



Review

Adolescent nicotine induces persisting changes in development of neural connectivity



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This article is dedicated to the memory of Amy Eppolito, a wonderful student, colleague, and friend.

ABSTRACT

Adolescent nicotine induces persisting changes in development of neural connectivity. A large number of brain changes occur during adolescence as the CNS matures. These changes suggest that the adolescent brain may still be susceptible to developmental alterations by substances which impact its growth. Here we review recent studies on adolescent nicotine which show that the adolescent brain is differentially sensitive to nicotine-induced alterations in dendritic elaboration, in several brain areas associated with processing reinforcement and emotion, specifically including nucleus accumbens, medial prefrontal cortex, basolateral amygdala, bed nucleus of the stria terminalis, and dentate gyrus. Both sensitivity to nicotine, and specific areas responding to nicotine, differ between adolescent and adult rats, and dendritic changes in response to adolescent nicotine persist into adulthood. Areas sensitive to, and not sensitive to, structural remodeling induced by adolescent nicotine suggest that the remodeling generally corresponds to the extended amygdala. Evidence suggests that dendritic remodeling is accompanied by persisting changes in synaptic connectivity. Modeling, electrophysiological, neurochemical, and behavioral data are consistent with the implication of our anatomical studies showing that adolescent nicotine induces persisting changes in neural connectivity. Emerging data thus suggest that early adolescence is a period when nicotine consumption, presumably mediated by nicotine-elicited changes in patterns of synaptic activity, can sculpt late brain development, with consequent effects on synaptic interconnection patterns and behavior regulation. Adolescent nicotine may induce a more addiction-prone phenotype, and the structures altered by nicotine also subserve some emotional and cognitive functions, which may also be altered. We suggest that dendritic elaboration and associated changes are mediated by activity-dependent synaptogenesis, acting in part through D1DR receptors, in a network activated by nicotine. The adolescent nicotine effects reviewed here suggest that modification of late CNS development constitutes a hazard of adolescent nicotine use.

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1. Introduction

1.1. Adolescent nicotine use

Adolescent use of nicotine products continues at a relatively high level. The vast majority of US adult smokers began smoking in adolescence (U.S. Department of Health and Human Services, 2012; Schepis and Rao, 2005), and show increased consumption of tobacco products relative to those who began later in life (Taioli and Wynder, 1991). Moreover, early smoking onset is a strong predictor of subsequent failure to quit (Kendler et al., 2013; Klein et al., 2013). Though teenage smoking rates have recently declined, a significant percentage of adolescents still experiment with cigarettes (Johnston et al., 2012), and use of smokeless nicotine-containing tobacco products is common and increasing (Nasim et al., 2012). The continuing high level of adolescent use of nicotine products prompts continuing study of potential hazards of use.

1.2. Adolescent neural development

It is now clear that adolescent brain development extends further into life than previously thought; can nicotine affect adolescent brain development? Previous research has documented that prenatal nicotine can alter CNS development (see Ernst et al., 2001 for review), but recently, continuing developmental plasticity of the CNS through adolescence has been documented. A wide range of CNS changes continue during adolescence, including but not limited to, synaptogenesis (Dwyer et al., 2009), selective synaptic pruning (Andersen et al., 2000), myelination (Paus, 2010), cortical areal size (Crews et al., 2007), anatomical connectivity of brain areas (Cunningham et al., 2002, 2008), patterns of functional connectivity (Supekar et al., 2009; Raznahan et al., 2011; Lydon et al., 2014; Somerville and Casey, 2010), electrophysiological activity (Sturman and Moghaddam, 2011), neurotransmitter-behavior relationships (Falco et al., 2014), and relative expression of different neurotransmitter receptor subtypes (Stanwood et al., 1997; Doura et al., 2008) and synaptic proteins (Counotte et al., 2010). In addition, functional characteristics of developing brain render the adolescent brain more prone to impulsive behavior (Stansfield and Kirstein,

2006; Adriani and Laviola, 2003), and more reactive to reinforcers (Adriani et al., 2002; Levin et al., 2007; Wilmouth and Spear, 2008), hence increasing the likelihood of human drug consumption during adolescence. Lydon et al. (2014) summarize work showing that the adolescent behavioral phenotype (in humans) also includes motivational and incentive-response systems different than adult CNS systems, contributing to adolescent smoking/nicotine consumption. The adolescent behavioral phenotype differs in many respects from adults, including higher impulsiveness, risk-taking, and responsiveness to incentives, poorer inhibitory control (see Lydon et al., 2014 for a discussion of these), and incomplete maturation of the frontostriatal connections used in decision making (Somerville and Casey, 2010). Different neurotransmitter systems appear to develop at different rates during adolescence, and may underlie or contribute to adolescent addictive/consumptive/incentive response behaviors. Chambers et al. (2003) concluded that DA systems are relatively more active than 5-HT systems during adolescence, corresponding to stronger excitatory and weaker inhibitory motivational systems at that age. O'Dell (2009) suggested that adolescents also have a relatively active glutamate (Glu) system and underdeveloped GABA system, contributing to robust reinforcement effects and weak withdrawal effect compared to adults. With respect to these developmental differences and then-limited behavioral work, Laviola et al. (1999, 2003) concluded that animal models are well-suited to the study of mechanisms of adolescent addiction.

A mere listing of some of the differences between adolescents and adults does not fully convey the possible consequences of modifying normal development of these multiple and complex systems. Chambers et al. (2003) reviewed data on neurodevelopment, concluding that "...effects of addictive drugs on dopamine systems may be accelerated during these developmental epochs, enhancing the progression or permanency of neural changes underlying addiction." Chambers and Potenza (2003) present a cogent summary of the complexity of adolescent CNS development as it may influence a variety of addictive behaviors in adolescence. In particular, continuing developmental plasticity as these multiple aspects of CNS structure/function progress toward adulthood raises the possibility that adolescent nicotine may alter growth and development of

CNS (Smith, 2003). This review summarizes recent findings showing the consequences of adolescent nicotine exposure on dendritic arbor plasticity in corticolimbic brain regions known to mediate emotion and reinforcement processing, and supporting lines of evidence suggesting lasting changes in connectivity induced by nicotine. Activity-dependent circuit reorganization, specific to circuits activated by nicotine and supported by developmentally differentiated brain connectivity and receptor expression, may underlie the persisting effects of adolescent nicotine. We suggest that lasting changes in dendritic morphology and associated behavioral consequences of adolescent nicotine represents a previously unknown hazard of early nicotine use.

1.3. Defining “adolescence”

Adolescence is a term difficult to define, even in humans, where age ranges are usually used as proxies for developmental stages. If one defines adolescence as the developmental period from the earliest incipient hormonal changes through puberty (cycling in females, sperm production in males) to full adult reproductive functioning, it ranges in the rat from about P28 for earliest prepubertal hormonal changes in females to about P38 for cycling in females to about P60–70 for full adult reproductive functioning (reliable impregnation and litters of 8 or more) in both sexes (see Spear, 2000 and Adriani and Laviola, 2004, for discussions of defining adolescence). Our first study, cited below, used a long dosing period of P22–69 to incorporate all of this extended definition of adolescence. Early work on adolescence sometimes included a longer dosing period (e.g., Belluzzi et al., 2004) and sometimes included dosing groups in later adolescence (e.g., Adriani et al., 2002, 2003), but rapidly concluded that very early adolescence appears to be a sensitive period for nicotine dosing.

As research advanced, it became clear that adolescent drug effects are more commonly seen in early adolescence, and ‘adolescence’ (perhaps more correctly labeled ‘early adolescence’) became defined in much of the adolescent drug research community as P28–42. Most recent studies use a similar age range, although specific ages vary by several days.

For a larger discussion of the processes involved in sexual differentiation in adolescence, including approximate ages, the reader is referred to a recent excellent review (Juraska et al., 2013).

2. Neuromorphological effects of adolescent nicotine

2.1. Dendrites, information processing, and connectivity

Dendrites are not ‘just’ an anatomical component of the neuron; their structure also impacts information transmission through the neuron. Dendritic factors affecting the ‘action potential decision’ include the number of synaptic inputs, their spatial distribution (distal vs proximal location), and electrical characteristics of the dendrite itself. Electrical characteristics include impedance effects on postsynaptic potentials, but also, somewhat surprisingly, direct effects of dendritic surface area (via impedance) on initiation of action potentials. Eyal et al. (2014) recently showed that increasing dendritic surface area increases the likelihood of, and speed of, generation of action potentials. Chklovskii (2004) and others have also shown that increasing dendritic surface area is closely related to increased synapse number and hence connectivity. Thus, an increase in dendritic size/surface area carries the potential for increased synaptic connectivity and more rapid initiation of action potentials, both of which affect information processing in CNS.

2.2. Adolescent nicotine and nucleus accumbens dendritic morphology

Adolescent nicotine has now been shown to structurally remodel dendrites in several areas of the CNS, and these changes then persist into adulthood. In the first experiment characterizing dendritic morphology following chronic nicotine exposure during the adolescent period, McDonald et al. (2005) dosed rats continuously via minipump with 2.0 mg/kg/d nicotine bitartrate from postnatal day (P) 22–69, an age range that encompasses the entirety of the adolescent period (Spear, 2000 – at that time, still being defined). Thirty days following the termination of nicotine dosing, medium spiny neurons (MSNs) from the nucleus accumbens (NAcc) shell were digitally reconstructed in three dimensions from Golgi-Cox stained tissue, using NeuroLucida software (Microbrightfield). Results from a morphometric analysis indicated significant net dendritic growth following nicotine, with the most prominent changes located at higher order (3rd and 4th) branching (“net” growth indicates that we could not, in this study, distinguish between actually stimulating growth, vs stabilizing transient branches that might otherwise regress; the “net” effect is greater dendritic area after nicotine). We note that the growth sequence of 1st, 2nd, 3rd, etc., indicates that later developing and hence presumably less stable/more plastic dendrites are affected by nicotine. These data were the first to show that adolescent nicotine exposure resulted in MSN dendritic plasticity in the NAcc shell and that changes in dendritic complexity were selective for more distal locations along the tree. In a subsequent experiment, McDonald et al. (2007) used a shorter dosing period (P29–43) and extended analyses to include a comparable adult nicotine dose group, and another cell type within the NAcc, the large cholinergic aspiny neuron. We showed that effects of nicotine on MSN dendritic morphology were detectable at a dose that was insufficient to significantly change dendritic morphology in adult animals. Nicotine-induced structural alterations were specific to the MSN cell type, as there were no detectable morphological differences in the dendritic architecture of large aspiny neurons in NAcc at either age. Subsequent analysis of branch length and branch number by branch order in the adolescent animals confirmed in this cohort that the overall increase in branch length was due to an increase in the number of third- and fourth-order branches, with no increase in average length. Therefore, it was concluded that adolescent nicotine stimulated the net growth of new MSN dendritic branches. Overall, these papers were the first to convincingly demonstrate nicotine-induced age-related modifications of MSN dendritic morphology in the NAcc, a brain region critical for processing the reinforcing properties of drugs of abuse.

Ehlinger et al. (2015) recently confirmed the finding that adolescent nicotine stimulates MSN dendritic growth, found that this growth occurs after a more limited dosing period (3X weekly IP injection, 0.5 mg/kg, P28–42), and showed that the elaboration is evident immediately upon the conclusion of dosing; it does not require a prolonged postdosing incubation period. The rapidly developing proliferation is also persistent, and remains at three weeks postdosing. This important study confirms our previously reported effects in NAcc shell with a different route of administration and shorter dosing period, indicating that proliferation is not dependent on route of administration, prolonged time of incubation/withdrawal, or long dosing period. It also is D1DR receptor dependent, and is accompanied by a transient proliferation of spine density, with persisting elevation of spine number. These will be discussed in more detail below. Finally, the rapid appearance of additional dendrites tend to indicate that what we term “net” growth for NAcc is most likely the result of actual stimulation of growth, as opposed to stabilization of transiently appearing dendrites.

2.3. Adolescent nicotine and medial prefrontal cortex dendritic morphology

Based upon emerging work implicating medial prefrontal cortex (mPFC) in addiction (e.g., Kalivas, 2008), we investigated whether adolescent nicotine affects dendritic structure in mPFC. Cortical pyramidal neurons are morphologically complex with basilar and apical dendritic trees that integrate and shape incoming information from different cortical layers and extracortical sources. As PFC undergoes a massive wave of plasticity during the adolescent period, and is a primary target for nicotine-induced plasticity and a critical component of a reinforcement circuit, we reconstructed pyramidal neuron dendrites in the prefrontal cortex from the same cohort for morphological analysis. For this study we used our P29–43 minipump dosing regimen (McDonald et al., 2007). Pyramidal cells from layer V of the prelimbic (PL) region of the medial prefrontal cortex were anatomically segregated into those exhibiting either a relatively simple or complex apical distal tuft, using a novel application of principal component analysis. Results revealed that adolescent nicotine resulted in increased branching complexity of basilar dendrites of neurons with complex apical tufts, while adult dosing induced increasing branching only in those with simple tufts. Thus, we concluded that both adolescent and adult nicotine induce growth of dendrites in mPFC neurons, but the effects are on different populations of neurons, with putatively different connectivity, at different ages (Bergstrom et al., 2008). Unlike the differences between MSNs and aspiny cell types, where MSNs are clearly part of the reinforcement system and aspiny neurons are not, classification of layer 5 pyramidal neurons by projection field or function is less clear. However, an emerging consensus supports the view that pyramidal neurons with less complex apical tufts, the type we termed ‘simple,’ are corticopontine and corticothalamic cells, while those with more complex apical tufts, the type we termed “complex,” are corticocortical and corticostriatal. (Groh et al., 2010; Morishima and Kawaguchi, 2006; Gao and Zheng, 2004). Thus, our adolescent nicotine dosing induced dendritic elaboration in putative corticocortical/corticostriatal neurons, while adult nicotine induced growth in putative corticopontine/corticothalamic neurons. Lee et al. (2014) present evidence suggesting that these two types of mPFC neurons also have functional distinctions, in that they respond to different inputs and have different response patterns. Lee et al. (2014) suggest that complex neurons (their type A) may be part of a detection system for amplifying responses to specific input, while simple cells (their type B) may integrate across inputs. While the many differences in methods limit us to speculation here, the notion that increasing synaptic inputs to complex neurons (as we see with adolescent nicotine) may strengthen reactions to nicotine, is roughly consistent with the Lee et al. (2014) findings. Finally, van Aerde and Feldmeyer (2015) in a recent review of mPFC pyramidal neuron subtypes, affirmed the type differences in apical tufts within Layer 5 (although terminology of that description has not yet reached consensus), and summarized electrophysiological distinctions between the two. More discussion of this connectivity and implications for addiction in relation to age of exposure occurs later in this paper.

2.4. Adolescent nicotine and basolateral amygdala dendritic morphology

As behavioral effects of adolescent nicotine include effects on anxiety-like behavior and fear conditioning (Slawecki et al., 2003; Smith et al., 2006; Iñiguez et al., 2009), we characterized dendritic morphology of basolateral amygdala (BLA) principal neurons, which are pyramidal-“like” neurons. In this experiment, rats were administered nicotine (0.5 mg/kg) intraperitoneally three times

weekly for two weeks (six total injections) from P32–43 (adolescence), or P60–71 (adulthood). Results of morphometric analysis showed that nicotine interacted in complex ways with age, apical/basilar dendrite, and hemisphere to induce dendritic changes in BLA. Principally, adult dosing resulted in right hemisphere basilar growth, creating a hemispheric difference in dendritic complexity where none existed in controls. For adolescents, however, there was a tendency toward left hemisphere growth of basilar dendrites, and some growth of apical dendrites. This tended to eliminate an intrinsic hemispheric difference in dendritic morphology observed in the adolescent group. As in the NAcc study, the impact of nicotine on dendritic arborization was not general to all neurons; evaluation of another region in the medial prefrontal cortex, the infralimbic cortex, revealed no significant effects of nicotine dosing at either age (Bergstrom et al., 2010). Also as in the NAcc and mPFC studies, dendritic elaboration was most evident at distal branches, which typically develop later in ontogeny (van Aerde and Feldmeyer, 2015; Ryan et al., 2015).

The functional consequences of nicotine-induced, hemisphere-dependent dendritic remodeling in the BLA are unknown. There are several reports, however, of lateralization of BLA function in both humans and rodent models (Baker and Kim, 2004; Adamec et al., 2005; Carrasquillo and Gereau, 2008; Alvarez and Banzan, 2011; Morris et al., 1999; Young and Williams, 2013). While the specific relation of functional lateralization to nicotine-induced dendritic elaboration, and the relation to BLA functioning, is unknown, our findings extend the notion that developing circuits in the adolescent CNS are differentially sensitive to nicotine-induced dendritic elaboration.

2.5. Adolescent nicotine and dendritic morphology in the bed nucleus of stria terminalis (BNST)

Here we used the protocol of the BLA study: 0.5 mg/kg nicotine, given IP 2X weekly from P32–43. In BNST, too, neurons in animals dosed with adolescent nicotine differed from controls: 3rd and 4th order dendrites were more numerous and had longer total length in dosed animals than in controls. In contrast to the results in structure reported for other areas, BNST neurons also underwent some lengthening of existing dendrites, as increases in both number of dendrites and average length were observed. This study did not include adult comparisons (Smith et al., 2015a,b). While the specific role of the BNST in addiction is not currently clear, a recent review summarized the connectivity-related evidence suggesting that interactions with known addiction-related structures position the BNST to be involved in addictions (Stamatakis et al., 2013).

2.6. Adolescent nicotine and dendritic alterations in dentate gyrus granule cells (DG)

Using the same dosing protocol as for BNST and BLA, we found that DG cells also exhibit alterations in dendritic branching patterns after adolescent nicotine. Similar to findings in amygdala, adolescent nicotine altered hemisphere-specific dendritic length in granule cells. Control animals had greater dendritic length in the right hemisphere, while nicotine administration reversed the hemispheric difference by inducing left hemisphere growth, primarily of new branches. For these neurons, we also did spine counts. As the spine density after nicotine was essentially unchanged, but the total length and complexity of dendrites was increased, the total number of spines (density \times length) was apparently increased. No adult comparison group was included in this study (Ehlinger et al., 2012b).

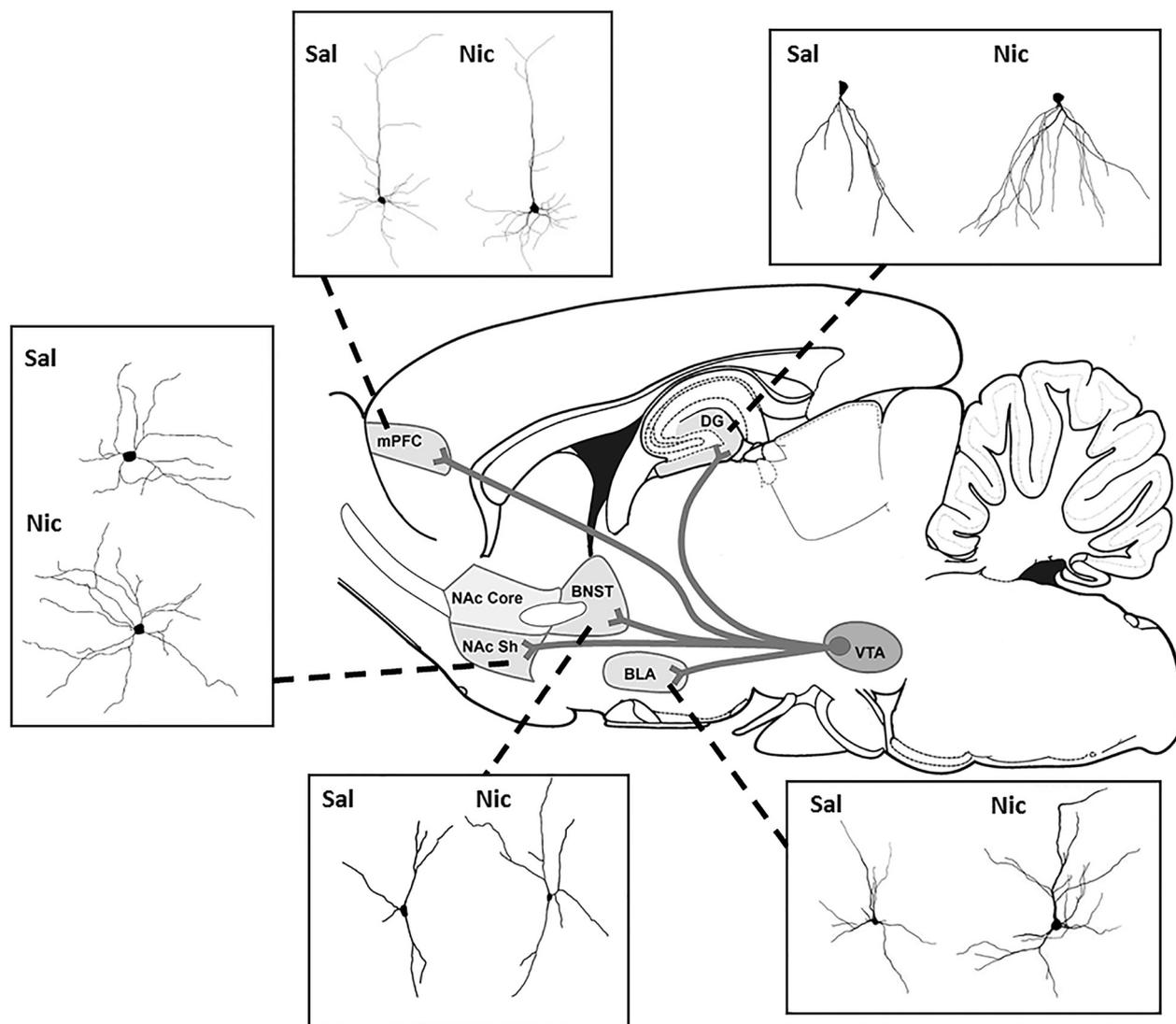


Fig. 1. Areas where dendritic branching is altered by adolescent nicotine. For each area evaluated, inserts show representative neuronal reconstructions from nicotine (Nic) and saline (Sal) treated animals. Legend: mPFC = medial prefrontal cortex, NAc Sh = nucleus accumbens shell, BNST = bed nucleus of stria terminalis, BLA = basolateral amygdala, DG = dentate gyrus, VTA = ventral tegmental area.

2.7. Anatomical specificity of adolescent nicotine effects

As summarized in Fig. 1, neurons in NAc shell, mPFC, BLA, DG and BNST have additional dendritic branching stimulated by adolescent nicotine. Although these changes in dendritic structure have now been found in several areas, they are not ubiquitous. McDonald et al. (2007) reported that, within NAcc, large aspiny neurons were not structurally affected by adolescent nicotine. Bergstrom et al. (2008) found that mPFC dendritic alterations were class-specific: adolescent dendritic structure in pyramidal cells with simple apical arbors was unchanged, although basilar dendrites of complex cells were affected. Bergstrom et al. (2010) reported that infralimbic pyramidal neurons were unaffected by nicotine, as were right hemisphere principal neurons. Ehlinger et al. (2012b) found no effect of adolescent nicotine on right hemisphere dentate neuron dendritic trees. Table 1 summarizes the patterns of effects, and non-effects, of adolescent nicotine in areas we have examined to date. Adolescent nicotine does affect dendritic structures in cells as shown in Table 1a; it does not affect cells shown in Table 1c. As noted, the Table 1a adolescent effects differ from the Table 1b adult effects; the adult 'no effect' table (Table 1d) also differs in some respects from the adolescent 'no effect' (Table 1c), indicating that the circuit

specificity for adolescent dosing differs from that for adult dosing, both with respect to which neurons are affected, and with respect to which are not affected.

2.8. Adolescent nicotine affects a different network than adult nicotine

As initially shown by Brown and Kolb (2001), adult nicotine can also induce some dendritic elaboration. However, the specific changes induced by adolescent nicotine differ from those induced by adult nicotine, not only in sensitivity to nicotine, but also in specific loci of effects. The studies cited above show that differential effects of nicotine by age are neither general (i.e., affect all neurons similarly) nor restricted to a single anatomical structure, as summarized in Table 1 and Fig. 1. Rather, the age-differentiated effects to date are somewhat specific to the circuitry generally describable as the extended amygdala (Koob and Volkow, 2010). As reviewed elsewhere (Koob and Volkow, 2010), this system subserves not only effects of reinforcement, but also stress reactions and emotional regulation in general. At this point in time, however, it is clear that adolescent nicotine stimulates a dendritic growth response from a neural population that includes NAcc MSNs, mPFC complex cells,

Table 1

Patterns of dendritic change after adolescent vs. adult nicotine. Note the differences in pattern between adult/adolescent effects (A vs B), and non-effects (C vs. D), and the pattern difference (A–C vs B–D) indicating age-specificity of the pattern of effects.

A. Changed after adolescent dosing		B. Changed after adult dosing	
Structure	Change	Structure	Change
NAcc shell MSNs	Inc branching, spines	NAcc shell MSNs	No sig effect/our dose
mPFC L5 pyr	Inc branching, complex	mPFC L5 pyr	Inc branching, simple
BLA principals	Inc branching, L only	BLA principals	Inc branching, R only
Dentate granules	Inc branching, L only	Dentate granules	Not eval/adults
BNST	Inc branching, length	BNST	Not eval/adults
Insula pyramidal	Inadequate staining	Insula pyramidal	Inc branching ^a
C. Unchanged after adolescent dosing		D. Unchanged after adult dosing	
Structure	Cell type	Structure	Cell type
NAcc	Large aspiny cells	NAcc	Large aspiny cells
mPFC	L5 pyramidal simple	mPFC	L5 pyramidal complex
BLA	Principal neurons, R	BLA	Principal neurons, L
Infralimbic ctx	L5 pyramidal	Infralimbic ctx	L5 pyramidal
Dentate granules	R hemisphere	Dentate granules	Not eval in adults

^a Included for completeness, although adolescent comparison group did not stain well. See Ehlinger et al. (2012a).

and left hemisphere BLA principal neurons, while adult administration stimulates a response from NAcc MSNs, mPFC simple cells, and right hemisphere BLA principal neurons. Additional areas altered by nicotine include BNST and dentate granule cells in adolescents and agranular insular cortex pyramidal cells in adults (Ehlinger et al., 2012a), although direct age comparisons for these have not been conducted to date. Adolescent and adult administration do not stimulate dendritic elaboration in identical neural populations, nor do they stimulate elaboration with the same dose sensitivity (at least for MSNs). Our findings suggest that (a) circuitry affected by nicotine (hence, connectivity before dosing) and (b) the resulting dendritic elaboration, and putative changes in synaptic connectivity (after dosing), are different for adult and adolescent CNS, and (c) at least for NAcc MSNs, the dose of nicotine required to induce elaboration in adolescents is lower than for adults.

2.9. Age-related differences in the network affected by nicotine

Age-, cell type-, and hemisphere differences in growth responses to nicotine thus imply that the networks affected by nicotine differ substantially by age, i.e., that nicotine stimulates dendritic growth in different combinations of neurons at different ages. While this concept is new to adolescent nicotine research, a recent paper suggests that natural reward processing utilizes somewhat different circuitry in adolescents and adults. Sturman and Moghaddam (2012) found that dorsal striatum participates in processing of reinforcement information (nose poke for food) in adolescents much more than in adults, with activity in anticipation of reward especially noted. In addition, slice preparations reveal that adolescent NAcc has local ‘wiring’ different than adults, in terms of response to DAD2 activation; the differences imply a greater involvement of GABA in adult DAD2-AMPA interactions than in adolescents (Huppe-Gourgues and O’Donnell, 2012). Mastwal et al. (2014) have found that DA-elicited structural plasticity is more robust in adolescents than in adults.

Neurochemically, adolescent networks differ in response to nicotine from adult networks; Shram et al. (2007) reported that c-fos, an immediate early gene marker for synaptic activity, was expressed more profusely to nicotine challenge in adolescents than adults in ventral tegmental area, n. NAcc shell, and BNST. Nicotine induces greater CREB activity in ventral striatum and PFC in adolescents than in adults (Philpot et al., 2010). Finally, proteins such as Arc (Schochet et al., 2005) and dendrin (Schochet et al., 2008) are induced in cortex more strongly in adolescents than adults in response to nicotine. While some of these latter findings cannot differentiate between age-selective connectivity vs receptor sensitivity differences, in toto they are at

least consistent with signaling/connectivity differences. Thus, the notion that adolescents and adults differ in aspects of neural organization/functioning/connectivity within the extended amygdala/dopamine reinforcement system, which may underlie some adult/adolescent differences in response to nicotine, is consistent with emerging literature.

3. Dendritic changes and synaptic connectivity

3.1. Adolescent nicotine, synaptic connectivity, and information processing

Do morphological changes after adolescent nicotine produce changes in synaptic connectivity and information processing? If nicotine-induced structural changes to dendrites are accompanied by changes in synaptic connectivity, this would imply that adolescent nicotine may induce changes in information processing mediated by these structures, with such changes probably enduring for as long as the structural changes endure. While changes in dendritic branching don’t provide direct confirmation of synaptic changes, we earlier noted that all branches of NAcc MSNs in nicotine-dosed animals were densely spined (McDonald et al., 2007); this by definition includes the new branches induced by nicotine, although we cannot identify new branches separately in Golgi-stained tissue. Ehlinger et al. (2015) recently found transient increases in spine density on MSN dendrites, and persisting increase in spine number (density × total branch length), after adolescent nicotine. We (Ehlinger et al., 2012b) also reported that, while spine density was not increased in dentate after adolescent nicotine, the estimate of total number of spines was similarly increased by increased total dendrite length. The sequence noted by Ehlinger et al. (2015), proliferation followed by regression in numbers, is characteristic of new synapse formation followed by stabilization, as summarized by Stoneham et al. (2010). Presence of spines on new branches is presumptive evidence of synaptic contacts on those new branches, as spine formation depends upon excitatory synaptic input (Segal et al., 2003). Adolescent nicotine dosing is also accompanied by activation of Arc, associated with dendritic growth and synaptic formation (Schochet et al., 2005) and permissive of experience-dependent firing changes (Ren et al., 2014). Nicotine specifically facilitates cortico-amygdala glutamatergic (Glu) synapses (Jiang and Role, 2008), and Glu synapses in turn drive changes in receptor subunit expression from NR2b to NR2a, reducing later activity-induced growth (Matta et al., 2011). Glu synapses also drive maturation of corticostriatal connectivity (Galiñanes et al., 2009). Adolescent nicotine dosing is followed by increases in mRNAs for DAD1 and DAD3 receptors in NAcc shell

(Smith et al., 2015b), suggesting a likely increase in actual numbers of receptors. Wheeler et al. (2013) found that adolescent nicotine induces a rapid (24 h) mRNA (D1DR, D3DR–Wheeler et al., 2013) and NR2b (Wheeler, unpublished observation) responses to nicotine challenge later in adulthood, suggesting that there are persisting changes in synapses responsive to nicotine following adolescent dosing. Such responses were not seen in control subjects not administered adolescent nicotine. While a complete summary is beyond the scope of this review, a number of papers have documented that adolescent nicotine results in persisting changes in signaling systems associated with synapses. Signaling systems with persisting changes include catecholaminergic (Trauth et al., 2001), serotonergic, and cholinergic systems (Slotkin et al., 2007, 2008; Slotkin and Seidler, 2008), hippocampal and striatal cannabinoid CB1 and mu opiate receptors (Marco et al., 2007), adenylyl cyclase (Slotkin et al., 2007), and gene expression (Doura et al., 2008), including expression for reelin, GAD67, and BDNF (Romano et al., 2014). These may be merely associated with changes in robusticity of existing synapses, but these findings would also be consistent with the formation of new synapses.

Thus, the presumptive new synapses, combined with altered geometry of the dendritic tree and probable resulting changes in postsynaptic receptors, render it highly likely that adolescent nicotine influences synaptic connectivity and mRNA expression, and hence information processing, as well as morphology. This conclusion is consistent with that of Chklovskii (2004), whose modeling work suggested that morphological alterations, such as those reported in these studies, may both alter and reflect the weight and formation of new synaptic connections between previously unconnected neurons, and that synaptic connectivity is largely a reflection of dendritic structure. Thus, the weight of evidence suggests that sustained increases in dendritic branching implies increased synaptic contacts.

3.2. What synapses might be involved in dendritic elaboration?

Ehlinger et al. (2015) recently identified D1DR receptors as crucial to dendritic elaboration in MSNs of NAcc shell. As noted above, we confirmed that adolescent nicotine induces dendritic elaboration immediately after a 3X weekly 0.5 mg/kg IP regimen of nicotine from P28–42, and also found a rapid and transient proliferation of dendritic spines. Dendritic elaboration, but not spine proliferation, was completely blocked by a D1DR blocker, SCH-23390. Clearly, this indicated that D1DR activity is necessary for dendritic elaboration in NAcc shell, but is not necessary for spine proliferation. Thus, at least two mechanisms operate in inducing structural change in NAcc by adolescent nicotine, one of which is D1DR receptor-dependent. Other information, discussed below, suggests that a second mechanism may involve glutamate or D2DR receptors.

While only D1DR receptors have been identified as underlying effects of adolescent nicotine thus far, other possible candidates include Glu and D2DR receptors. Khan et al. (1998) suggested that D2DRs are most densely located in distal dendrites of pyramidal neurons in the rodent cortex, rather than near the soma. Dense localization of D2DRs has also been shown in distal portions of dendrites in the nucleus accumbens (Fisher et al., 1994). It is also known that subtypes of glutamate receptors have different localization on distal versus proximal dendrites. Recently, it has been shown that depending on the subunit composition of glutamate receptors, these receptors will be targeted to either the somato-dendritic compartment or to the distal portions of dendrites (Kayadjanian et al., 2007). Layer V cortical neurons are most responsive to NMDA receptor stimulation in the proximal portions of dendrites, but most responsive to AMPA receptor stimulation in the distal portion of dendrites (Dodt et al., 1998). D1DR and Glu receptors have also been suspected by other investigators of involvement in persisting

effects of adolescent nicotine. Brenhouse et al. (2008) reported a transient elevation of D1DRs in PFC during adolescence, and suggested that they are associated with heightened response to reinforcement during adolescence. Counotte et al. (2011) associated attention deficits in the 5-choice serial reaction time task (5-CSRTT) with reduced mGluR2 signaling on Layer 5 mPFC pyramidal neurons, the same class of neurons which Bergstrom et al. (2008) found altered by adolescent nicotine.

3.3. Adolescent nicotine and altered adult electrophysiological activity

Recent work of Goriounova and Mansvelder (2012a) have demonstrated that, for mPFC, altered synaptic connectivity after adolescent nicotine is more than an inference from anatomical data. In an excellent series of studies summarized in their short review, they showed that adolescent nicotine leads to transient reductions in spike-timing dependent potentiation (STDP), followed in the adult by increases in STDP. These changes can then interact with later applications of Glu-acting drugs (Goriounova and Mansvelder, 2012b). Their electrophysiological findings appear to be largely linked to Glu systems, as they found transient increases in mGluR2 following adolescent nicotine, followed in turn by lasting decreases (Counotte et al., 2011). This series of studies demonstrates changes in receptor and physiology aspects of synapses following adolescent nicotine. Further, their lab has found that a behavioral characteristic, attention, shifts in parallel with their reported synaptic changes. The alteration in Glu functioning after adolescent nicotine strongly suggests that Glu receptors are involved in lasting effects of adolescent nicotine, possibly including structural changes.

3.4. Human networks change across adolescence

Recent work indicates that substantial changes in network occur between the prepubertal period and young adulthood in humans (Supekar et al., 2009; Uddin et al., 2011). Power et al. (2010) reported that human functional brain networks continue to develop in complexity and interconnectivity into adulthood. This has been confirmed by Keulers et al. (2012), with long-range connectivity continuing to develop across adolescence in many brain regions, Qin et al. (2012) for connectivity related to amygdala and emotional processing, and Stevens et al. (2007) for connectivity related to response inhibition. It is apparent that multiple regions exhibit continuing connectivity development through adolescence, presumably reflective of continuing synaptogenesis, and in some cases axonal growth (Cunningham et al., 2002). Gee et al. (2013) have even shown a reversal of amygdala-prefrontal connectivity direction during the early adolescent period, emphasizing the extent to which connectivity change may occur. The particulars of connectivity development are beyond the scope of this review, but a theme of much research on the developing CNS is that neural systems are more susceptible to drug-induced 'shaping' during than after development.

3.5. Human network changes associated with adolescent smoking

Altered connectivity in nicotine-dependent humans has been detected by fMRI (Smolka et al., 2006); while that study did not specifically target adolescent smoking onset, we noted previously that most humans who smoke begin doing so in adolescence; thus, the connectivity changes reported by Smolka are likely to represent effects of early onset smoking. While spatial resolution is not as high in human fMRI data as in our anatomical studies, Vollstädt-Klein et al. (2011) found cue reactivity in moderately dependent smokers was roughly consistent with our findings of dendritic changes,

that is, smoking cues elicited activity in amygdala and hippocampus in moderately dependent smokers. Galvan et al. (2011) recently reported fMRI data that individuals who smoked during adolescence have impairments in prefrontal cortical functioning. Musso et al. (2007) reported that young adults, who on average initiated smoking at age 15, have altered fMRI activity in frontal attentional networks. Buzzell et al. (2014) found that the N2 (a negative going deflection occurring 250–300 ms post stimulus) component of the event related potential (ERP) was reduced in college students with a smoking history, even when limited smoking history did not induce significant impairments in cognitive control. This finding is significant, as the source of the N2 is believed to be the anterior cingulate cortex, important in cognitive control/performance monitoring.

Collectively, these data, while limited, are roughly consistent with the notion that adolescent nicotine may also ‘drive’ some aspects of connectivity development in humans, as it appears to ‘drive’ dendritic branching and presumptive synaptic connectivity in rats. That is, we propose that nicotine-induced dendritic expansion also induces expansion of synaptic contacts and thus increases the connectivity of the expanded neurons with their respective input sources, with potential output changes as noted in Section 2.1. We particularly note that changes in cortical activity associated with nicotine dependence in humans are roughly consistent with the dendritic elaboration in putatively corticocortical neurons we reported in mPFC after adolescent nicotine (Bergstrom et al., 2008), and that these findings in humans are consistent with our neuroanatomical findings, and with the Mansvelder group’s electrophysiological and behavioral data following adolescent nicotine (Gorionova and Mansvelder, 2012a,b). The human data are consistent with the findings of Raznahan et al., (2011) who showed that functional connectivity of brain during development was related to developing anatomical complexity, and speculated that interference with these interconnected processes might underlie some forms of pathology; we suggest that aspects of addiction may be included in this definition of pathology involving dendritic structure.

3.6. Circuitry effects of adolescent nicotine

If adolescent nicotine drives some changes in connectivity, exactly which circuits are affected? First, there is the issue of putative new synapses. Withers et al. (2011) reviewed studies showing that dendritic growth precedes and determines synapse development, suggesting that dendritic elaboration elicits neurite outgrowth from nearby axons, presumably by secreting various growth factors. This is at least consistent with the findings of Chklovskii (2004) that structure and information processing correspond in dendrites. It seems reasonable to presume that at least some of the newly formed putative synapses are associated with the original synaptic input to the affected neurons, as the original inputs are nearby and thus receive stronger input from growth factors than fibers more distal in the concentration gradient. Denser afferent input to a given neuron presumably affects the firing probability of the recipient neurons when the afferent neuron fires, and that in turn affects neurotransmitter output onto neurons to which the recipient neuron projects. The earlier cited work of Eyal et al. (2014) also suggests that more extensive dendritic elaboration may in itself increase the firing probability of the affected neurons to synaptic input. Logically, then, putatively greater synaptic input affects output of the recipient neuron, and subsequently the downstream areas to which the recipient neuron projects. To where do the affected neurons project? We know the anatomy from much previous work: accumbens medium spiny neurons project primarily to striatum, our ‘complex’ mPFC neurons primarily to striatum and cortex, BLA neurons to accumbens, subiculum

and other associated parts of the extended amygdala, dentate granule cells to hippocampus proper, and BNST neurons to areas of hypothalamus. By direct observation and by extension, then, our findings imply that adolescent nicotine induces persisting alteration of information processing in circuits including n. accumbens shell (by observation) and (BLA input to) core, mPFC complex neurons, mPFC and NAcc input to striatum, mPFC input to other areas of cortex, BLA principal neurons, BNST proper, areas of hypothalamus, dentate gyrus, subiculum, and hippocampus proper. Nicotine in adolescence thus alters a complex and extensive circuitry in brain, and some aspects of that circuit differ from that affected by nicotine in adults. Parenthetically, as much of this circuitry is also involved in feedback loops regulating firing of dopamine neurons in VTA, it has the potential for alteration of DA activity persisting for the duration of the connectivity changes, i.e., indefinitely into adulthood, as no point for reversion of the changes has been identified. The several complex circuits implied by this listing also imply that adolescent nicotine may affect CNS functioning beyond addictive behaviors. While much research on potential consequences of nicotine-induced circuit alterations has not yet been done, Mojica et al. (2014) recently reported that adolescent nicotine alters functioning in hypothalamic CRF systems; this is consistent with our observation of BNST changes, and our inference of changes in BNST input to hypothalamus.

Might these adolescent-specific changes underlie some of the increased risks associated with adolescent nicotine use? Lydon et al. (2014) summarize evidence that, in humans, ‘damage’ to the PFC during continued maturation is related to continuing use. Our data suggest that a neural basis for such ‘damage’ (which we would term altered functioning/connectivity) might be altered dendritic structure and putative synaptic connectivity secondary to nicotine exposure. The existence of ‘damage’ in several areas other than PFC suggest that functional changes after adolescent nicotine are not limited to functions subserved by PFC.

3.7. Are dendritic changes driven by activity?

We consider it plausible that nicotine-activated synaptic activity guides some of the altered patterns of connectivity induced by nicotine in adolescence. Activity-dependent dendritic growth has been generally established (see Emoto, 2014 for review). If activity-dependent dendritic growth and synaptogenesis underlies the nicotine-induced changes we have observed, we expect that the pattern of actual synaptogenesis will follow the pattern of increased neural activity induced by nicotine, that is, synaptogenesis and elaboration of connectivity will occur in areas activated by nicotine. This pattern is likely to contrast with the patterns induced, for example, by sensory enrichment. In the latter, we observe increased complexity in areas associated with primary and secondary sensory processing (cf Baroncelli et al., 2010 for review), while in nicotine-induced changes we observe increases in complexity in areas associated with reinforcement processing (and also stress responsivity and emotion), as defined earlier. In each case, it appears that the pattern of enhanced activity ‘drives’ the patterns of developing connectivity. Mastwal et al. (2014) recently reported that adolescent mice are particularly susceptible to activity-dependent structural and functional plasticity driven by dopamine; axonal bouton formation in this circuit is effected by two-photon activation. In agreement with the activity-driven hypothesis for dendritic elaboration, Ehlinger et al.’s (2015) observation that branching is fully developed the day after conclusion of dosing implies that the administration of nicotine (as opposed to withdrawal from nicotine) induces branch growth and spinogenesis, consistent with the notion of activity-induced synaptogenesis.

4. Consequences associated with altered dendritic morphology

4.1. Behavioral phenotypes

Speculatively, as increased connectivity occurs in the 'adolescent wiring diagram' of brain, it may also strengthen adolescent-typical behavioral phenotypes generated by this system, causing them to persist into adulthood. Nicotine-induced dendritic proliferation may also limit further proliferation, e.g., in response to developmental or environmental events. While the data on which to base this statement are currently limited, Kolb reported that nicotine administration (in young adult rats) foreclosed later elaboration in response to enrichment (Hamilton and Kolb, 2005) or motor activity (Gonzalez et al., 2005). Ehlinger et al. (2015) found that control animals continued to exhibit developmental dendritic elaboration during our three-week postdosing survival period, while nicotine-dosed animals showed no further developmental effect during the survival period beyond the nicotine elaboration effect. It appears that nicotine dosing may 'stamp in' the 'wiring diagram' inducing by the dosing, rendering it resistant to further developmental/environmental modification. While some behavioral and neurochemical evidence roughly consistent with this speculation exists (e.g., Wheeler et al., 2013), it is beyond the scope of this review, and much additional evidence would be required to confirm it. We note that Spear and Swartzwelder (2014) have very recently developed the notion that adolescent exposure to another addictive drug, alcohol, results in persistence of many adolescent behavioral phenotypes; there is now at least the suggestion that persistence of adolescent phenotypes should be investigated after adolescent nicotine. As noted, evidence for this is limited, but it is not inconsistent with the Lydon et al. (2014) review that adolescent-specific neural systems are 'damaged' by nicotine/smoking.

4.2. Addiction-related behavioral changes

Long-lasting changes in behaviors subserved by structures altered by adolescent nicotine have now been clearly documented. The best-documented changes in actual behavior are in addiction-related behaviors. Adolescent nicotine induces a lasting change in sensitization to nicotine tested later in adulthood. Adriani et al. (2003) first showed that adolescent nicotine sensitized rats to a later nicotine challenge, and McDonald et al. (2005) showed that effects in an adult two-day sensitization protocol (saline challenge Day 1, 0.5 mg/kg nicotine challenge day 2, measuring activity in an open field) are altered by prior adolescent nicotine dosing. Animals which received prior adolescent nicotine showed a tolerance to the hypoactivity-inducing effects of nicotine in the challenge, compared to subjects who received saline during adolescent development. We have since replicated this effect several times (e.g., Smith et al., 2015b), and also shown that this lasting effect in adults can be induced by as little as a single adolescent nicotine dose in a distinctive environment (Brielmaier et al., 2007). Bracken et al. (2011) recently confirmed that adolescent nicotine induces adult nicotine sensitization in the rat. In addition to lasting changes in sensitization, adolescent nicotine leads to enhanced self-administration of nicotine in adult mice (Adriani et al., 2006) and rats (Adriani et al., 2003); this, however, was not confirmed by Weaver et al., (2012) in rats.

4.3. Emotional behaviors

In addition to changes in addiction-related behaviors, aspects of emotional behavior are altered by adolescent nicotine. Slawecki (Slawecki et al., 2003) and Smith et al. (2006) have each shown

that adolescent nicotine is followed by a long-lasting increase in anxiety-like behavior, which is not characteristic of adult nicotine dosing. In addition, Smith et al. (2006) reported that fear conditioning in the adult is altered by prior adolescent nicotine dosing, but not by prior adult nicotine dosing. Iñiguez et al., 2009 recently confirmed that adolescent nicotine alters later emotional responses in adulthood. As elements of the extended amygdala which are altered by nicotine dosing (such as BLA and BNST) have been implicated in emotional behaviors, the finding that adolescent nicotine induces persisting changes in systems beyond addiction-related circuits *per se* is hardly surprising (e.g., Mojica et al., 2014)

4.4. Cognition

Finally, a few studies have shown changes in aspects of cognition following adolescent nicotine. Spaeth et al. (2010) found impairments in contextual fear conditioning after adolescent nicotine, consistent with the DG cell changes we (Ehlinger et al., 2012) have found. Romano et al. (2014) reported persistent modulation of cognition in mice, along with increased BDNF mRNA expression after adolescent nicotine. Mateos et al. (2012) reported persisting effects on memory of adolescent nicotine (or a cannabinoid agonist), tested in the novel object test. Counotte et al. (2011) reported persisting changes in the 5-CSRTT after adolescent nicotine, as have Schneider et al. (2012). Fountain et al. (2008) found persisting effects on serial pattern learning in adults following adolescent nicotine. As noted, these persisting cognitive effects are roughly consistent with findings of persisting changes in mPFC (Bergstrom et al., 2008) and DG (Ehlinger et al., 2012b) morphology after adolescent nicotine, and the electrophysiological changes reported by the Mansvelder group.

4.5. Interim summary—behavior

The majority of this paper is devoted to evidence that adolescent nicotine alters neural connectivity, in a somewhat adolescent-typical fashion. Such alteration achieves major significance only when it alters CNS functioning and behavior. To date, there are only a few studies examining possible persisting behavioral change. Nevertheless, evidence suggests that adolescent nicotine has persisting effects to enhance responses to nicotine, to strengthen some negative emotional behaviors, and to alter cognitive functioning. Our anatomical findings to date suggest that these areas of behavior are fruitful areas to study for evidence of persisting behavioral change. We also suggest that studies to establish causal relationships (e.g., direct manipulation of structure to determine functional change) are needed to strengthen what is now only an association between structural change and some behaviors.

5. Summary and implications

5.1. Summary

Adolescent nicotine activates somewhat different patterns of dendritic growth responses than that of adult nicotine. Dendritic branching alterations after adolescent nicotine have now been documented in five brain regions (Fig. 1), roughly the extended amygdala as defined by Koob and Volkow (2010). The areas altered by adolescent nicotine differ in some respects from those altered by adult nicotine. Evidence suggests that the lasting changes in dendritic structure are paralleled by altered synaptic connectivity. These observations suggest that, in many ways, the adolescent brain reacting to nicotine is a somewhat different brain than the adult brain. The conclusion that the adolescent brain is a 'different' brain, specifically with respect to nicotine effects, is generally consistent with recent noninvasive imaging studies showing that

substantial changes in functional connectivity normally develop during adolescence. We suggest that adolescent nicotine has lasting effects on brain and behavior by modifying the pattern of activity-dependent synaptogenesis, particularly for D1DR and also for a non-D1DR type of synapse, thus ‘sculpting’ an altered pattern of connectivity. The notion of persistently altered connectivity after adolescent nicotine, implied by our anatomical data, is supported by behavioral and electrophysiological studies, and studies of persistently altered neurochemistry.

5.2. Implications: a new hazard of adolescent substance abuse

Altering neural and behavioral development may now be seen as a new category of hazard of early adolescent nicotine abuse, and presumably of early substance abuse in general. We do not now know the full extent to which addictive drugs consumed in adolescence alter structural and functional neurobehavioral development, but research with nicotine has proceeded to the point where such effects must be considered a real possibility with other addictive drugs. There are innumerable questions, now without answers, which this statement raises: which drugs, what consequences, at what consumption ages, what drug/subject characteristics confer the most risk, how persistent are effects? There is insufficient evidence to provide real guidance at this point, but a conservative inference from the available data (full citation is beyond the scope of this review) is that it is prudent to avoid use of DA-active drugs, as the findings of Ehlinger et al. (2015) indicate that nicotine alters dendritic growth by acting through D1DRs. This may include addictive substances, and possibly therapeutic drugs which affect DA systems, during early adolescence. While “avoid drug use in adolescence” is not new advice, the consequences for neural development have not been previously known. Our findings underscore the importance of preventing consumption of addictive substances in early adolescence.

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