approaching addiction interventions from this foundation as a promising first step in articulating prevention and intervention to the adolescent age group. Compellingly, in largely overlapping neural networks, those four features include: (1) Puberty; (2) Surge of cognitive skills (3) Sculpting out of self; and (4) Changing social landscape. Collectively, consideration of these factors, and their interplay, highlights several important themes to consider in developing novel clinical addiction approaches with this age group.

Benefit of a prosocial perspective on prevention and intervention. First, consistent with G. Stanley Hall’s “storm and stress” (Hall, 1904) perspective of adolescence, many existing adolescent-focused prevention and intervention approaches hinge on “problem-focused” perspectives in substance use and its resolution. However, this does not play to the nature of the adolescent brain, which is increasingly being recognized as *evolving* and *adaptive* (Giedd, 2015). As cited by Ellis (Ellis et al., 2017), integrating considerations of adolescent neurodevelopment would likely generate more positive treatment outcomes if we took a positive, adaptive-focused perspective that plays to and enhances adolescents’ existing strengths in resilience, natural penchant to cognitive flexibility, and socially-adaptive and prosocial growth. This is an arena that is gaining increasing traction in adolescent addiction contexts (Cousijn et al., 2018, Feldstein Ewing et al., 2018). Non-traditional, but potentially highly impactful examples here could include clinical approaches that engage



adolescents in helping younger peers, pairing problem users up with more successful youth in the same age group, and engaging adolescents in avenues for more successful positive change in their peer and greater social communities (Yeager et al., 2017).

A relevant point in this examination is that while a handful of emerging studies are beginning to include prosocial, resilience-focused models of adolescent behavior (Yeager et al., 2017, Ellis et al., 2017, Cousijn et al., 2018, Feldstein Ewing et al., 2018, Foulkes et al., 2018), a careful synthesis of these models has not yet been created. This is a critical avenue for future work, and will likely require not only examination of quantitative, but also mixed-method, and qualitative research, as much of this emerging research is still in its inception and early stages of implementation.

Maximizing their drastically developing cognitive skills. Adolescents are in the midst of experiencing a surge of new cognitive skills; at the most fundamental level, adolescents' brains are organized toward and ready for adaptation (Giedd, 2015). Leagues ahead of the natural adaptive skills of adults who are often clunky at social modification, adolescents are primed to quickly, and often seamlessly, integrate novel information and behavioral adjustment that facilitates their capacity to rapidly adapt and adjust in numerous (different) novel and shifting social and community contexts (Giedd, 2015, Giedd, 2018). To this end, adolescents are arguably better prepared to modify and shift their behavior successfully than adults (Davidow et al., 2016), who are much less facile in adapting their behavior to be congruent in novel social contexts. Here, we believe that potentially novel clinical approaches, and particularly those that incorporate the role of social and family context in youth substance use behavior, are likely to show promise for catalyzing reductions in adolescent substance use. Examples of this include adolescents' capacities to drastically reduce use when they are outside of risk environments (e.g., when adolescents with substance use disorders easily transition to zero use during time in experiential education programs). The greatest challenge here may be to identify how best to work with adolescents' developing cognitive skills to translate potential reductions in use in one context

(e.g., while on experiential education programs; while in treatment), to other social contexts (e.g., when they return from programs into social environments that may be populated by substance-using peers, or parents).

Harnessing drive for autonomy. One aspect of addiction treatment that is largely overlooked in existing treatments is adolescents' inherent drive for autonomy. The social psychology literature echoes adolescents' strong desire for sculpting out their own place of standing (Yeager et al., 2017). Here, we believe that non-traditional approaches that allow adolescents to engage and utilize their voice for change, may give them the opportunity to channel this inherent drive toward positive contributions within their peer and sociocultural communities. Non-traditional approaches of promise include encouraging adolescents to engage as advocates for change in positive arenas of interest (e.g., social justice; political domains) (Yeager et al., 2017). Additionally, it is worthwhile to consider that while adolescents are developing their "voice", they are developing meta-cognition, including how to self-reflect on how their choices and behaviors may impact others, from more immediate levels (friends, family) to broader spheres of communication (e.g., school, social media). Clinical efforts that work with adolescents to identify the lines of connection (e.g., between their developing self → the ideas that their developing self has → the behaviors in which that developing self engages → how those ideas/behaviors can instantiate change in the broader sociopolitical community) may help adolescents play an active role in their evolving sense of self.

Parents are not out of the picture yet. The last consideration that we believe may be underdiscussed in current addiction approaches, that largely happens on a one-on-one treatment level in adult addiction treatment, is the role of the family in addiction treatment outcomes. While adolescents "look like" adults, by and large, many continue to live in family contexts throughout the adolescent years. Further, data continue to reflect that the developing brain is modified by parent factors (Telzer et al., 2013a) (Guassi Moreira and

Telzer, 2018). Similarly, parent and family-based approaches still continue to show some of the largest successes in adolescent addiction treatment outcomes (Feldstein and Miller, 2006). Relevant to the shifting social contexts of adolescents, parents and families can represent one beneficial constant in a world of ever-evolving social landscapes. Thus, here, we encourage clinicians to incorporate parents and families whenever practical and possible to maximize positive development and change.

**Summary and Future Directions.** This reviews offers one step toward understanding the nature of the developing adolescent brain, and how those neurodevelopmental data can inform next-step modifications or innovations to adolescent addiction treatment. This represents one critical foundational element in a much-larger cascade of health care approaches for this age group. In other words, in order to have adolescent addiction interventions generate maximal impact, they have to be effective, but they also have to be accessible to and specific for this age group. We suggest four key neurodevelopmental factors that we believe will enhance addiction treatment approaches (e.g., puberty, developing cognitive skills, sense of self, social landscape) and directly-linked clinical approaches that we believe will enhance treatment outcomes in this age group (e.g., prosocial perspectives, developing cognitive skills, drive for autonomy, and inclusion of parents/families). And, we encourage methods for examining adolescent treatment response, and highlight their related neural relevance, including: working towards consensus for common adolescent treatment outcomes (e.g., past month days of substance use); examining pre-post changes in interference in functioning, as assessed with empirically-validated “problems” measures; conducting comparable follow-up windows of adolescent treatment outcomes (e.g., 3, 6, 9, and 12 months); evaluating and reporting outcomes across all types of adolescent substance use; and evaluating parent/family factors in adolescent substance use outcomes. Already, at present, the field is moving very rapidly in the domain of methodological, statistical, and technological innovations, including rapid advances in predictive algorithms and machine learning (Casey et al., 2018). Our team

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represents one lab explicitly linking the integration of neuroimaging technology into the adolescent treatment context (Feldstein Ewing et al., 2016b), and similar advances in identifying and understanding variability are emerging in other adolescent treatment fields (e.g., eating disorders) (McAdams, 2017). We look forward to seeing innovations that stem from the integration of these neurodevelopmental perspectives in adolescent addiction treatment approaches and outcomes.

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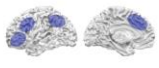
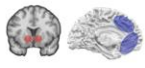
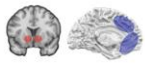
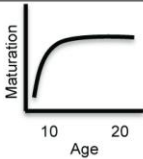

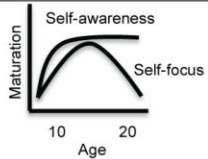
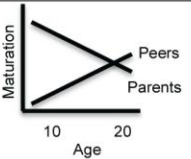
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Figure 1: Summary of the tasks of adolescence. Brain systems: Blue designates cortical regions, red subcortical. Common social cognition networks are involved in changes in self-processing and navigating the novel social landscape. Age patterns: Adolescent-emergent, linear and adolescent-specific age patterns are depicted. Treatment relevance: Relationship between tasks and treatments are summarized.

**Table 1:** Recommended methods for examining adolescent treatment response and related neural relevance

<b>Recommended methods for examining adolescent treatment response</b>	<b>Related neural relevance</b>
(1) Work toward consensus for common adolescent treatment outcomes, such as: past month days of substance use	Allows a continuous measure of potential neurotoxic impact in the developing brain
(2) Examine pre-post change in interference in functioning, as assessed with empirically-validated “problems” measures	Adolescents may have non-symptomatic substance use; this is one way to disaggregate experimentation from more problem levels of use
(3) Conduct comparable follow-up windows of adolescent treatment outcomes such as: 3, 6, 9 and 12 months	Consistent and comparable outcome assessments on a neural level due to rapid neurodevelopment
(4) Evaluate and report outcomes across all types of adolescent substance use	Different substances may have different levels of impact and interaction on the developing brain
(5) Evaluate parent/family factors in adolescent substance use outcomes	We do not yet have a strong sense of how family interactions affect addiction processing in the developing brain; this is an important direction for future work
(6) Evaluate social (peer) relationships in adolescent substance use outcomes	Social (peer) factors are strongly implicated in the developing brain; this is an important direction for adolescent treatment response



	Puberty	Cognitive change	Sense of self	Social landscape
Brain systems	Multi-system			
Age pattern				
Treatment relevance	-Identifying prosocial sources of novelty seeking to replace substances	-Enhanced ability to use cognitive strategies -Recognition that cognitive skills are context-dependent	-Harness increased desire for autonomy -Examine role of introspection in substance use	-Identify prosocial sources of reward -Seek out positive peer influences -Acknowledge continued role of parents on behavior