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Effect of Chronic Adolescent Nicotine Exposure on Anxiety in Adulthood

Bilal Ashraf

*The College of William & Mary*
Abstract

Adolescents appear to be uniquely vulnerable to nicotine and its reinforcing effects which contributes its addictive potential (Levin et al., 2007). Additionally, chronic adolescent nicotine exposure may cause long-term changes in the brain pathways that mediate anxiety (Slawecki et al., 2003). The Bed Nucleus of the Stria Terminalis (BNST) has been suggested as part of the anxiety pathway (Walker & Davis, 2009) and has been implicated in one animal model of anxiety known as the Light Enhanced Startle Effect (LES). The research question this thesis addressed was: Will adolescent nicotine exposure cause long-lasting changes in anxiety that persist into adulthood? Based on existing literature, we hypothesized that exposing adolescent rats to nicotine would cause a change in anxiety behavior measured in LES when the animals were later tested as adults. Adolescent Sprague-Dawley rats were exposed to either nicotine (.15 mg/kg, .40 mg/kg) or saline from postnatal days 28-42. On approximately postnatal day 67 in early adulthood, the effect of earlier adolescent nicotine exposure on anxiety was assessed in the light-enhanced startle paradigm. Adult males exposed to nicotine as adolescents showed significant increases in anxiety measured in LES compared to saline controls. Conversely, adult females showed no significant changes in anxiety behavior as a result of prior adolescent nicotine exposure. These findings suggest nicotine exposure during adolescence can produce long-lasting changes in the neural pathways that mediate anxiety that persist into adulthood. Differential development of the BNST in males versus females, particularly in terms of nicotinic acetylcholine receptor density, is considered as one explanation for the observed sex differences. The possibility that nicotine may differentially affect anxiety measured in reflexive versus volitional (choice-based) response measures is also discussed in relation to how current findings may be integrated with existing literature.
Effect of Chronic Adolescent Nicotine Exposure on Anxiety in Adulthood

According to the Center for Disease Control (2011), tobacco is the leading cause of preventable death in the United States. Despite efforts to educate adolescents about tobacco’s harmful effects, smoking patterns in young adults have risen (Lantz, 2003). The Campaign for Tobacco Free Kids (2013) suggests that over 80% of adult smokers began smoking before 18 years of age. Adolescents have higher responsiveness to incentives and reward, which is correlated to increased dopamine activity in the nucleus accumbens, a brain structure linked to reinforcement and addiction (Ernst et al., 2006). In animals, adolescent rats self-administer more nicotine than their adult counterparts (Levin et al., 2007), suggesting adolescents are more vulnerable to the reinforcement effects of nicotine and therefore dependence. Adolescents also have weak harm-avoidance and inhibition systems, correlated to age-specific alternations in amygdala and medial/ventral prefrontal cortex activity, respectively (Ernst et al., 2006). These neural alterations may be linked to a disregard for one’s health, increased risk taking and novelty seeking behavior, and problems with impulse control characteristic of the adolescent period.

There is an additional relationship between nicotine exposure in adolescence and the emergence of anxiety and depression-like symptoms in adulthood (Slawecki et al., 2003; Iniguez et al., 2009; Trauth et al., 2000) indicating that smoking patterns that initiate in adolescence may have serious long-term psychiatric implications. In particular, it is well known that adolescence is an important period for the development of neural pathways that mediate anxiety (Spear, 2000). Since anxiety is the most common condition in psychiatric disorders (Kessler et al. 1994), the role of chronic adolescent nicotine exposure to the anxiety pathway is of particular importance.
Adolescent nicotine exposure may be critical in altering the development of the anxiety pathway. Throughout the brain, cholinergic receptors known as nicotinic acetylcholine receptors, or nAChRs, respond to nicotine as well as to endogenous acetylcholine. NACRs, especially α4β2 subtypes, are implicated in the anxiety pathway in both people and animals. Research by Roni and Rahman (2011) indicate antagonists for nAChRs, such as the α4β2 antagonist lobeline, have anxiolytic effects in animals. Roni and Rahman (2011) exposed mice to lobeline at 7-8 weeks of age and then tested them in the elevated plus maze, or EPM. The EPM is an animal model of anxiety in which rodents traverse “open” versus “closed” arms of a simple plus maze. Bright and open spaces are naturally aversive to rodents. Increased time in the open arms or increased number of open arm entries indicates a decreased state of anxiety. Mice injected with .04 mg/kg lobeline prior to EPM testing, spent more time in the open arms and made more open arm entries compared to the saline-exposed control (Roni & Rahman, 2011) indicating α4β2 receptors may play an important role in anxiety expression. Nicotine, therefore, a potent and common agonist of the α4β2 receptor, has the potential to affect anxiety.

Literature concerning nicotine’s role in anxiety is mixed. Some studies suggest that acute nicotine can have an anxiolytic effect in the short term (Cao et al., 1993; Brioni et al., 1994). Nicotine’s capacity to reduce anxiety is consistent with the idea that smoking one cigarette can produce a relaxing effect (Parrott, 1999). However, this idea has been countered by evidence suggesting the decrease in anxiety reported after nicotine intake is actually due to a nicotine-induced reduction in the negative effects of nicotine depletion which occur over a period of smoke-free abstinence. That is, nicotine may not be anxiolytic per se but may decrease negative symptoms of withdrawal leading to the perception that smoking can reduce stress (Parrott, 1999). Other studies indicate that acute nicotine may be anxiogenic (Ouagazzal et al., 1999; File et al.,
Because it is unclear whether acute nicotine is anxiogenic (Ouagazzal et al., 1999; File et al., 1998) or anxiolytic (Cao et al., 1993; Brioni et al., 1994), evidence from acute nicotine’s effects cannot be used to postulate its effects in chronic use. As such, it is critical to study the effects of long-term nicotine use on the anxiety pathway, and particularly during adolescence, a period of growth and structural remodeling in the brain (Smith, 2000). Davis and Shi (1999) demonstrated a crucial role of the Bed Nucleus of the Stria Terminals of the Amygdala (BNST), in anxiety, in rodents using the Light Enhanced Startle (LES) paradigm. The LES paradigm takes advantage of the fact that rats are nocturnal and find bright light aversive, presumably due to enhanced risk of predation in bright (e.g. open field) vs. dark (e.g. burrow) situations (Walker & Davis, 1997). Walker and Davis (1997) demonstrated that startle reactions elicited by loud noises in the presence of a bright light were enhanced compared to startle reactions to the same noise stimuli under dark conditions. This is the light-enhanced startle effect. Light-enhanced startle assesses anxiety in a reflexively elicited response measure (i.e., startle). This feature of the LES paradigm will be further discussed later. Importantly, Davis and Shi (1999) found that startle amplitude in the anxiety-eliciting bright condition was reduced after inactivating the BNST with
a glutamate antagonist, NBQX. These findings imply that the BNST is involved in the expression of anxiety (Davis & Shi 1999).

Adolescent animals appear to be especially vulnerable to the long-term neurobiological effects of nicotine. An increase in receptor density is one manner in which the nervous system can become more sensitive to a ligand. Abreu-Villacca et al. (2004) reported that adolescent nicotine exposure in rats causes a robust upregulation of nAChRs in the midbrain that was long lasting. To the extent nicotine is anxiogenic, this outcome could be taken to imply that an individual who smokes tobacco in adolescence may be more likely to develop anxiety-like symptoms in adulthood.

Some research is consistent with this possibility. Slawecki et al. (2003) applied nicotine via transdermal patches to male adolescent rats. The animals were tested two to three weeks later in young adulthood in the open field paradigm. In the open field paradigm, a rat is placed in the center of a chamber with an open top and walls too high to escape. The latency to exit the center and move to the perimeter of the field and the number of perimeter and center square entries, are measured. Less time spent in the center of the open field and less overall movement is indicative of anxiety. Slawecki et al. (2003) found that animals exposed to nicotine as adolescents had a lower latency to escape to the perimeter, as well as fewer square crossings, indicating increased anxiety in a potentially dangerous, novel environment in which they could be evolutionarily vulnerable to predation. This is an important observation because it suggests that exposure to nicotine in adolescence can cause changes in anxiety behavior that persist into adulthood (see also Trauth et al., 2000). Smith et al. (2006) further observed that rats exposed to nicotine in adulthood as opposed to adolescence did not show similar alterations in anxiety behavior. The outcome of these experiments suggest that adolescent nicotine exposure can have a significant
and potentially long-lasting impact on the neural anxiety pathway in adulthood. Moreover, this impact may be attributable to nicotine’s effect on the development of the anxiety pathway because adolescent but not adult exposure has been shown to alter anxiety behavior.

Existing literature implies that chronic adolescent nicotine exposure may durably alter the neural anxiety pathway. While some studies have supported this (Slawecki et al., 2003; Smith et al., 2006; Trauth et al., 2000), these studies have measured anxiety in paradigms that require voluntary, non-reflexive, behavior (i.e., a rat choosing to move from one location to another in the Open Field test or EPM). The Light Enhanced Startle paradigm measures changes in the rat’s acoustic startle reflex and therefore permits assessment of how nicotine affects anxiety in a reflexive as opposed to voluntary response measure. Currently there are no published studies that examine the long-term effects of adolescent nicotine exposure on anxiety measured in LES. Because response systems that engage reflexive versus voluntary behavior may be mediated by different brain structures, and affected by anxiety in unique ways, the present research sought to address this gap in the literature by examining the impact of chronic adolescent nicotine exposure on anxiety measured in the LES paradigm.

*Research Hypothesis and Predictions*

The research question this thesis addressed was: Will adolescent nicotine exposure cause long-lasting changes in anxiety that persist into adulthood? We hypothesized that exposing adolescent rats to nicotine would cause a change in anxiety behavior measured in LES when the animals were later tested as adults. Sprague-Dawley rats were exposed to nicotine for 15 consecutive days during adolescence. Following a long period of abstinence, which extended beyond withdrawal and into adulthood, animals were tested in the LES paradigm, modeled after procedures previously established in literature (Walker & Davis, 1997). Literature reviewed
above suggests that nicotine exposure can alter the density of midbrain nAChRs, which are themselves linked to anxiety (Abreu-Villaca et al., 2004). Findings from behavioral studies further suggest that adolescent nicotine can produce durable changes in anxiety behavior measured in paradigms such as the open field (Slawecki et al., 2003; Trauth et al., 2000; Smith et al., 2006). The core prediction of the present research is that adolescent nicotine exposure will produce changes in anxiety that persist into adulthood measured in the LES paradigm. Support for this prediction would imply that chronic adolescent nicotine exposure causes persistent developmental changes in the brain pathways that mediate anxiety.

Method

Subjects
Fifty-one Sprague-Dawley (25 male and 26 female) rats were obtained from the breeding colony of the Department of Psychology at The College of William & Mary. Animals were weaned on PD21 and housed individually in hanging wire-mesh cages. Rats were under a 14 hr/10 hr light-dark cycle and had access to food and water ad libitum. Animal care was carried out in accordance with approved IACUC protocols.

Apparatus
Light-enhanced startle testing occurred in three identical small startle cages. The startle cages served as functional restraint cages (Coulbourn Instruments, Model E05-20) which were themselves placed inside larger sound and light-attenuating startle chambers (Coulbourn Instruments, Model E10-24). The sides and bottom of each startle cage were constructed of flat black plastic, and the lid of each cage consisted of a rounded convex steel-bar grate that could be clasped to the frame of the cage. Startle cages measured 18.5 cm x 11 cm x 9.5 cm (height measured from base of plastic floor to top of convex lid). Each startle cage could be placed
inside its own larger startle chamber such that animals could be trained and tested individually. The startle chamber consisted of a wooden box lined with sound-attenuating acoustic foam padding and the interior of the chamber measured 52 cm X 52 cm X 30.5 cm (L x W x H). The center of each chamber lid housed a 7.5 cm high-frequency speaker that could deliver a 50-ms burst of white noise (rise time 0 ms) that served as the stimulus to elicit startle reactions. The amplitude of startle stimuli delivered by the speaker was controlled by software and varied between 100 dB, 105 dB and 115 dB (C scale). Each startle cage was placed upon a 5-lb maximum output transducer platform (Coulbourn Instruments, Model E45-15) located beneath the speaker of the chamber lid such that the distance between the speaker and lid of the startle cage was 15 cm. Startle reactions to the 50-ms noise bursts were measured by strain gage load cells which served as response sensors in the transducer platforms. The transducer recorded voltage displacement proportional to the force applied to it and peak voltage displacement occurring within the first 200 ms from startle stimulus onset transformed into grams of force served as the dependent measure.

A 26-W, General Electric compact fluorescent light bulb could be turned on to provide bright illumination of the chamber (1876 lux, measured from the center of the startle platform). The bulb was centered on the left interior wall of the startle chamber and was positioned 19 cm from the chamber floor. In this position the bulb was located 30 cm from the center of the startle cage which held the animal during sessions. All data recording and stimulus delivery was controlled by LabLinc V (Coulbourn Instruments) hardware and software. The light-enhanced startle chamber is shown in Figure 1.
**Procedure**

Rats were counterbalanced into 3 experimental groups, with respect to weight, litter, and sex. Each group consisted of approximately 18 subjects, with equivalent males and females, as possible. The three experimental groups consisted of: low dose of nicotine (0.15 mg/kg), high dose of nicotine (0.40 mg/kg) or vehicle control (saline). Nicotine was nicotine tartrate dissolved in saline and titrated to a pH of 7.4.

**Nicotine Exposure.** Beginning on PD28, and ending on PD42, rats were exposed twice daily to intraperitoneal (I.P.) nicotine or saline injections depending on group designation. Injections occurred once in the morning (approximately 0830) and once in the early afternoon (approximately 1430). Rats were weighed prior to each injection and received 1 ml/kg mixed nicotine solution based on body weight. Following the PD28-42 injection series, rats remained in home cages in the absence of nicotine creating an abstinence period of 38-39 days, which was followed by LES testing.

**LES Test Procedure.** Rats were tested for LES on PD66 or PD67. Each LES test session was comprised of two 20-min phases with each phase separated by a 5-minute rest period. During Phase 1 rats were placed in the startle chamber and after 600 s were exposed to 30, 50-ms startle stimuli, ten at each of three different dB amplitudes (100 dB, 105 dB, 115 dB). The interstimulus interval (ISI) between each startle stimulus was 30 s. The distribution of different dB startle stimuli was pseudo-randomly distributed such that a given dB startle stimulus could occur no more than two times in succession and that the different amplitude startle stimuli
occurred in blocks of three (i.e., [115→100→105], [105→115→100]). Phase 1 was conducted in the dark with no chamber illumination. Following the completion of Phase 1, rats were removed from the chambers and exposed to a 5-minute rest period in a separate transport cart. At the end of the 5-minute rest period rats were returned to startle chambers and Phase 2 was initiated. Phase 2 was an identical replication of Phase 1 except that Phase 2 was conducted in the presence of a bright (26-W compact fluorescent) light. During Phase 2, 30 startle stimuli at each of the three different dB amplitudes were presented during the 20-min session. Phase 1 and Phase 2 were discriminated only by the absence (Phase 1) or presence (Phase 2) of the bright light. For each animal, a mean startle score averaging across Phase 1 trials at each startle pulse amplitude and a corresponding mean startle score averaging across Phase 2 trials at each startle amplitude was computed. Comparison of difference scores (Phase 2 mean - Phase 1 mean) was used to evaluate differential effects of nicotine on the magnitude of LES.

Results

Raw peak startle data were subjected to preliminary analysis in order to assess the presence of the basic LES effect on the test day. An overall within-subject ANOVA collapsed across all over variables (dB amplitude, drug dose, sex) compared peak startle in Phase 1 versus Phase 2. The analysis revealed a significant main effect of Phase, F(1,50)=64.96, p < .001. As shown in Figure 2, peak startle during Phase 2 in the presence of the bright light was higher than peak startle during Phase 1 in the dark. This is the light-enhanced startle effect. Figure 2 also shows the computed difference score (Phase 2 mean – Phase 1 mean).

Insert Figure 2 about here
The main difference score data from the LES test were analyzed in a 3 (dB amplitude: 100, 105, 115) X 3 (Drug: saline, 0.15 mg/kg nicotine, 0.40 mg/kg nicotine) X 2 (Sex: male, female) ANCOVA with test box as the covariate. The analysis revealed a significant 3-way dB X Drug X Sex interaction, $F(4, 88)=2.82, p = .03$, and no other main effect or interaction. The source of the 3-way interaction appeared to be different patterns of responding across dB amplitude and drug doses in males and females (see Figure 3 and Figure 4). This appearance was confirmed by dB X Drug interaction contrasts conducted separately on test data from males and females. In males, there was a significant dB X Drug interaction, $F(4, 42)=3.30, p = .019$. As can be seen in Figure 3, adolescent males exposed to nicotine generally showed higher levels of light-enhanced startle relative to saline controls. In females, there was no dB X Drug interaction, $F(4, 44)<1$, and as suggested by findings illustrated in Figure 4, nicotine failed to have any effect on the magnitude of light-enhanced startle in females.

Fisher post-hoc tests (Keppel, 1982) were conducted to evaluate whether adolescent nicotine exposure altered the magnitude of LES in adult animals as suggested by data from Figure 3. In males: compared to saline controls, significantly higher LES was observed in the 0.15mg/kg condition for the 100dB startle probe; significantly higher LES was observed in both the 0.15 mg/kg and 0.40 mg/kg nicotine conditions relative to saline treated animals in the 105 dB startle probe condition, and significantly higher LES was observed in the 0.40 mg/kg nicotine condition relative to saline controls in the 115 dB startle condition. Because the dB X Drug
contrast conducted on data from females failed to reveal any main effect (or interaction as previously indicated) no further statistical tests were conducted on data from females.

**Discussion**

We predicted that adolescent nicotine exposure would produce changes in anxiety that persist into adulthood, measured in the LES paradigm. That prediction was supported but depended importantly on sex. Adolescent nicotine exposure enhanced anxiety measured in LES in males (Figure 3) but not in females (Figure 4) when compared to saline controls. The general increase in anxiety behavior following adolescent nicotine exposure is supported by results from other studies (Slawecki et al., 2003; Smith et al., 2006; Trauth et al., 2000). The BNST is known to play a role in anxiety (Davis et al., 2009). Furthermore, LES which measures anxiety modulation of reflexively elicited startle behavior is itself a test in which the BNST has been critically implicated (Davis and Shi, 1999). It is likely that alterations in this “reflexive anxiety” pathway containing the BNST is responsible for the observed effects of adolescent nicotine on LES.

Nicotine exposure is known to cause nAChR upregulation (Trauth et al., 1999; Nashmi et al., 2007), but can also cause down regulation of nAChRs (Changeux, 2010), depending on the nAChR subunit and location. Given the role of nAChRs in some forms of anxiety discussed earlier (see Roni & Rahman, 2011), alteration of nAChR density in the anxiety pathway may be involved in the pattern of outcomes observed in this experiment. As discussed earlier, adolescence is an important period of development for the pathways that mediate anxiety (Spear, 2000). As a result, chronic exposure to nicotine that occurs during adolescence might be expected to have different effects than chronic exposure in adulthood (Caldarone et al., 2008) or acute exposure in adolescence (Cheeta et al., 2001). These considerations imply adolescence
may be a uniquely vulnerable period for nicotine’s impact on nAChR density in brain systems that mediate anxiety.

A major finding in this experiment was that anxiety in females appeared to be unaffected by adolescent nicotine exposure, in contrast to more apparent effect of nicotine in males. This is In the elevated plus maze (EPM), Caldarone et al. (2008) revealed that adult female mice exposed to chronic nicotine showed increase in anxiety-like behavior but males did not, a pattern opposite to that observed here. Trauth et al. (2000) reported similar findings following chronic adolescent nicotine exposure. In the open field paradigm, females demonstrated increased anxiety behavior and males showed no change (Trauth et al., 2000). [It should be noted that Trauth et al. (2000) exposed animals to nicotine between PD30 and PD47.5, whereas the present study did so between PD28 and PD42.] There may be important developmental changes in the anxiety pathway in rats between PD28 and PD30 or between PD42 and PD47.5 that could potentially account for differences in outcome. Finally, Cheeta et al. (2001) found in the social interaction test, in which likelihood of interacting with a novel specific stranger is taken to index anxiety, that adolescent female rats were more susceptible to the anxiolytic effect of acute nicotine exposure. These studies are not identical in outcome and differ in pattern of nicotine dosing (chronic vs. acute) but they nonetheless suggest a strong correlation between effect of nicotine on anxiety and sex. Unlike the present findings, they suggest that females are more susceptible to the anxiety altering effects of nicotine (see Table 1 for comparison of select findings from the literature compared to outcomes of the present experiment).

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Insert Table 1 about here

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One source for such deviation may be found in comparison of the response systems that are required in different models of anxiety. The Elevated Plus Maze, Open Field Test, and Social Interaction tests discussed earlier may all be characterized as volitional tests that measure choice behavior in which the animal may choose to locomote into or out of different arms of a maze or choose an area of the field to enter. The LES paradigm uniquely relies on an involuntary reflex (the startle reflex) that does not rely on volition or choice. Considered this way, findings of the present experiment might imply that nicotine’s effect on anxiety modulation is different in reflexive versus volitional control systems.

Moreover, brain regions mediating “reflexive anxiety” and “volitional anxiety” may develop differently in males versus females. The encapsulated region of the BNST is 97% larger in adult males when compared to females (Hines et al., 1992). As stated earlier, the BNST is crucial in the expression of anxiety measured by LES (Davis et al., 2009). Interestingly, inactivation of the BNST does not cause a change in performance, in rats, in the open field paradigm (Crestani et al., 2010) but does affect the magnitude of LES (Davis & Shi, 1999). This indicates that the BNST may not play a role in anxiety expressed in the open field paradigm. Thus, when nicotine alters a pathway that contains the BNST, the effects may be expressed in changes in LES, but not the open field. Because the BNST is physiologically different in males and females, nicotine’s effects would be expected to depend on the sex, as was observed in the present study. One speculation is that observed sex differences reported here may be due to differential receptor density between males and females in the BNST. If this is correct, then chronic nicotine exposure might have different effects on upregulation (or downregulation) of nAChRs in the BNST in males versus females.
Trauth et al. (1999) suggest that nicotine exposure causes an upregulation of nAChRs in the cerebral cortex. There are synaptic connections between the cerebral cortex and lateral amygdala that are strengthened by nicotine exposure (Huang et al., 2008). This could lead to increased activity of the amygdala. Several regions within the amygdala are implicated in the anxiety pathway (Davis and Walker, 2009). Therefore, increased activity in the amygdala might be expected to increase anxiety levels. Importantly, Trauth et al. (1999) demonstrated that adolescent nicotine exposure causes greater upregulation of nAChRs in males compared to females. To the extent this occurred as a result of adolescent nicotine exposure in the present research, this might be associated with differential enhancement of amygdala activity males. Greater enhancement of anxiety pathway activity in males compared to females might lead to the expression of enhanced anxiety behavior in males relative to females, as was observed in the present experiment.

**Future Directions**

One future direction would be to explore more directly the specific neural alterations that mediated behavior effects of adolescent nicotine exposure seen in this research. One direction would be to examine to what extent alteration in cortical nAChRs played a role in our findings. Site-specific administration of antagonists, that are specific to different nAChR subtypes, and/or molecular knockout techniques may provide approaches to better address this issue. By administering nAChR antagonists to the regions of the cortex that connect to the lateral amygdala, we could effectively suppress any effects of nicotine in that region. If antagonist administration prior before every nicotine injection in adolescence eliminates the effect of nicotine on anxiety we observed, this would imply that the cortex-lateral amygdala pathway plays a critical role in nicotine’s effect on the anxiety pathway expressed as changes in LES.
Clinical Implications

The present findings also have important clinical implications. Taken together with other available research on long-term effects of nicotine, a general consensus emerges. Adolescent nicotine exposure is associated with long-term changes in the anxiety pathway and an increase in overall anxiety behavior, as well as increased risk of nicotine dependence (Slawecki et al., 2003; Smith et al., 2006; Trauth et al., 2000). In humans, McKenzie et al. (2010) found that adolescent “occasional smokers” who scored high on anxiety and depression scales were more likely to become addicted to nicotine in early adulthood. They further suggested that these adolescents and young adults use cigarettes to help alleviate depression and anxiety symptoms. There is also evidence that adolescents are more vulnerable to the effects of stress. In animal studies, adolescent rats are more likely to display anxiety-like behavior when exposed to stressors (Slawecki et al. 2005) and the adolescent period itself is recognized as a unique period of psychosocial stress in humans (Spear, 2000). Given the “self-medication” hypothesis suggested by McKenzie et al. (2010) adolescents may be more apt to turn to nicotine to relieve their stress. Individuals who begin smoking in adolescence may thus be particularly vulnerable to nicotine in adulthood, as (and perhaps particularly when) they are exposed to novel stressors. In sum, the suggestion here is that adolescent nicotine may increase adult anxiety. As a result, adolescents exposed to nicotine may be especially vulnerable to perceived stress-reducing effects of nicotine which then perpetuates continued drug use progressing to addiction (as illustrated in Figure 5).
Continued research that clarifies the effects of nicotine on the anxiety pathway may be an essential step toward breaking escalating patterns of drug use in vulnerable populations.
References


Existing literature concerning effects of nicotine exposure on anxiety in males and females.

### Summary of Effects of Nicotine on Anxiety

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Figure Captions

Figure 1. Light-enhanced startle chamber.

Figure 2. Mean raw peak startle during Phase 1 and Phase 2 during the light-enhanced startle test. Phase 1 and Phase 2 means are shown averaged across all other variables (dB amplitude, drug dose, sex). The overall difference score (Phase 2 mean – Phase 1 mean) is also shown. Brackets represent standard errors.

Figure 3. Mean difference score (Phase 2 mean – Phase 1 mean) for males during the light-enhanced startle test as a function of dB amplitude and adolescent nicotine exposure condition. Brackets represent standard errors.

Figure 4. Mean difference score (Phase 2 mean – Phase 1 mean) for males during the light-enhanced startle test as a function of dB amplitude and adolescent nicotine exposure condition. Brackets represent standard errors.

Figure 5. Conceptual Model Illustrating How Adolescence, Nicotine and Anxiety Contribute to Addiction. Anxiety problems in adolescents can lead to nicotine self-medication, which may in turn lead to increased anxiety, as evidenced by the current findings.
FIGURE 1. Light-enhanced startle chamber.
**FIGURE 2.** Raw Peak startle illustrating the basic light-enhanced startle effect on the test day. The overall difference score (Phase 3 mean – Phase 1 mean) is also shown.

[Bar chart showing Raw Peak Startle (LES effect) for Phase 1 (dark), Phase 2 (light), and Diff (Phase 3 mean – Phase 1 mean).]
FIGURE 3. Light-enhanced startle in adult males on the test day following adolescent nicotine exposure.
FIGURE 4. Light-enhanced startle in adult females on the test day following adolescent nicotine exposure.
**FIGURE 5.** Anxiety symptoms in adolescents can cause nicotine self-medication and escalating nicotine use.