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TOPICAL REVIEW

Nicotine and the adolescent brain

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Abstract Adolescence encompasses a sensitive developmental period of enhanced clinical vulnerability to nicotine, tobacco, and e-cigarettes. While there are sociocultural influences, data at preclinical and clinical levels indicate that this adolescent sensitivity has strong neurobiological underpinnings. Although definitions of adolescence vary, the hallmark of this period is a profound reorganization of brain regions necessary for mature cognitive and executive function, working memory, reward processing, emotional regulation, and motivated behavior. Regulating critical facets of brain maturation are nicotinic acetylcholine receptors (nAChRs). However, perturbations of cholinergic systems during this time with nicotine, via tobacco or e-cigarettes, have unique consequences on adolescent development. In this review, we highlight recent clinical and preclinical data examining the adolescent brain's distinct neurobiology and unique sensitivity to nicotine. First, we discuss what defines adolescence before reviewing normative structural and neurochemical alterations that persist until early adulthood, with an emphasis on dopaminergic systems. We review how acute exposure to nicotine impacts brain development and how drug responses differ from those seen in adults. Finally, we discuss the persistent alterations in neuronal signaling and cognitive function that result from chronic nicotine exposure, while highlighting a low dose, semi-chronic exposure paradigm that may better model adolescent tobacco use. We argue that nicotine exposure, increasingly occurring as a result of e-cigarette use, may induce epigenetic changes that sensitize the brain to other drugs and prime it for future substance abuse.

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Introduction

Adolescence is a period of transition from childhood to adulthood marked by characteristic behavioral changes, including increased risk-taking, novelty-seeking and peer associations that are thought to ease successful transition to independence and autonomy in adulthood (Spear, 2000; 2013). During this developmental window, the brain is sensitive to novel experiences with major experience-dependent plasticity occurring in executive control and decision-making regions, particularly in the

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prefrontal cortex (Bernheim *et al.* 2013). It is also, however, a time of increased vulnerability to drug abuse (Chambers *et al.* 2003; Crews *et al.* 2007). Initiation of substance abuse typically occurs during this period, with progression from use of alcohol and tobacco in early teens to illegal substances at later ages (Lai *et al.* 2000; Hanna *et al.* 2001; Biederman *et al.* 2006). Almost 90% of adult smokers started before the age of 18 (Substance Abuse and Mental Health Services Administration, 2011). Whereas tobacco use in teens is now declining as a result of government regulation (Farrelly *et al.* 2013; U.S. Department of Health and Human Services, 2014), the use of electronic nicotine delivery systems, or e-cigarettes, is escalating rapidly (Centers for Disease Control and Prevention, 2013; Camenga *et al.* 2014). Although marketed as a smoking cessation aid, and a safer alternative to smoking, e-cigarettes are not subject to FDA regulation and can be purchased by minors in many states (Paradise, 2014).

There is a substantial literature that shows nicotine to be a neuroteratogen that exerts long-term, maturational effects at critical stages of brain development (Slotkin, 2004; Ginzel *et al.* 2007; Dwyer *et al.* 2008, 2009). As discussed in the present review, adolescence is a sensitive period for maturation of brain circuits that regulate cognition and emotion, with resulting vulnerability to the effects of nicotine and tobacco. Although relevant clinical work is discussed, this review focuses primarily on adolescent rodents, which exhibit many of the same physiological and behavioral changes as human adolescents (Spear, 2000) and are more appropriate experimental models for drug studies. We argue that the rapidly changing, immature adolescent brain has differing sensitivity to drugs such as nicotine and tobacco, and drug exposure during this time can lead to long-term changes in neural circuitry and behavior.

What is adolescence?

Adolescence is a transitional period from childhood to adulthood that is conservatively estimated to last from 12 to 18 years of age in humans and from postnatal (P) days 28 to 42 in rats (Spear, 2000; Fig. 1). It is conserved across mammalian species, with humans and rodents exhibiting similar physiological and behavioral changes (Spear, 2007; 2013). However, defining the boundaries of this period and what it encompasses is contentious. Some report that changes signaling its onset emerge as early as age 10 in humans or P21 in rats (Sturman & Moghaddam, 2011; Hollenstein & Lougheed, 2013; Burke & Miczek, 2014). Similarly, maturation may not be complete until the mid 20s in humans or around P55 in rodents (Laviola *et al.* 2003; Burke & Miczek, 2014). Since adolescence as a whole has no obvious events to signal its beginning or end and individual as well as sociocultural differences influence the timing and duration of this period, its boundaries remain a grey area (Fig. 1).

Many definitions equate adolescence with sexual maturation, or puberty (Fig. 1). Although timing of hypothalamic–pituitary–gonadal axis reawakening and resulting maturation of reproductive function overlaps in humans and rodents (Spear, 2000; Varlinskaya *et al.* 2013), puberty is temporally restrictive, lasting about 5 years in humans (Sun *et al.* 2002) and 10–20 days in rodents (Sisk & Zehr, 2005; Schneider, 2013). In humans, the onset of puberty is thought to signal adolescence, but onset can vary widely depending on sex (gender), socioeconomic status, and nutritional state (Spear, 2000). Furthermore, there is growing evidence that sexual maturation is occurring progressively earlier in the US and some European countries (Euling *et al.* 2008; Aksglaede *et al.* 2009; Biro *et al.* 2013; Cabrera *et al.* 2014). The underlying causes remain unclear although some suggest higher rates of obesity (Biro *et al.* 2013) while others suggest epigenetic and environmental influences (Aksglaede *et al.* 2009; Meeker, 2012; Hagen *et al.* 2014) as the main contributing factors. These variations in pubertal timing further complicate the validity of equating adolescence to puberty. Sex-related variation in pubertal timing is also seen in rats (Vetter-O'Hagen & Spear, 2012; Schneider, 2013; Varlinskaya *et al.* 2013), and the adolescent peak in novelty-seeking seems to be independent of gonadal hormone changes (Vetter-O'Hagen & Spear, 2012). Moreover, the relatively rapid changes in neural systems involved in emotional and reproductive function that occur during puberty do not match the maturation of other cognitive systems that extend further into the adolescent period (Dahl, 2008). Pre-pubertal increases in neuroactive adrenal steroids, such as the androgens dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS), have also been associated with neurobehavioral changes of adolescence in humans and non-human primates, but corresponding effects are not seen in rodents (Spear, 2000; Forbes & Dahl, 2010). Other definitions emphasize the adolescent growth spurt although changes in body weight are not correlated with adolescent neurobehavioral changes (Spear, 2000). Whereas physical changes are important components of adolescence and help set its boundaries, the hallmark of this period is a major reorganization of forebrain circuitry (Fig. 1).

Normative structural and neurochemical maturation of the adolescent brain

Structural changes. Adolescent behavioral alterations, including both deficits and improvements, are paralleled by a dynamic structural and functional reorganization of the brain. The adolescent brain does not mature

by becoming larger but rather through prolonged reorganization of grey matter, white matter, and associated neurochemical systems. The increasing cognitive capacity of the adolescent coincides with a decrease in cortical grey matter thickness, resulting from experience-dependent loss of synapses and a concomitant strengthening of the remaining connections (Ostby *et al.* 2009; Gogtay & Thompson, 2010; Paus, 2010). Grey matter volume and density decreases during adolescence in the pre-frontal cortex, parietal cortex and basal ganglia, which are critical for executive function, sensory processing, and motivated behaviors (Giedd *et al.* 1999; Sowell *et al.* 1999; 2001). There are corresponding increases in white matter, which is thought to reflect increased myelination and axonal diameter, resulting in increased efficiency of impulse transduction (Paus, 2010). The changes in grey and white matter that occur during adolescence are not homogeneous throughout the brain, but differ regionally, with phylogenetically older brain regions maturing earlier than the newer ones (Gogtay *et al.* 2004). The imbalanced maturation of subcortical emotional and reward-focused systems as well as cortical executive and impulse control systems is thought to underlie adolescent increases in risk-taking behavior, particularly in social settings (Casey *et al.* 2011; Smith, 2013).

Functional magnetic imaging techniques, coupled with graph theory, have recently allowed assessment of functional connectivity between brain regions that show similar activation patterns (Rubinov & Sporns, 2010). The pronounced structural and neurochemical changes during adolescence are paralleled by increases in functional connectivity, which play a significant role in the development of cognitive control (Luna *et al.* 2010). Adolescence is a transition period in which the organization of functional networks shifts from local interactions in children to more distributed connectivity in young adults (Fair *et al.* 2009; Hwang *et al.* 2010; Satterthwaite *et al.* 2013). Maturation of inhibitory control is associated with improved long-range functional connectivity between frontal and subcortical regions with simultaneous decreases in short-range, within-region connectivity in the frontal and parietal cortices (Hwang *et al.* 2010). Similarly, maturation of working memory reflects greater activation of the executive network containing the fronto–parietal–cerebellar network and less activation of the default mode network (medial orbital frontal cortex, middle and inferior temporal cortex, precuneus, and angular gyrus) (Satterthwaite *et al.* 2013). These changes in functional connectivity during adolescence contribute to the development of executive function and cognitive control, which is attributed, at least in part, to the maturation of the dopamine system (Padmanabhan *et al.* 2011; Fig. 2).

Neurochemical changes. In addition to structural remodelling, the adolescent brain undergoes substantial neurochemical maturation (Fig. 2). The dopaminergic system, in particular, experiences a profound reorganization that is likely critical for the development of motivated behaviors and associative learning (O'Donnell, 2010; Wahlstrom *et al.* 2010). In rodents, dopamine receptor binding site expression exhibits a pattern of overproduction followed by both region- and cell type-specific pruning that is more robust in males (Teicher *et al.* 1995; Andersen *et al.* 1997; 2000; Brenhouse *et al.* 2008; Naneix *et al.* 2012). There is

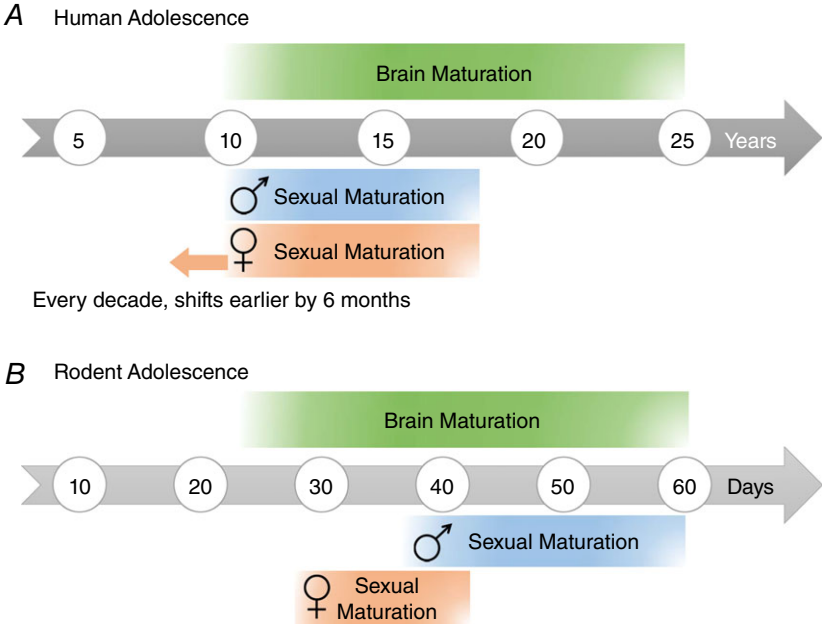

Figure 1. Adolescence is a developmental transition period with no clear hallmarks signaling its start or finish
Many define adolescence as equivalent to sexual maturation or puberty. However, maturation of neural systems extends beyond the period of sexual maturation, an effect seen in both humans (*A*) and rodents (*B*). Although puberty is an important component of adolescence, this transitional period is distinguished by the dramatic maturation and remodeling of the brain. Human age is defined by years, and rodent age is defined by postnatal days.

also late maturation of dopamine innervation, particularly in the anterior prefrontal cortex (Cao *et al.* 2007; Naneix *et al.* 2012; Fig. 2). Firing of limbic dopamine cells in the ventral tegmental area is higher in adolescents than adults (Placzek *et al.* 2009; McCutcheon *et al.* 2012), and neurotransmitter turnover in target regions is greater (Tarazi *et al.* 1998; Moll *et al.* 2000; Naneix *et al.* 2012). Peak levels of extracellular dopamine are seen during late adolescence in the nucleus accumbens (Philpot *et al.* 2009), and there is late maturation of psychostimulant-induced dopamine release in ventrolateral and dorsal striatum (Cao *et al.* 2007; Matthews *et al.* 2013).

During adolescence, there are also major functional changes in the dopamine system that parallel changes in emotional regulation and cognitive function (Wahlstrom *et al.* 2010; Naneix *et al.* 2012; Garske *et al.* 2013; Spear, 2013). Dopamine D_2 receptor stimulation of fast-spiking interneurons in the prefrontal cortex does not emerge until late adolescence with the recruitment and maturation of local GABAergic activity (Tseng & O'Donnell, 2007; O'Donnell, 2010; Fig. 3). Furthermore, important D_1–NMDA receptor interactions in cortical pyramidal neurons that are necessary for mature cognitive and attentional processing are still developing during this time (Tseng & O'Donnell, 2005; Fig. 3). Ventral hippocampal input to the medial prefrontal cortex is also strengthened during late adolescence by a D_1 receptor-mediated emergence of an NMDA receptor GluN2B subunit function (Flores-Barrera *et al.* 2014). In the nucleus accumbens, D_1 and D_2 receptor responses are also immature, resulting in decreased synaptic interaction between this region and the prefrontal cortex (Benoit-Marand & O'Donnell, 2008; Fig. 4). In accumbal medium spiny neurons, D_1 receptor modulation of NMDA responses is age-specific with cell excitability decreased in adolescents and increased in adults (Huppé-Gourgues & O'Donnell, 2012*a*). Similarly, D_2 receptor activation has age-specific effects on AMPA-evoked cell excitability, and D_2–AMPA receptor interactions recruit the activation of GABA interneurons in adults but not adolescents (Huppé-Gourgues & O'Donnell, 2012*b*). These findings indicate a functional switch in reward processing during adolescent development mediated by dopamine regulation of GABA interneurons (Fig. 4).

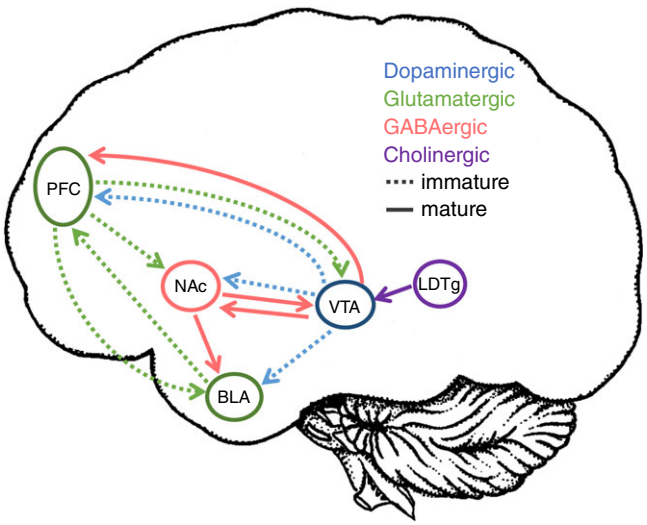

Figure 2. The immature adolescent brain undergoes substantial growth, reorganization, and pruning
At the start of adolescence, connectivity between the prefrontal cortex (PFC) and limbic regions is immature, as indicated by dashed lines. As adolescence proceeds, this connectivity markedly increases and completes development last. Similarly, dopaminergic projections from the ventral tegmental area (VTA) continue to develop into early adulthood and are strongly influenced by cholinergic projections from the laterodorsal tegmental nucleus (LDTg). The nucleus accumbens (NAc), on the other hand, develops earlier than associated prefrontal cortical regions, as indicated by solid lines, which may consequently lead to the characteristic expression of increased novelty-seeking and risk-taking behavior. Furthermore, with the immature projections from the basolateral amygdala (BLA) to the PFC, discrepant maturational timelines of cortical and subcortical regions leads to diminished executive control of reward and motivated behavior.

Adolescent alterations in dopamine firing activity have been shown to induce structural and functional changes in mesocortical pathways (Mastwal *et al.* 2014). Phasic activity in these neurons is naturally induced by reward-related or motivationally salient events, whereas tonic activity occurs spontaneously (Grace *et al.* 2007; Schultz, 2007). In the ventral tegmental area, tonic firing of dopamine neurons is increased during adolescence and phasic firing is prolonged (McCutcheon & Marinelli, 2009; McCutcheon *et al.* 2012). Optogenetic studies have shown that phasic dopamine firing in adolescents, but not adults, facilitates the formation of mesofrontal axonal boutons, resulting in enhanced mesofrontal circuit activity and suppressed psychostimulant-induced locomotion (Mastwal *et al.* 2014). The D_2-like dopamine receptor agonist, quinpirole, blocks this effect in adolescents, whereas cortical plasticity is enhanced in adults by D_2 receptor blockade (Mastwal *et al.* 2014).

Other studies have implicated a lack of adolescent D_2 receptor function in both risk-taking and anxiolytic behaviors, with negative correlations found between those behaviors and D_2 receptor levels in the nucleus accumbens (Falco *et al.* 2014; Mitchell *et al.* 2014). D_2 receptor activation by quinpirole infusion into the ventral striatum decreases risk-taking behavior in adolescent rats (Mitchell *et al.* 2014). In contrast, impaired impulse control and learning of an association between an odor and a palatable reward coincides with an adolescent peak of D_1 receptor expression in olfactory cortices (Garske *et al.* 2013). Performance on this task is enhanced by administration of a D_1 agonist or a D_2 antagonist (Garske *et al.* 2013). These findings suggest that adolescent maturation of

subcortical and cortical dopamine circuitry is critical for emotional regulation, impulse control, and associative learning.

Adolescence also appears to be a critical period for maturation of the mesocortical dopamine system, during which it is vulnerable to gene–environment interactions. Dopamine neurons of the ventral tegmental area only begin to express the netrin-1 receptor UNC5C during adolescence (Manitt *et al.* 2010; Auger *et al.* 2013). While the other netrin-1 receptor, DCC (deleted in colorectal cancer), is expressed earlier, adolescence is a period in which it exerts unique effects on the organization of mesocortical dopamine circuitry (Grant *et al.* 2007; 2009; Manitt *et al.* 2011). Animals that are haploinsufficient in either *unc5c* or *dcc* show enhanced mesocortical dopamine innervation and function as adults with diminished behavioral response to psychostimulant drugs (Auger *et al.* 2013). Adolescent isolation, which results in stress during a major period of social development, results in epigenetic hypermethylation of the tyrosine hydroxylase gene in mesocortical dopamine neurons, but only in a mouse model with a genetic risk for neuropsychiatric disease (Niwa *et al.* 2013). These molecular changes result in several neurochemical and behavioral deficits that are blocked by a glucocorticoid receptor antagonist (Niwa *et al.* 2013). Social isolation during adolescence also results in long-term impairment of impulse control and decision making on a rat gambling task (Baarendse *et al.* 2013). In adults that were isolated as adolescents, pyramidal neurons of the prefrontal cortex are insensitive to modulation of synaptic response amplitude by dopamine and do not develop the late onset inhibitory regulation by D_2 receptors that is seen in normal adults (Tseng & O'Donnell, 2007). Chronic adolescent treatment with the D_2-like agonist, quinpirole, also decreases dopamine fiber and receptor density in prefrontal cortex, and inhibits normal adult maturation of contingency degradation behavior, which is the causal relationship between actions and their consequences (Naneix *et al.* 2013). Thus, rapidly maturing dopamine systems may be especially sensitive to disruption by environmental influences during adolescence, with long-term consequences on behavior and associated psychopathologies such as drug abuse or schizophrenia.

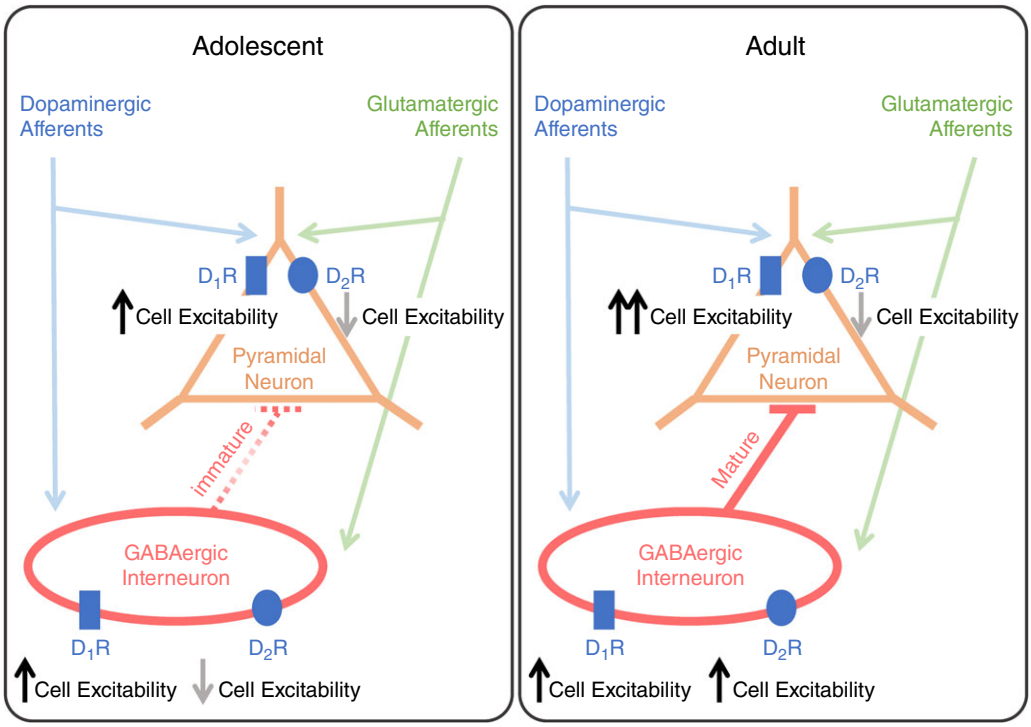

Figure 3. Microcircuitry of the prefrontal cortex (PFC) showing developmental differences in dopamine function
Adolescents (left) lack mature dopamine D_1–glutamate receptor interactions on prefrontal cortical pyramidal neurons, and acquisition of this element is vital for the development of cognitive and attentional processes. In addition, D_2 receptor-mediated GABAergic inhibitory control of prefrontal cortical activity is still immature, as indicated by the dashed lines, demonstrating that cognitive processing within the PFC and other limbic regions is profoundly different in adolescence than in adulthood (right).

Nicotine uniquely alters adolescent brain development

Nicotinic acetylcholine receptor pharmacology. Nicotinic acetylcholine receptors (nAChRs) are pentameric ligand-gated ion channels that are widely distributed in human and rodent brain throughout all developmental phases (Zoli *et al.* 1995; Broide & Leslie, 1999; Pentel *et al.* 2006). nAChRs are composed of homomeric ($\alpha7$–$\alpha10$) or heteromeric ($\alpha2$–$\alpha6$, $\beta2$–$\beta4$) subunits, which contribute to a diverse receptor pharmacology by regulating agonist affinity/efficacy, ion selectivity, desensitization, and downstream signalling (McGehee, 1999; Gotti *et al.* 2006; Dani & Bertrand, 2007).

Each nAChR subtype exhibits distinct patterns of expression and function throughout the central and peripheral nervous systems (Perry *et al.* 2002; Gotti *et al.* 2006). The most abundant neuronal subtype is the $\alpha4\beta2$ nAChR, which has high affinity for nicotine (Dani & Bertrand, 2007). These receptors desensitize at nicotine concentrations lower than those required for activation (Fenster *et al.* 1999) and, as a result, are mostly desensitized in brains of smokers (Brody *et al.* 2006). Another common neuronal subtype is the homomeric $\alpha7$ nAChR, which has lower affinity for nicotine compared to other nAChRs and desensitizes rapidly at high nicotine concentrations (Albuquerque *et al.* 1998; Dani & Bertrand, 2007). The $\alpha3\beta4$ nAChR subtype has low agonist affinity with slow desensitization kinetics (Luetje & Patrick, 1991; Papke & Heinemann, 1991), and although largely restricted to caudal brain regions (Winzer-Serhan & Leslie, 1997; Perry *et al.* 2002), $\alpha3\beta4$ nAChRs serve a vital role in modulating nicotine addiction pathways (Gallego *et al.* 2012; Toll *et al.* 2012; Leslie *et al.* 2013).

Neuronal nAChRs are central regulators of neurophysiology and signaling in addiction pathways (Dani & Balfour, 2011; Leslie *et al.* 2013). nAChRs are widely distributed in neuroanatomical areas implicated in tobacco addiction (Gotti & Clementi, 2004), and nAChR activation in these regions regulates monoamine neurotransmitter systems, particularly dopamine, which is strongly implicated in reward processing and drug reinforcement (Gotti *et al.* 2006; Albuquerque *et al.* 2009). Indeed, heterologous nAChRs that contain $\alpha4$, $\beta2$, and other subunits ($\alpha4\beta2^*$ nAChRs) are key regulators of the mesolimbic dopamine system, mediating nicotine-induced firing and burst activity of midbrain dopamine neurons in the ventral tegmental area (Livingstone *et al.* 2009; Li *et al.* 2011; Zhao-Shea *et al.* 2011; Leslie *et al.* 2013). $\alpha7$ nAChRs on glutamate afferents

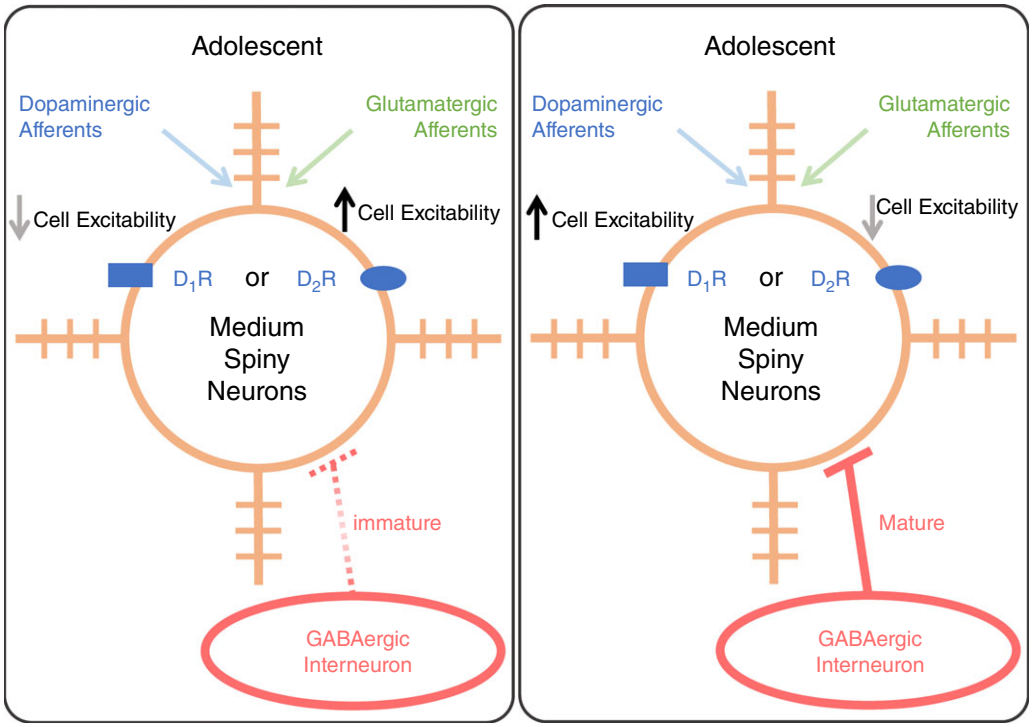

Figure 4. Microcircuitry of the nucleus accumbens (NAc) showing developmental differences in dopamine function
Adolescents (left) lack mature accumbal D_1–NMDA receptor interactions and D_2–AMPA receptor interactions. In addition, GABAergic inhibitory control of medium spiny neuron activity in the NAc is still immature, as indicated by the dashed lines, illustrating that long term potentiation (LTP)/long term depression (LTD) within the NAc and associated limbic regions is profoundly different in adolescence from in adulthood (right).

also indirectly modulate dopamine release in the prefrontal cortex and fine tune dopamine neuron firing in the ventral tegmental area (Mameli-Engvall *et al.* 2006; Livingstone *et al.* 2009). In contrast, $\alpha3\beta4$ nAChRs are expressed predominantly in the medial habenula and interpeduncular nucleus, stimulating both acetylcholine and glutamate release in these nuclei (Perry *et al.* 2002; Grady *et al.* 2009; Fowler *et al.* 2011), as well as dopamine release in the hippocampus (Cao *et al.* 2005).

Functional immaturity of nicotinic receptors during adolescence. Neuronal nAChRs exhibit distinct patterns of expression that parallel key developmental events within the cholinergic system and are critical regulators of brain maturation from prenatal development through adolescence (Dwyer *et al.* 2009). In rodents, $\alpha4\beta2^*$ and $\alpha7$ nAChR expression and binding are higher in many brain regions in adolescents than in adults (Adriani *et al.* 2003; Doura *et al.* 2008). *In vitro* rubidium efflux assays have shown $\alpha4\beta2^*$ nAChRs to have higher functional activity in the cortex, hippocampus, striatum, and thalamus during this period (Britton *et al.* 2007; Kota *et al.* 2007). Furthermore, in the transition from adolescence to adulthood, there is a complex and sex-dependent pattern of functional maturation of nAChRs that regulates [^{3}H]dopamine release in the ventral striatum (Azam *et al.* 2007).

Nicotine enhances neuronal activity, as measured by c-*fos* mRNA expression, more robustly in adolescents than adults in several reward-related regions, including the nucleus accumbens shell, basolateral amygdala, and ventral tegmental area (Shram *et al.* 2007; Dao *et al.* 2011). Patterns of nicotine-induced c-*fos* expression in sensory and limbic cortices also change with adolescent maturation (Leslie *et al.* 2004). Furthermore, both nicotine and the $\alpha7$ nAChR-selective agonist A-582941 increase expression of another activity related gene, *arc*, in both medial prefrontal and ventrolateral orbital cortices of adolescent rats much more than that of adults (Schochet *et al.* 2005; Thomsen *et al.* 2008). Electrophysiological studies have shown an early adolescent onset of nicotine-enhanced frequency-evoked responses in auditory cortex that reflects both thalamocortical and intracortical response components. This nicotine effect is mediated by $\alpha4\beta2^*$ nAChRs, develops rapidly, and peaks during adolescence, with a sex-dependent time course of subsequent decline (Kawai *et al.* 2011). Unique effects of acute nicotine exposure on monoamine neuronal activity are also seen in adolescents. Dopamine neurons of the ventral tegmental area are more sensitive in adolescents than adults to nicotine-induced long-term potentiation associated with plasticity of glutamate receptor function (Placzek *et al.* 2009). Furthermore, initial exposure to nicotine induces unique effects in adolescence on the ascending serotonin system, as measured by double-labelling for *c-fos* and tryptophan hydroxylase, with a broader spectrum of targets and a different dose–response function than in adults (Bang & Commons, 2011). Acute nicotine also increases extracellular serotonin overflow in the nucleus accumbens shell, while decreasing both dopamine and serotonin in adolescent medial prefrontal cortex as compared to adults (Shearman *et al.* 2008).

The altered neuronal sensitivity to nicotine during adolescence is paralleled in behavioral responses (Fig. 5). Following acute drug exposure, nicotine enhances locomotor activity in adolescent rodents, but decreases it in adults (Cao *et al.* 2010). Acute nicotine treatment also reduces anxiety in adolescent male rats (Cheeta *et al.* 2001; Elliott *et al.* 2004; Cao *et al.* 2010). Furthermore, adolescents associate a greater rewarding effect with nicotine in conditioned place preference studies (Vastola *et al.* 2002; Belluzzi *et al.* 2004; Shram *et al.* 2006; Brielmaier *et al.* 2007; Kota *et al.* 2007; Torres *et al.* 2008) and exhibit a unique vulnerability to oral

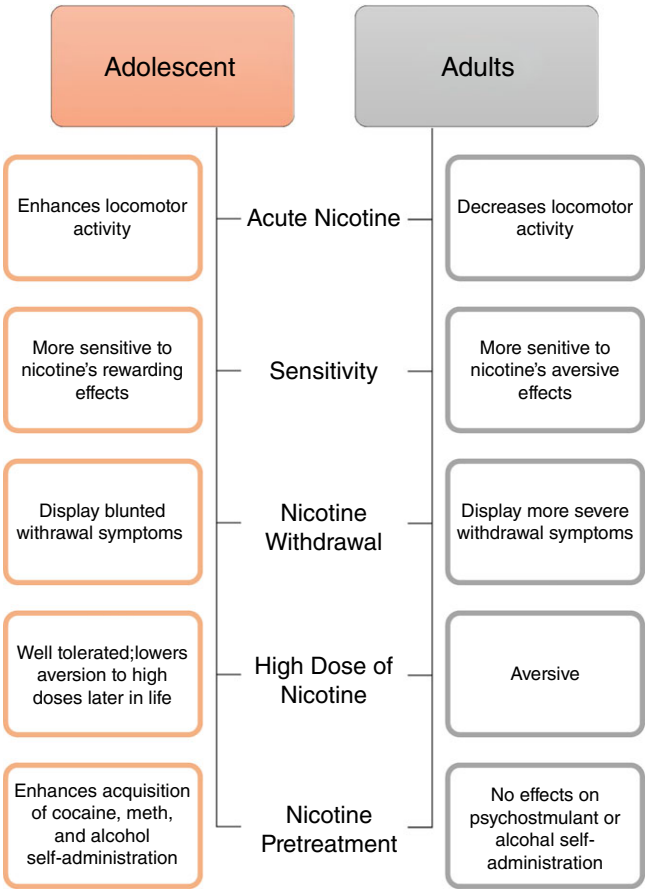

Figure 5. Preclinical studies using rodent models indicate that nicotine produces age-specific behavioral responses
Adolescents exhibit greater behavioral sensitivity and susceptibility to other drugs of abuse after nicotine exposure. In contrast, adults display either opposite or no response to nicotine treatment.

self-administration during the early adolescent period (Adriani *et al.* 2002). Adolescent rats also readily acquire intravenous nicotine self-administration and take more nicotine than adults (Chen *et al.* 2007; Levin *et al.* 2007; Natividad *et al.* 2013). In contrast, adolescents show less aversion to nicotine than adults (Adriani *et al.* 2002; Shram *et al.* 2006; Torres *et al.* 2008) and less prominent withdrawal symptoms following chronic nicotine exposure (O'Dell *et al.* 2006; Shram *et al.* 2008). This shift in balance between the positive and negative effects of nicotine that occurs in adolescence (Fig. 5) may underlie an increased vulnerability to smoking and the use of e-cigarettes.

Long-term effects of chronic adolescent nicotine exposure. Chronic nicotine exposure during adolescence produces alterations in neurochemistry and behavior that differ markedly from those in adulthood. Adults are more responsive than adolescents to nicotine-induced upregulation of $\alpha4\beta2^*$ and $\alpha7$ nAChR binding sites; in contrast, adolescents exhibit greater downregulation of $\alpha6^*$ nAChRs than adults following chronic nicotine treatment (Collins *et al.* 2004; Doura *et al.* 2008).

Chronic nicotine treatment also produces age-specific effects on monoamine systems, with serotonin systems particularly vulnerable during adolescence. Biochemical studies have shown that chronic, high-dose nicotine exposure during adolescence results in altered indices of serotonin receptor function, with decreased 5-HT_2 receptor binding in terminal regions and a switch in signalling of 5-HT_{1A} receptors from stimulation to inhibition of adenylyl cyclase activity (Xu *et al.* 2002). Chronic nicotine treatment during adolescence also alters subsequent response of the serotonin system to nicotine later in life, suggesting that nicotine may elicit life-long detriments in serotonergic signalling (Slotkin & Seidler, 2009; Slotkin *et al.* 2014). Whereas chronic high-dose nicotine treatment has been reported to result in age-specific decreases in adolescent striatal serotonin transporter (SERT) densities (Collins *et al.* 2004), a 4 day low-dose intravenous treatment results in region-specific changes in serotonergic function, which include elevated SERT binding in prefrontal cortex and basolateral amygdala as well as increased serotonin content and turnover in the nucleus accumbens (Dao *et al.* 2011). This semi-chronic nicotine treatment models the brief, low-dose initiation of adolescent smoking behavior, with distinct behavioral and neurochemical consequences during adolescence (Fig. 6). This nicotine pretreatment also induces serotonin release and $5HT_{1A}$ receptor activation that leads to enhanced D_2 receptor function in adolescents but not adults (Dao *et al.* 2011). These lasting age-specific alterations result in increased quinpirole-induced locomotion and acquisition of cocaine self-administration (McQuown *et al.* 2007; Dao *et al.* 2011). Adolescent D_3 receptor function is also enhanced by this nicotine treatment paradigm, through CRF-1 receptor activation, resulting in enhanced quinpirole-induced penile erection (Mojica *et al.* 2014).

Although striatal dopamine transporters have been reported to be upregulated by nicotine in adolescents but not adults, very few age differences have been reported in the effect of chronic nicotine on presynaptic markers of dopaminergic function (Collins *et al.* 2004; Dao *et al.* 2011). However, repeated nicotine treatment has been shown to induce elevated mesocortical dopamine release in adolescents but not adults (Counotte *et al.* 2009; Dao *et al.* 2011). Additionally, chronic adolescent nicotine exposure induces unique and persistent dendritic remodeling in the prelimbic cortex (Bergstrom *et al.* 2008) and in the nucleus accumbens shell (McDonald *et al.* 2007), where the effects are mediated by D_1 receptors (Ehlinger *et al.* 2015).

Chronic nicotine exposure during adolescence also has long-term consequences on cognitive behavior. Adolescent, but not post-adolescent, treatment with nicotine has been shown to result in diminished cognitive function as adults with reduced attention span and enhanced impulsivity (Trauth *et al.* 2000; Counotte *et al.* 2009; Counotte *et al.* 2011). These cognitive disturbances are associated with reduced presynaptic mGluR2 protein and function on excitatory synapses in the prefrontal cortex, which alters the rules for spike timing-dependent plasticity in prefrontal networks (Counotte *et al.* 2011; Goriounova & Mansvelder, 2012). Attentional deficits in adults that received adolescent nicotine can be rescued by local infusion of a group II mGluR agonist (Counotte *et al.* 2011). Emotional responses also exhibit long-term alterations following adolescent nicotine treatment, with enhanced anxiety and fear (Slawecki *et al.* 2003; Smith *et al.* 2006). Furthermore, adolescent but not adult nicotine treatment can result in a depression-like state in adulthood that is normalized by treatment with nicotine or anti-depressants (Iñiguez *et al.* 2009).

Clinical implications

Tobacco use remains the major cause of premature death in the United States, with 30% of cancer deaths and 18% of all deaths directly attributable to smoking (Burke *et al.* 2008). Approximately 90% of adult smokers initiate tobacco use before the age of 18 years (Substance Abuse and Mental Health Services Administration, 2011), and those who do not start smoking in adolescence are unlikely to ever do so (Sussman, 2002). Teen smokers are significantly more likely to use other drugs (Lai *et al.* 2000; Hanna *et al.* 2001; Biederman *et al.* 2006), engage in high-risk sexual behavior (Rashad & Kaestner, 2004; Jackson *et al.* 2012), and develop psychiatric disorders than

non-smokers (McKenzie *et al.* 2010; Kollins & Adcock, 2014). Whereas proof of cause and effect is often difficult to obtain in clinical studies (Mathers *et al.* 2006), use of animal models has provided substantial evidence that the limbic system, which controls cognition, emotion, and drug reward, is actively maturing during adolescence and is uniquely vulnerable to long-term modification by nicotine. Although many preclinical studies have used chronic, high-dose nicotine exposure protocols that do not model early smoking behavior, more recent studies have indicated that even brief exposure to a low dose of nicotine can produce lasting change in the adolescent brain. Even a single day of nicotine treatment in adolescent rats can enhance sensitivity to aversive stimuli later in life (Iñiguez *et al.* 2009), a finding that supports the concept that teen smoking may not only be co-morbid with mood-related disorders but may actually induce them (John *et al.* 2004; Klungsoyr *et al.* 2006; Flensborg-Madsen *et al.* 2011). Although epidemiological data suggest that tobacco acts as a 'gateway' to subsequent substance abuse (Kandel *et al.* 1992; Lai *et al.* 2000; Degenhardt *et al.* 2010), it is not clear from human studies whether this reflects social influences or a drug effect (Lindsay & Rainey, 1997; Anthony, 2012). However, brief treatment of adolescent rats with a low dose of nicotine, equivalent to one to two cigarettes per day for 4 days, enhances acquisition of self-administration for cocaine, methamphetamine and alcohol, induces cocaine locomotor sensitization, and enhances sexual arousal (McQuown *et al.* 2007; McQuown *et al.* 2009; Dao *et al.* 2011; Figs 5 and 6). Such findings provide substantial support for a neurobiological sensitization mechanism (Kandel & Kandel, 2014).

Although dopamine is clearly involved, animal studies also point to the unique sensitivity of the adolescent serotonin system to regulation by nicotine (Shearman *et al.* 2008; Bang & Commons, 2011; Dao *et al.* 2011). Such findings are consistent with a clinical study that revealed a highly significant association between a polymorphism of the SERT promoter region and the initiation of smoking, using both case-control analysis and family-based designs (Kremer *et al.* 2005). In a recent study, 15 out of the 16 top-ranked single nucleotide polymorphisms associated with teen smoking or nicotine dependence were also found to be involved in dopaminergic signaling pathways, although none were significant when controlled for multiple comparisons (O'Loughlin *et al.* 2014). Another key feature of the adolescent effects of nicotine, as seen in animal studies, is the unique sensitivity of the early adolescent period as compared to late adolescence and adulthood (Laviola *et al.* 2001; Cao *et al.* 2010; Dao *et al.* 2011; Kawai *et al.* 2011). This finding provides a biological basis for the clinical observation that age of first cigarette use is a critical determinant of tobacco dependence, with those who started in their early teens having the greatest difficulty quitting (Cengelli *et al.* 2012; Kendler *et al.* 2014). The concept that early and late adolescence are periods of differing vulnerability to drugs of abuse is also supported by recent evidence from both human and animal studies that early adolescence is a time of increased sensitivity to alcohol use (Spear, 2015), whereas late adolescence may be a time of greater vulnerability to the rewarding effects of cocaine (Wong *et al.* 2013). Sex differences in nicotine sensitivity at different phases of adolescence have also been reported in preclinical studies (Cao *et al.* 2010; Kawai *et al.* 2011; Lenoir *et al.* 2015), and are consistent with clinical observations of differing developmental trajectories of tobacco use in males and females (Chen & Jacobsen, 2012).

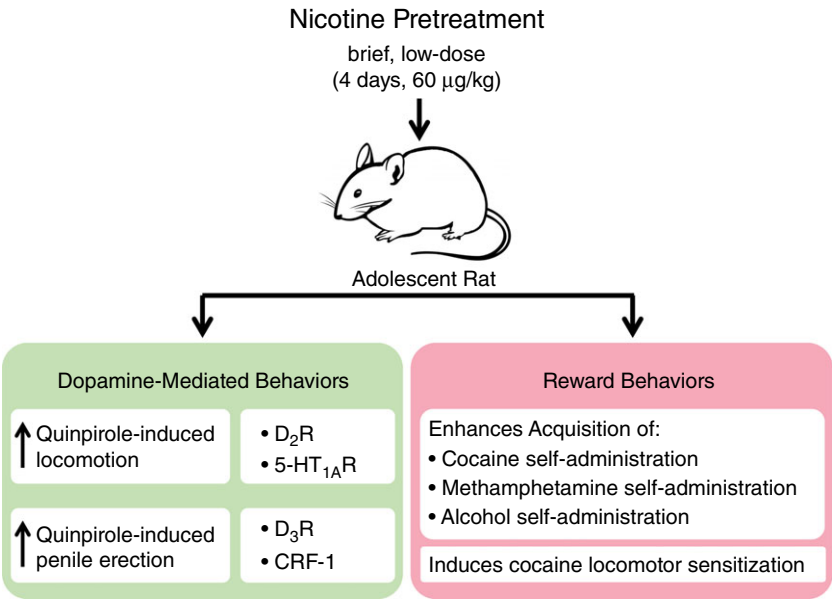

Figure 6. Nicotine pretreatment alters dopamine-mediated behaviors, neuronal activation, and reward sensitivity in adolescent rats
We have found that brief, low-dose nicotine pretreatment during early adolescence enhances quinpirole-induced locomotion, an effect that is mediated by D_2 and 5-HT_{1A} receptors. Nicotine also enhances quinpirole-induced penile erection, an effect that is mediated by D_3 and CRF-1 receptors. Furthermore, nicotine pretreatment during adolescence sensitizes reward responses to drugs of abuse, enhancing the acquisition of cocaine, methamphetamine, and alcohol self-administration. Nicotine pretreatment also induces cocaine locomotor sensitization to low doses of cocaine. These effects are age-specific and are not present during late adolescence or adulthood.

One important aspect of adolescent nicotine exposure is the long-lasting neurochemical and behavioral changes that result. Such findings suggest that nicotine may induce epigenetic changes in the neural genome. Recent evidence has been provided for transgenerational epigenetic effects of fetal nicotine exposure on lung function, suggesting that nicotine can create lasting, multigenerational alterations in the epigenome (Rehan *et al.* 2012; Leslie, 2013). A series of studies investigating the 'gateway' effect of nicotine also found that chronic nicotine exposure sensitizes cocaine behavioral responses and long-term potentiation in the nucleus accumbens, amygdala, and hippocampus (Levine *et al.* 2011; Huang *et al.* 2013, 2014). These effects are both unidirectional in that cocaine does not affect nicotine-induced responses and result from inhibition of histone deacetylase (Kandel & Kandel, 2014). Although such findings demonstrate epigenetic mechanisms that could mediate nicotine 'gateway' effects, these studies were performed in adult mice. Future studies should take into consideration that adolescence, a period of dynamic maturation and enhanced drug sensitivity, is the typical period when initiation of smoking occurs. In doing so, they may uncover novel epigenetic mechanisms mediating age-specific behavioral and neurochemical alterations after adolescent nicotine exposure.

With increasing evidence that aberrant activation of nAChRs during adolescence triggers lasting changes in neuronal signalling, use of drugs containing nicotine may have potentially severe consequences for teen addiction, cognition, and emotional regulation. Thus, not only tobacco but also e-cigarettes must be considered as serious threats to adolescent mental health. E-cigarettes were initially introduced as a promising tool for smoking cessation. However, lack of federal regulations and a wide selection of flavors make e-cigarettes not only accessible, but also appealing to young people (Grana *et al.* 2014). Indeed, emerging clinical evidence reveals that more teenagers currently use e-cigarettes than tobacco (Dutra & Glantz, 2014; Wills *et al.* 2015). Between 2011 and 2013, the use of e-cigarettes amongst teens has tripled with more than a quarter of a million youths having experimented with 'vaping' in 2013 (Bunnell *et al.* 2015). Even amongst current adolescent smokers, e-cigarettes increase the likelihood of perpetuating and increasing tobacco use (Dutra & Glantz, 2014; Lee *et al.* 2014). Teenagers who use e-cigarettes are also more likely to escalate to smoking tobacco (Dutra & Glantz, 2014; Wills *et al.* 2015). Current data indicate that nicotine disrupts normative limbic development and primes behavioral susceptibility to drugs of abuse (McQuown *et al.* 2009; Dao *et al.* 2011). Together, this raises serious concerns for the impact of e-cigarettes on public health, suggesting that they may be a new 'gateway' to both future tobacco use and substance abuse.

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Additional information

Competing interests

The authors declare no conflicts of interest.

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