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Adolescence and Addiction

Vulnerability, Opportunity, and the Role of Brain Development

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Introduction

Adolescence is a transitional period in human development when an individual is no longer considered a child but has not yet achieved full adult status in society (Dahl, 2004). This "in-between" quality of adolescence can be observed across several domains. For example, changes in hormone levels contribute to a pubertal growth spurt (typically around 12 for girls, 13.5 for boys) during which many adolescents experience an asynchronous development of different bodily parts: the growth of the arms and legs often outpaces that of the trunk. In the realm of psychosocial development, adolescents also demonstrate "in-betweeness" in terms of a progressive maturation over time in their sense of identity, autonomy, sexuality, morality, and so on, which makes them think, feel, and interact with their world sometimes like adults, sometimes not. For example, many adolescents spend increasingly more time in the presence of their peers as they grow older and gain a sense of adult-like independence about the choices they make in their romantic life and the way they spend their leisure time, yet they remain dependent on their parents financially.

The transitional nature of adolescence also plays out in terms of brain development. Differential rates of neural maturation have been observed in reward- or motivation-related and executive control-related brain regions (Steinberg, 2004; Casey, Jones, & Somerville, 2011). Dopamine-rich limbic regions supporting behavioral motivation and reward processing reach heightened levels of functioning around puberty, earlier than prefrontal cortical regions, which support cognitive (inhibitory) control and continue to mature into the third decade of life (Gogtay et al., 2004). This is considered to result in an imbalance in motivation versus control and underlies an increased vulnerability for risky decisions and behaviors (e.g., Spear, 2010). That is, while adolescents experience heightened motivation to pursue high sensation and novel rewards, their capacity to internally regulate these drives is limited or inconsistent by comparison to that of adults. Importantly, context matters in terms of risky decision

The Wiley Handbook on the Cognitive Neuroscience of Addiction, First Edition.
Edited by Stephen J. Wilson.

making, as adolescents appear more influenced than younger and older individuals by rewards that are salient or novel, immediately available, and oftentimes associated with peer approval.

In some instances, adolescents' risk-tasking tendencies may result in positive outcomes. Indeed, several authors suggest potential adaptive benefits, including the promotion of exploration of novel environments and social interactions (e.g., Spear, 2010). However, in other contexts risky behavior (e.g., accepting a car ride from an intoxicated friend, engaging in unprotected sex, experimenting with drugs) can lead to dangerous or even deadly outcomes (accidents, sexually transmitted disease, addiction). Consequences of risky behaviors during adolescence are the leading preventable causes of morbidity and mortality in this age group and, as such, are a major focus of prevention and intervention efforts.

In this chapter we focus on a particular kind of risky behavior: cigarette smoking. Cigarette smoking is a leading cause of disease and death worldwide (American Cancer Society, 2010) and, while smoking rates have declined since the mid-1990s, nearly 20% of adults in the United States still identify as daily smokers (Agaku, King, & Dube, 2014). Consequently, research into the antecedents and consequences of cigarette smoking remains a major public-health imperative. Importantly, the age at which one initiates smoking appears to be strongly related to continued smoking into adulthood, the majority of adult daily smokers initiating before the age of 18 (US Department of Health and Human Services, 2012). Adolescents initiate cigarette smoking at disproportionately high rates, despite widespread knowledge of its health-compromising and long-term consequences. Psychosocial factors clearly play a role in adolescent smoking initiation, but determining the role of the developing adolescent brain in this deleterious behavior has only recently received attention.

In the sections that follow we start by briefly highlighting findings from structural and functional imaging studies of normative brain development as a means to better understand how/why the adolescent brain may be susceptible to risk taking in a general sense. In this regard, we take a developmental cognitive neuroscience perspective and consider several key decision-related brain systems during adolescence, including reward processing and cognitive control. Next we consider how smoking may have a unique profile of effects on adolescents by comparison to older users that may ultimately contribute to continued use. As part of this analysis, we highlight contributions from functional imaging studies to our understanding of adolescent smoking. Finally, we consider ways in which our understanding of adolescent brain development and sensitivity to nicotine may help inform smoking prevention and intervention efforts.

Adolescent Brain Development

Structural changes in the adolescent brain have been well documented in a number of reviews (Lenroot & Giedd, 2006; Giedd & Rapoport, 2010). While the gross physical appearance of the brain during adolescence is similar to that of adults in terms of its overall size, weight, and gyrification (Caviness, Kennedy, Richelme, Rademacher, & Filipek, 1996; Giedd et al., 1996), significant changes continue to occur during this period of development. Longitudinal magnetic resonance imaging (MRI) studies have demonstrated that gray-matter (GM) volume peaks in late childhood before undergoing progressive thinning through adolescence and into young adulthood

(Gogtay et al., 2004). While a reduction in GM likely reflects several microstructural events, a key process is synaptic pruning – the loss of underused synaptic boutons between neurons. Pruning is thought to enhance information processing within localized brain regions by increasing the speed and specificity of communication between neurons. Synaptic pruning provides a mechanism by which the brain can change itself so as to fit optimally in its environment (Andersen, 2003; Luna, Garver, Urban, Lazar, & Sweeney, 2004).

From a developmental perspective, a key finding from longitudinal MRI studies is that GM changes are not uniform across the entire brain; this confirms and extends earlier post-mortem histological work (e.g., Huttenlocher & Dabholkar, 1997). Instead regional variability exists, as primary sensory and motor cortices thin (or mature) earlier than regions of higher order association – like the prefrontal and temporal cortices, which progress along more protracted trajectories, into the twenties. Moreover, subcortical structures, including the ventral striatum (VS), also show continued maturation (GM thinning) throughout adolescence (Sowell, Thompson, Holmes, Jernigan, & Toga, 1999). In line with the imbalance model of adolescent risk-taking, which posits an earlier maturation of subcortical regions such as the amygdala and nucleus accumbens than of prefrontal regions, the majority of individuals in a recent longitudinal study demonstrated an earlier maturation of the amygdala and/or nucleus accumbens than of the prefrontal cortex (Mills, Goddings, Clasen, Giedd, & Blakemore, 2014). This variability in rates of brain development has important implications for our understanding of brain–behavior relationships. Given that specific regions of the cortex support distinct neural computations and that behavior is supported by networks of brain regions acting together, differential maturation across the brain may result in overall network function and behavior that is mature in some regards yet immature in others.

Structural MRI studies have also observed changes in white matter (WM) throughout the adolescent period. Linear increases in WM volume and density have been observed throughout childhood and adolescence, peaking in middle age (Giedd, 2008; Paus et al., 1999). The increase in WM volume is thought to be associated with myelination, a process that aids the functional integration of widely distributed circuitry (see Luna, Padmanabhan, & O'Hearn, 2010 for discussion), although alternative explanations have been suggested, including changes in axonal caliber (Paus, Keshavan, & Giedd, 2008).

The development of magnetic resonance techniques, such as diffusion tensor imaging (DTI; Basser & Jones, 2002), have allowed even greater insight into the development of WM during adolescence. DTI is sensitive to the properties of the diffusion of water molecules and, due to the interaction of water molecules with tissue structures, information can be gained about brain structure development. More specifically, fractional anisotropy (FA) values – a quantification of the extent to which the diffusion of water molecules in the brain displays anisotropic properties (water molecules located in fiber tracts are more likely to be anisotropic than water molecules in the rest of the brain and diffuse in parallel to a tract of myelinated axons) – is a common metric used in DTI studies that provides information on the structural integrity of WM. Results of DTI studies indicate increased FA throughout adolescence in brain areas associated with important cognitive functions such as memory and attention (Barnea-Goraly et al., 2005; Hasan et al., 2008). The increases occur predominantly in frontal brain regions (for a review, see Schmithorst & Yuan, 2010)

and are positively associated with cognitive functioning, including working memory (Nagy, Westerberg, & Klingberg, 2004) and information processing (Mabbott, Noseworthy, Bouffet, Laughlin, & Rockel, 2006).

Given these changes in WM, the adolescent brain, still undergoing the process of myelination, may not be as efficient or rapid in executing cognitive functions or in efficiently integrating the many signals associated with incentive processing (Watanabe & Sakagami, 2007; Grace, Floresco, Goto, & Lodge, 2007). In terms of the dynamics between reward and control brain regions, the maturation of frontostriatal WM structures, still continuing through adolescence, may also contribute to an increased capacity for cognitive control as individuals develop into adulthood (Liston et al., 2006).

Additional work has extended these findings on structural development to provide insight into sex differences. The consideration of sex differences in research on adolescent risk taking is critical, given the different rates of risk taking across the sexes during this developmental period in general (Byrnes, Miller, & Schafer, 1999), but also on account of sex differences that are present throughout all phases of drug abuse (see Becker & Hu, 2008 for review). In terms of cigarette smoking, sex differences in the age of smoking initiation have been observed across a range of studies, adolescent males demonstrating a lower age of initiation than adolescent females (for review see Okoli, Greaves, & Fagyas, 2013). While the mechanisms underlying sex differences in smoking behavior are complex and involve factors across many levels of analysis, sex differences in the structural development of reward and cognitive-control brain regions during adolescence are a key component for understanding these behavioral differences.

The most consistent sexual dimorphism in brain structure is a difference in total brain size, the male brain approximately 10% larger than the female – a difference not entirely accounted for by sex differences in body size (Reiss, Abrams, Singer, Ross, & Denckla, 1996; Witelson, Beresh, & Kigar, 2006). Other differences emerging from the literature depend on adjustments that are made to account for total brain volume, and thus are difficult to interpret (for a review, see Giedd, Raznahan, Mills, & Lenroot, 2012). While determining sex differences between brain areas may shed light on differences in rates of cigarette initiation in males and females, key to the present discussion is the relative rate of development of reward and control brain regions within each sex. Both males and females show evidence for progressive thinning of GM and increases in WM through adolescence (De Bellis et al., 2001; Lenroot et al., 2007). However, some of the changes in brain structure that occur throughout the adolescent period appear to be associated with puberty, as effects of pubertal development – not simply of age – on structural brain development have been observed in large-scale longitudinal studies. (Goddings et al., 2014). Such pubertal effects may reflect the actions of pubertal hormones on the brain; but they may also result from other mechanisms, such as chromosome effects and experiential differences associated with puberty across the sexes (Davies & Wilkinson, 2006; Blakemore, Burnett, & Dahl, 2010; McCarthy, Arnold, Ball, Blaustein, & De Vries, 2012). In line with differences in the timing of puberty processes across the sexes, with the earlier start of gonardarche in females (around 11 on average) than in males (around 12 on average), and with the effects of puberty on brain development, longitudinal studies that use adolescent samples have noted sex differences in the developmental trajectories of many brain structures through adolescence, peak GM volumes occurring earlier for females than for males (Lenroot et al., 2007).

Such sex differences in developmental trajectories of brain structure through adolescence raise interesting questions in terms of the timing of the experience of an imbalance between reward and control functions and in terms of how this might render some individuals more vulnerable to cigarette use than others. Important conceptual and methodological advances have taken place in recent years – especially a heightened awareness of the need to account for allometric scaling (Giedd et al., 2012), to use appropriate measures of pubertal status (Blakemore et al., 2010), and to consider design aspects such as the matching of samples on chronological age or pubertal status (Lenroot & Giedd, 2010). Such advances will help us address these questions in future research.

In line with the continued developments in brain structure through adolescence, functional magnetic resonance imaging (fMRI) studies have demonstrated developmental differences in the functioning of brain regions associated with reward processing and cognitive control. Across a range of studies, adolescents have shown greater VS responses than adults during reward anticipation (e.g., Galvan et al., 2006; van Leijenhorst et al., 2010) and less striatal activity than adults when assessing the incentive value for upcoming trials (Geier, Terwilliger, Teslovich, Velanova, & Luna, 2010). Although this pattern of activity has not been observed in all studies (e.g., Bjork et al., 2004), the majority of studies suggest a heightened responsiveness during reward anticipation in adolescents (see Galvan, 2010 for discussion). This hyperresponsiveness to incentives seems especially likely to occur in the presence of peers (Chein, Albert, O'Brien, Uckert, & Steinberg, 2010). This is important for the consideration of adolescence risk behaviors because risk taking, including smoking initiation (Delorme, Kreshel, & Reid, 2003), often occurs in social contexts (see Albert, Chein, & Steinberg, 2013 for review). Findings from these studies suggest that adolescents may be vulnerable to behavior directed at rewards where the value of the incentive has not been adequately assessed.

In terms of cognitive control, adolescents often exhibit the capacity to employ sophisticated executive functions in order to engage in voluntary, planned behavior. In research on adolescents' abilities to control behavior, two core executive functions have received the greatest attention: response inhibition and working memory. Response inhibition refers to the ability to inhibit habitual, behaviorally entrenched responses in order to direct behavior toward a more goal-appropriate response. For example, in the antisaccade task – which is a widely used index of oculomotor inhibitory control – participants are asked to inhibit reflexive saccades toward a bright dot when it appears on a black background. Such an ability is important for goal-directed behavior, as it allows an organism to resist engagement in reflexive responding and to engage in a more deliberative processing of stimuli before making a decision to engage or withdraw (Cacioppo, Gardner, & Berntson, 1999; Knoch & Fehr, 2007). Working memory refers to the ability to maintain a representation of one's goals in mind. Engaging working memory allows people to keep on task for long enough to reach their desired long-term goals.

Adolescents demonstrate near-adult levels of performance on inhibitory control and working memory tasks, but they continue to become more accurate on such tasks into late adolescence and early adulthood (e.g., Munoz, Broughton, Goldring, & Armstrong, 1998; Luna et al., 2004; for review, see Best, Miller, & Jones, 2009). fMRI studies reveal that, while adolescent behavior may look a lot like adult behavior on cognitive tasks, its functional circuitry during these tasks resembles that of adults

performing a more difficult task (e.g., Scherf, Sweeney, & Luna, 2006). Also, while adolescents can clearly engage inhibitory control and working memory processes, the consistency with which they can maintain these processes over a span of time is not yet adult-like. Indeed, there is evidence for a continued maturation of the ability to engage brain regions necessary for the sustained maintenance of cognitive control sets through adolescence (Dosenbach et al., 2007; Velanova, Wheeler, & Luna, 2009).

It may be expected that, given this hyperactivity in reward-related regions and the continued maturation of cognitive-control abilities, adolescents would demonstrate greater difficulty than adults in directing behavior toward long-term goals in contexts in which salient rewards are present. Indeed, elegantly designed tasks manipulating the affective contexts associated with decision making and risk taking have demonstrated that adolescents have greater difficulty recruiting executive functions in the context of appetitive cues (Somerville, Hare, & Casey, 2011) and that they take more risks than adults in these contexts (Figner, Mackinlay, Wilkening, & Weber, 2009; Gardner & Steinberg, 2005).

While hypersensitivity to rewards and immaturities in cognitive control create an adolescent-specific vulnerability to risky behaviors, the unique functioning of the adolescent brain presents a number of opportunities. The heightened reward sensitivity during adolescence may be an asset if behavior is oriented toward positive outcomes. Indeed, research has repeatedly demonstrated boosts in cognitive functions, even those control functions that adolescents typically perform less accurately than adults, when rewards are associated with the execution of those functions (Jazbec et al., 2006; Hardin, Schroth, Pine, & Ernst, 2007). Task-related brain regions also demonstrate enhanced activity during such incentive-motivated behaviors (Geier et al., 2010; Padmanabhan, Geier, Ordaz, Teslovich, & Luna, 2011). Thus there is some evidence that the heighted sensitivity to rewards during adolescence may be an asset if directed at positive behaviors and outcomes.

The Adolescent Brain and Smoking

The normative development of brain regions in the frontostriatal circuitry discussed above, including of the VS and of the dorsolateral prefrontal cortex (DLPFC), is particularly relevant to the current consideration of adolescent cigarette use, as the developing regions are implicated in cigarette-cue reactivity in adults (Everitt & Robbins, 2005; Lee, Lim, Wiederhold, & Graham, 2005; Engelmann et al., 2012; Kang et al., 2012). As the VS exhibits hypersensitivity to rewards during adolescence while the DLPFC, implicated in the cognitive regulation of cigarette craving (Kober et al., 2010), undergoes protracted development through the same period, the adolescent-specific neural instability may render adolescents, by comparison with adults, especially susceptible to the allure of appetitive smoking cues via increased craving.

Evidence suggests that prefrontal function differs between adolescent smokers and their nonsmoking counterparts. Using fMRI, Galvan and colleagues probed this question by asking adolescent smokers and nonsmokers to perform a response inhibition task and a risky decision-making task, both of which are known to elicit prefrontal engagement. Although there were no overall group differences in activation, adolescent smokers showed differential engagement according to their level of dependence: in both the response inhibition and the risky-choice tasks, the level of

dependence modulated the activation of numerous cortical regions, including the bilateral middle prefrontal gyrus, the left inferior frontal gyrus, the right superior frontal gyrus, and the cingulate gyrus (Galvan, Poldrack, Baker, McGlennen, & London, 2011; Galvan et al., 2013). Given the late development of the prefrontal cortex, it is possible that smoking may influence the trajectory of brain development during this critical developmental period. Future studies are warranted to determine whether the observed neurobiological differences precede or result from smoking.

Given the strong relationship between cue reactivity and subsequent smoking behavior in adults, more recent work has aimed to uncover the neural mechanisms underlying cigarette-cue reactivity in adolescents. Adolescent-smoking onset has consistently been associated with exposure to tobacco advertisement (Emery, Choi, & Pierce, 1999; Lovato, Linn, Stead, & Best, 2003; Wills et al., 2007), which suggests that adolescents are particularly susceptible to cigarette ads (Upadhyaya, Drobes, & Wang, 2006). Indeed Rubinstein and colleagues reported that smoking cues elicited greater activation than neutral (nonsmoking) cues in the mesolimbic reward circuit in adolescent smokers (Rubinstein et al., 2011). A control group of adolescent nonsmokers did not neurobiologically differentiate smoking from nonsmoking cues (Rubinstein et al., 2011). Work from our laboratory has found similar results in a large sample of adolescent and adult smokers and nonsmokers who viewed age-appropriate smoking cues (videos) while undergoing fMRI. Following the presentation of each smoking and nonsmoking (control) video, participants rated their craving level. By comparison to adult smokers, adolescent smokers demonstrated greater activation in the VS. Interestingly, we found significant individual differences in the link between neural activation and craving, such that greater cue-induced cigarette craving was associated with greater VS activation in the adolescent smokers only; furthermore, the VS mediated the relationship between craving, the fMRI cues, and subsequent urges to smoke (after the scan) in adolescent smokers only (Do & Galvan, under review). Together, these data suggest that the developing striatum may be particularly vulnerable to the effects of cigarette advertisements in adolescent smokers.

These findings beg a follow-up question: Is the adolescent brain susceptible to all smoking ads, including those that attempt to deter from smoking, or only to those that promote smoking? A recent study from our laboratory suggests that adolescent smokers are more sensitive than adult smokers to ads that both promote and deter smoking. Several countries have implemented graphic, pictorial warnings on cigarette packaging, in an effort to reduce smoking. Initial outcomes are promising, showing reduced smoking initiation rates, increased awareness of health consequences, negative reactions to smoking cues, and increased cessation rates (Hammond, Reid, Driezen, & Boudreau, 2013; Partos, Borland, Yong, Thrasher, & Hammond, 2013). In 2010, the US Food and Drug Administration (FDA) released 36 graphic warning labels depicting potential negative outcomes of smoking to appear on tobacco products. These graphic warnings included images of blackened lungs, a cancer patient, and decaying teeth among other emotionally aversive images. Litigation claims have delayed implementation in the US, but preliminary surveys examining the efficacy of these images among young or potential smokers are encouraging: graphic warning labels on cigarette packaging increased the perception of the dangers of smoking and reduced the social appeal of cigarette smoking (Peters et al., 2007; McCool, Webb, Cameron, & Hoek, 2012; CDC, 2013; Pepper, Cameron, Reiter, McRee, & Brewer, 2013). Our study investigated neural responses to the proposed FDA graphic warning

labels in adolescent and young adult smokers and nonsmokers (Do and Galvan, invited resubmission). While undergoing fMRI, thirty-nine 13–18-year-old adolescent and forty-one 25–30-year-old adult smokers and nonsmokers rated their desire to smoke when presented with emotionally graphic FDA warning labels and, by comparison, with nongraphic labels. Adolescent smokers exhibited greater craving reduction than adult smokers in response to the warning labels. Smokers versus nonsmokers evinced blunted recruitment of insula and DLPFC in response to the graphic labels – an effect that was stronger in adolescent smokers. Although the Family Smoking Prevention and Tobacco Control Act requiring the new FDA warning labels has been challenged, this study provides new evidence in support of the efficacy of the proposed US health warning labels on cigarettes and characterizes neural mechanisms that may underlie this effect in a US sample. Importantly, our data suggest that emotional systems are responsive to the graphic nature of the labels and that adolescent smokers and nonsmokers are particularly responsive, both behaviorally and neurobiologically, to the proposed labels.

Persistent Effects of Adolescent Smoking on Brain Development

Beyond the early stages of cigarette initiation and dependence, it is perhaps not surprising, given the extensive brain development occurring at this time, that nicotine exposure during adolescence may have negative neurobiological consequences that persist into adulthood. In line with the view of adolescence as a vulnerable period for the effects of nicotine, higher rates of daily cigarette smoking have been observed following early versus late adolescent smoking onset (Chen & Millar, 1998; Everett et al., 1999). This is consistent with animal models of nicotine dependence, as adolescent rats acquire nicotine self-administration at a faster rate than adult rats (Chen, Matta, & Sharp, 2007) and also demonstrate higher rates of self-administration (Levin, Rezvani, Montoya, Rose, & Schwartzwelder, 2003).

Given that initial reinforcement consequences may set the stage for subsequent cigarette use, this greater propensity on the part of adolescents to quickly uptake nicotine at high rates may be partly explained by adolescents' increased sensitivity to reward. Indeed adolescent rats exhibit enhanced sensitivity to nicotine reward across many paradigms by comparison to adults (e.g., Adriani, Macri, Pacifici, & Laviola, 2002; Shram & Le, 2010), as well as a reduced sensitivity to nicotine's aversive effects (Shram, Funk, Li, & Le, 2006). In humans, earlier initial smoking experiences have also been associated with a more pleasant experience and an increased probability of recurrent use (Buchmann et al., 2011). A second adolescent-specific vulnerability that may help explain the increased uptake of cigarette smoking during this developmental period upon nicotine exposure is the normative tendency of adolescents to approach potential rewards without sufficient consideration of the consequences. This may render adolescents more likely to continue smoking once they have been exposed, since a normatively heightened incentive motivation toward cigarette use overrides a still maturing cognitive-control system.

Differential neurobiological adaptations in response to nicotine exposure across age groups are also likely to be important (e.g., Cruz, DeLucia, & Planeta, 2005; Schochet, Kelley, & Landry, 2005). Much more work needs to be undertaken to

determine how the increased plasticity of the adolescent brain interacts with nicotine exposure, but existing work suggests that changes must take place quickly after nicotine exposure, as the time course from smoking initiation to nicotine dependence during adolescence seems to be rapid (Dierker, Swendsen, Rose, He, & Merikangas, 2012). Adolescents report nicotine dependence symptoms within days or weeks of the onset of occasional smoking (DiFranza et al., 2000).

In terms of long-term effects into adulthood, a protracted behavioral profile that persists beyond one month of nicotine abstinence after adolescent exposure, characterized by anxiety (Slawecki, Thorsell, Khoury, Mathe, & Ehlers, 2005; Smith et al., 2006), depressed mood (Iniguez et al., 2009), and anhedonia (Ribeiro-Carvalho et al., 2011), has been observed in rodent models of adolescent exposure to nicotine. Long-term effects of adolescent nicotine exposure on cognition have also been observed, including deficits in serial-pattern learning (Fountain, Rowan, Kelley, Willey, & Nolley, 2008) and in spatial and recognition memory (Mateos et al., 2011), as well as increased impulsivity (Counotte et al., 2009). In line with the view of adolescence as an especially vulnerable developmental period on account of the persistent effects of environmental perturbations, many of these persistent effects appear to be specific to adolescent, but not adult only, nicotine exposure (e.g., Iniguez et al., 2009; Counotte et al., 2009; Bracken, Chambers, Berg, Rodd, & McBride, 2011).

While the underlying neurobiological changes accompanying the persistent behavioral effects of adolescent nicotine exposure remain to be fully defined, animal studies have observed neurotoxic effects of nicotine on the developing adolescent brain. Persistent cellular damage has been observed in the midbrain, hippocampus, and cerebral cortex following adolescent nicotine exposure (Trauth, Seidler, McCook, & Slotkin, 1999; Trauth, Seidlier, & Slotkin, 2000; Abreu-Villaca et al., 2003). Persistent changes in nicotinic acetylcholine receptor expression (Trauth et al., 1999) and acetylcholine synaptic function (Slotkin, Ryde, & Seidler, 2007), as well as persistent changes in noradrenergic, dopamine, and serotonergic system functioning (Trauth, Seidler, Ali, & Slotkin, 2001; Xu, Seidler, Cousins, Slikker, & Slotkin, 2002; Counotte et al., 2009), have also been observed following adolescent nicotine exposure. As in the case of the persistent behavioral effects of adolescent nicotine exposure, there is some evidence that the effects of nicotine on neurobiology are less persistent after adult than after adolescent exposure (Trauth et al., 1999; Adriani et al., 2003; Slotkin, Ryde, Mackillop, Bodwell, & Seidler, 2008).

Establishing the adolescent-specific, persistent effects of nicotine exposure in humans is much more difficult, given the more limited capacities to control for confounding factors and to limit nicotine exposure to the developmental periods of interest. However, a burgeoning literature on young adult smoking provides some evidence for the persistent negative effects of adolescent-specific nicotine exposure. Young adult smoking may in many cases be a progression from adolescent smoking, but results from a 2012 national survey on drug use observed an increase from 623,000 in 2002 to 1.1 million in 2012 in the number of individuals initiating cigarette use at the age of 18 or later (Substance Abuse and Mental Health Services Administration, 2013). These recent changes in the smoking landscape allow for a consideration of the consequences of adolescent versus young adult smoking onset on trajectories of nicotine dependence.

Important foundational research on the prevalence and characteristics of college smoking suggests that young adult smokers are a heterogeneous group. On the basis of patterns and contexts of tobacco use, Sutfin, Reboussin, McCoy, and Wolfson (2009)

identified five subgroups of smokers: heavy smokers (28%), moderate smokers (22%), social smokers (19%), puffers (26%), and no-context smokers (4%). Only heavy smokers were daily smokers, most of the sample demonstrating patterns of nondaily smoking. A complementary study using a longitudinal design adopted a data-driven approach to identify distinct trajectories of smoking among college students; this was a longitudinal study spanning four annual assessments after college entry. Caldeira et al. (2012) identified five distinct smoking trajectories: stable not smoking (71.5%), low and stable smoking (13.3%), low and increasing smoking (6.5%), high and stable smoking (5.5%), and high and decreasing smoking (3.2%). Smoking patterns were relatively stable over the course of the 4-year study, suggesting that intermittent smoking may not be a transitory phenomenon, but one that may be stable for at least a number of years. Crucially, age at first cigarette predicted smoking subgroups, heavy smokers being more likely to report a younger age of smoking initiation than social smokers or puffers (Sutfin et al., 2009). Age at first cigarette also distinguished distinct smoking trajectories, high and stable smokers smoking for longer periods than high and decreasing smokers (Caldiera et al., 2012). Such findings highlight the role of adolescent onset in smoking and suggest that nondaily, young adult light smokers who initiate in late adolescence or early adulthood may be less vulnerable to the effects of nicotine and may be experiencing fewer of the persistent effects of nicotine associated with smoking during adolescence. Further studies comparing adolescent and young adult onset in smoking, especially through fMRI technologies, will be important to test this theory.

Intervention Opportunities

Given these vulnerabilities associated with nicotine exposure during adolescence, the development of preventive interventions to discourage or delay the onset of smoking is crucial. Multicomponent interventions that have demonstrated effectiveness at reducing the prevalence of adolescent smoking have targeted beliefs about smoking and have focused on the development of skills to resist social influences that encourage smoking (e.g., Sussman, Dent, & Stacy, 2002; Botvin & Griffin, 2004; Flay, 2009). There is little evidence for the long-term effectiveness of the majority of these programs (for review see Wiehe, Garrison, Christakis, Ebel, & Rivara, 2005), and researchers have called for the consideration of adolescent neurobiological development and decision making when designing interventions to prevent substance use (Lopez, Schwartz, Prado, Campo, & Pantin, 2008). A greater consideration of the cognitive capacities of adolescents during the periods and in the contexts in which smoking initiation often occurs – that is, in affectively charged contexts, in the presence of peers – will likely enhance the effects on interventions on smoking behaviors. Building adolescent decision-making capacities in affectively charged conditions, as occurs to some extent in the existing interactive intervention components (e.g., Tobler & Stratton, 1997; Black, Tobler, & Sciacca, 1998), may render the skills learned during interventions more effective and more likely to be executed also in the real-life contexts in which cigarette initiation most often occurs.

Looking beyond individual adolescents and involving school (Sun, Skara, Sun, Dent, & Sussman, 2006), family (Lochman & van den Steenhoven, 2002), and wider community (e.g., Biglan, Avry, Smolkowski, Duncan, & Black, 2000) contexts will

likely be necessary, given adolescents' normative tendency toward impulsive responding in affectively charged contexts. Interventions in such contexts will rely less on attempting to curb developmentally normative adolescent tendencies to approach novel and potentially rewarding stimuli such as cigarettes, and more on reducing the number of smoking opportunities encountered by adolescents.

In terms of efforts to reduce adolescent smoking once it has begun, the hypersensitivity to rewards manifest during adolescence may present opportunities for interventions. Contingency-management approaches to cigarette reduction attempt to encourage smoking abstinence by manipulating the contingencies associated with cigarette smoking (see Prendergast, Podus, Finney, Greenwell, & Roll, 2006). By enhancing the value associated with a target behavior (e.g., continued abstinence) through the provision of an incentive, they aim to encourage the allocation of cognitive resources to the achievement of the target behavior. Contingency-management approaches targeting adolescents have shown some promise (e.g., Krishnan-Sarin et al., 2006; Reynolds, Dallery, Shroff, Patak, & Leraas, 2008) and, given the increased enhancement of executive functions through the allocation of incentives during adolescence, this approach will likely be a fruitful area for adolescent smoking intervention.

Conclusion

While there is still much knowledge to be uncovered on this important topic, the studies reviewed here suggest that the dynamic nature of the adolescent brain may render it particularly susceptible to smoking initiation and to the effects of cigarette smoking. The evidence underscores the importance of targeting adolescents for smoking reduction, since they constitute a population that may be vulnerable to smoking but whose unique brain configuration also provides unique opportunities for intervention. Eradicating this significant public-health issue will greatly ameliorate the health-compromising and psychosocial risks of cigarette smoking.

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