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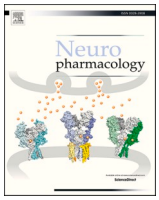

Invited review

Molecular and neuronal mechanisms underlying the effects of adolescent nicotine exposure on anxiety and mood disorders

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A R T I C L E I N F O

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A B S T R A C T

Tobacco addiction is highly co-morbid with a variety of mental health conditions, including schizophrenia, mood and anxiety disorders. Nicotine, the primary psychoactive compound in tobacco-related products is known to functionally modulate brain circuits that are disturbed in these disorders. Nicotine can potently regulate the transmission of various neurochemicals, including dopamine (DA), γ-amino-butyric acid (GABA) and glutamate, within various mesocorticolimbic structures, such as the ventral tegmental area (VTA), nucleus accumbens (NAc) and prefrontal cortex (PFC), all of which show pathologies in these disorders. Many neuropsychiatric diseases have etiological origins during neurodevelopment, typically occurring during vulnerable periods of adolescent or pre-natal brain development. During these neurodevelopmental periods, exposure to extrinsic drug insults can induce enduring and long-term pathophysiological sequelae that ultimately increase the risk of developing chronic mental health disorders in later life. These vulnerability factors are of growing concern given rising rates of adolescent nicotine exposure via traditional tobacco use and the increasing use of alternative nicotine delivery formats such as vaping and e-cigarettes. A large body of clinical and pre-clinical evidence points to an important role for adolescent exposure to nicotine and increased vulnerability to developing mood and anxiety disorders in later life. This review will examine current clinical and pre-clinical evidence that pinpoints specific mechanisms within the mesocorticolimbic circuitry and molecular biomarkers linked to the association between adolescent nicotine exposure and increased risk of developing mood and anxiety-related disorders.

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1. Introduction

The nature of tobacco dependence has changed significantly over the decades, both in terms of delivery formats and relative content of nicotine, the primary psychoactive compound believed to underlie its addictive liability. Beyond its strong addiction potential, nicotine dependence shows exceptionally high co-morbidity with a variety of neuropsychiatric disorders, including schizophrenia, mood and anxiety disorders and co-dependence with other drugs, such as alcohol and cannabis. Decades of pre-clinical neuroscience research has clarified many of the acute and long-term effects of nicotine on the mammalian brain. In addition, it is well established that nicotine can modulate multiple neurotransmitter systems involved in the regulation of mood and anxiety, including dopamine (DA), GABA, glutamate, serotonin (5-HT) and acetylcholine. These neurotransmitter systems require functional regulation by precise neurodevelopmental mechanisms for proper, long-term function. In addition, alterations in these neuropharmacological substrates and their underlying molecular signaling cascades, may serve as critical biomarkers for multiple neuropsychiatric conditions, including mood and anxiety disorders.

The onset of nicotine dependence occurs most often with adolescent neurodevelopmental periods. Nevertheless, despite being a readily available drug that is consumed by millions of adolescents worldwide, there remains a paucity in understanding the precise neuropathological effects caused by exposure to nicotine during vulnerable periods of brain development. Despite the general decrease in overall tobacco use over the past several decades, this knowledge gap is a growing public health concern given the current rise in adolescent nicotine use and the advent of novel nicotine delivery tools such as e-cigarettes, which were initially marketed as tools to assist in the reduction of nicotine dependence (National Center for Chronic Disease Prevention, 2016). This relative rise in teen vaping trends, despite the overall drop in use of traditional smoking formats, has been termed a new smoking epidemic, (Jones and Salzman, 2020), comprising a 10% increase in adolescents using

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e-cigarettes between 2017 and 2018 and representing ~ 1.3 million teenagers in the United States alone (Jones and Salzman, 2020; Farzel et al. 2019).

Adolescence represents a critical period of brain development during which enormous changes are taking place at the synaptic, molecular and anatomical levels of brain structure and function. These developmental sequelae are equally important in the developing male and female brain, although rates of nicotine exposure and addiction have been shown to differ across the sexes (Pampel, 2006). Growing clinical and pre-clinical evidence is expanding our understanding of the specific neurobiological mechanisms that may underlie the pathophysiological sequelae linked to adolescent nicotine exposure and increased risk of developing mood and anxiety-related disorders. These effects also extend to long-term cognitive deficits which may be secondary to the increased risk of affective mental health disorders. In this review, we will critically evaluate current clinical and pre-clinical evidence that is elucidating specific neural biomarkers that may render individuals at specific risk for the development of mood and anxiety disorders following chronic adolescent nicotine use.

1.1. Nicotine exposure during adolescence: A growing public health crisis

Although global rates of tobacco addiction have been steadily decreasing over the past several decades, tobacco-related diseases remain the number one global cause of preventable mortality (U.S. Department of Health and Human Services, 2014). Numerous trends in nicotine consumption, particularly among adolescents, continue to raise alarm. Historically, given the widespread legal availability of nicotine-containing products and despite widespread imposition of age-restrictions on purchasing tobacco, the vast majority (~95%) of lifelong smokers begin their habits during adolescence (Edvardsson et al., 2009; Taioli and Wynder, 1991; Stanton et al., 1991). In addition, considerable evidence has demonstrated that the adolescent brain is more susceptible to the dependence producing effects of tobacco, given that adolescents may develop tobacco dependence at substantially lower concentrations of nicotine and over shorter periods of time (Kandel and Chen, 2000; O'Loughlin et al., 2003).

Electronic cigarettes (E-cigarettes) were initially marketed as a method for gradually quitting traditional cigarettes via their purported ability to replicate many of the sensory cues associated with cigarettes and the ability of the user to titrate nicotine exposure levels over time (Siu, 2015). In contrast to traditional cigarettes, nicotine concentrations can be regulated in e-cigarettes and some of the carcinogens associated with traditional tobacco smoking were claimed to be mitigated (Fernández et al., 2015). However, e-cigarette vaping has become a highly popular smoking and nicotine delivery system for both adult and adolescent populations (Schneider and Diehl, 2016; Yoong et al., 2018). Furthermore, in addition to the established addictive potential of nicotine found in vaping products, the wide variety of flavoured nicotine products is considered a major driver of adolescent use of e-cigarettes as these products offer the user a far greater range of appetitive cues and sensory experiences combined with nicotine consumption, relative to traditional cigarette formats (Hefner et al., 2017).

1.2. Vulnerability of the adolescent brain

Adolescence represents a unique period of neurodevelopment and generally spans the ages of 10–24 years in the human brain (Gavin et al., 2009; Sylwester, 2007). During this developmental window, multiple, complex changes are occurring at the synaptic, molecular and network levels of brain organization. First, the onset of hormonal maturational processes and exposure to sex steroids can strongly influence synaptic and network structural changes and pruning events in the male and female brains (Arain et al., 2013; Spear, 2000). During adolescence, critical changes in network connectivity are simultaneously occurring, for example, connections between higher order executive control regions in the frontal cortex are establishing regulatory control over sub-cortical emotional processing regions including the mesolimbic and amygdala circuitry (Benes, 2001; Giedd et al., 1999). Indeed, the lack of strong functional connectivity between these neural regions is believed to underlie the corresponding lack of impulse control and increased vulnerability to peer-related negative influences on risky behaviours commonly reported during adolescence (Arain et al., 2013; Blakemore, 2012; Gardner and Steinberg, 2005), underscoring the increased risk that adolescents will begin experimenting with tobacco and will be more likely to develop tobacco dependence during this epoch. In addition to these important connectivity events, major developmental changes are occurring in neurotransmitter systems critical for regulating modulatory influences within these circuits, including dopamine (DA), GABA and glutamate (Arain et al., 2013; Andersen et al., 1997; Li and Xu, 2008; Spear, 2000; Wahlstrom et al., 2010), all of which are strongly influenced by nicotine exposure (Goriounova and Mansvelder, 2012; Laviolette and van der Kooy, 2004; Laviolette and van der Kooy, 2003; Hudson et al., 2020; Picciotto and Corrigall 2002; Grieder et al., 2012; Tan et al., 2009).

Importantly, while there are profound and obvious differences between rodent and human brain complexity, human adolescent brain development can be experimentally modelled in rodents, given the many similarities in anatomical, neurochemical, molecular signaling, hormonal and synaptogenesis events common in both human and rodent adolescent brain maturation (Agoglia et al., 2017; Semple et al., 2013). Depending on sex and species, rodent adolescent brain development is generally considered to occur sometime between post-natal days 30–49 (McCutcheon and Marinelli, 2009). Despite this variation, rodent modelling of adolescent brain development offers the experimental advantage of precision control over drug exposure, both temporally and concentration-wise, as well as controlling environmental differences, none of which can be completely controlled for in clinical epidemiological approaches in human populations. Thus, to gain a complete picture of the causal mechanisms underlying the effects of neurodevelopmental nicotine exposure to increased risks for neuropsychiatric symptoms, it is essential to vertically integrate the findings from both clinical and pre-clinical studies when drawing mechanistic inferences about these correlations.

The confluence of intricate neural developmental processes, increased risk-taking behaviours and lack of impulse control, represents a profound vulnerability to the potential toxic effects of nicotine exposure on adolescent brain development. Given the strong epidemiological evidence demonstrating that a majority of life-time smokers initiate their tobacco habits during adolescence (Edvardsson et al., 2009; Taioli and Wynder, 1991), there is an urgent need to more clearly understand the precise neurobiological effects of nicotine exposure during these critical neurodevelopmental windows. More importantly, it is necessary to further clarify which specific neuropsychiatric vulnerabilities may be increased following adolescent nicotine exposure and understand the underlying neural biomarkers that may place specific individuals and populations at risk.

Nicotine's association with anxiety, mood disorders and associated symptoms.

Nicotine dependence is co-morbid with a wide variety of neuropsychiatric conditions, including schizophrenia and mood and anxiety disorders (Breslau et al., 1993; Hartz et al., 2018; Martínez-Ortegaa et al., 2017; Moran et al., 2013; Sagud et al., 2019). However, the extent to which nicotine-related toxic insults during adolescent brain development may serve to increase the risk for developing mental health symptoms in later life is poorly understood. Many pre-clinical and clinical studies have demonstrated a strong association between tobacco dependence and increased anxiety symptoms, an effect that is moderated by early life exposure to nicotine (Moylan et al., 2013). However, since human clinical studies are typically reliant on self-reported records of tobacco use and recall of early exposure timelines from participants, causal interpretations are difficult to apply to retrospective studies. In

terms of the potential relations between smoking and mood and anxiety disorders, causality may run in multiple directions. For example, individuals with higher trait anxiety levels are more likely to report smoking behaviours (Sonntag et al., 2000; Swendsen et al., 2010), suggesting that nicotine dependence may serve as a self-medication strategy to mitigate pre-existing anxiety symptoms, rather than causing these symptoms *per se*. Alternatively, anxiety-related symptoms may develop due to underlying genetic factors that simply render the individual more susceptible to the addictive properties of nicotine and/or other co-morbid substance dependencies, independently of the effects of nicotine itself on the developing brain. The critical question is thus, does exposure to nicotine during critical periods of adolescent brain development, trigger a pathophysiological process towards the development of mood and anxiety disorders?

A plethora of clinical studies have demonstrated strong associations with tobacco use and the presence of mood and anxiety-related disorders. Among adolescents, smoking behaviours are strongly associated with increased anxiety and mood disorder symptoms, even when controlling for socioeconomic status and other confounding variables (Brown et al., 1996; Cuijpers et al., 2007; Sonntag et al., 2000). In addition, smoking incidence has been shown to increase the likelihood of panic disorder and panic attack onset (Isensee et al., 2003; Moylan et al., 2013). Furthermore, tobacco dependence is associated with increased odds of anxiety disorders in both males and females, with odds ratios of 2.2 and 2.6, respectively (Breslau et al., 1991). Beyond this strong associational evidence, causal relationships between smoking and depressive disorders have also been reported. For example, Boden et al., using a fixed-effects regression and structural equation modelling procedure, examined depression symptoms at ages 18, 21 and 25 in male and female subjects. These analyses found evidence of significant co-morbidity between tobacco dependence and the presence of depressive symptoms at each age point, with no reported sex differences. Using statistical techniques of structural equation modelling to fit a reciprocal causation model revealed that the best-fitting model was indicative of a *unidirectional* association between tobacco dependence and symptoms of depression, but interestingly, no evidence for a reverse causality effect (i.e. depression being a cause for smoking behaviours). Similarly, Mojtabai and Crum (2013) examined the association between smoking and the subsequent new onset prevalence of mood or anxiety disorders, using data from the longitudinal National Epidemiologic Survey on Alcohol and Related Conditions (NESARC; Grant et al., 2009). This comprehensive analysis included potential associations between regular smoking behaviours *preceding* the onset of major depression, dysthymia, manic episodes, generalized anxiety disorder, panic disorder, social phobia, specific phobias, and post-traumatic stress disorder (PTSD). Regular smokers displayed significantly higher diagnoses of new onset mood and anxiety disorders; however, this effect was significantly more pronounced in the younger aged cohorts (18–49 years) relative to older smokers, again suggestive of an effect of age of smoking onset on the association between tobacco dependence and these disorders. Beyond this epidemiological evidence, there is an urgent need to understand the precise neuroanatomical and neurophysiological underpinnings related to these risk factors. Both clinical and pre-clinical evidence is increasingly pointing to the pathophysiological effects of neurodevelopmental nicotine exposure on the mesocorticolimbic circuitry as causal factors in these co-morbidities.

Neurobiological mechanisms associated with adolescent nicotine exposure and mental health vulnerability.

Nicotine derived from smoking products rapidly hits the brain's ubiquitous nicotinic receptor (nAChR) populations within 20 s after inhalation (Le Houezec 2003). Due to the remarkable heterogeneity of specific nAChR subtypes within the mammalian brain, combined with high regional variations in the relative concentrations of specific sub-units in discrete brain regions, we are only now beginning to understand which specific receptor subtypes may underlie select psychoactive properties of nicotine, including its addictive properties. Like many drugs with addictive potential, nicotine has been shown to produce both rewarding and aversive effects in humans and other animals. **Acutely and chronically, clinical and pre-clinical evidence has implicated a critical role for the mesocorticolimbic circuitry, including the VTA, Nac and PFC, in the psychotropic effects of nicotine** (Goriounova and Mansvelder, 2012; Grieder et al., 2012; Laviolette and van der Kooy, 2004; 2003; Laviolette et al., 2008; Picciotto and Corrigall, 2002; Rose and Corrigall, 1997; Tan et al., 2009; Volkow et al., 2007; Wall et al., 2017). The acute rewarding and aversive stimulus properties of nicotine are largely mediated through its actions in the VTA (David et al., 2005; Laviolette and van der Kooy, 2003a,b). Thus, while the initial rewarding effects of nicotine are mediated through non-DAergic VTA substrates, following chronic exposure to nicotine, the rewarding properties of nicotine along with its aversive withdrawal effects switch to a DA-dependent pathway, dependent upon intra-NAc DA receptor transmission (Laviolette and van der Kooy, 2003; Laviolette et al., 2008; Tan et al., 2009). In addition, pharmacologically modulating DAergic receptor transmission can profoundly alter both the behavioural processing of nicotine's rewarding vs. aversive conditioning effects and concomitantly alters the neuronal signatures associated with these motivational properties of nicotine, directly in the NAc medium spiny and interneuron populations (Sun and Laviolette, 2014).

Within the VTA itself, the acute rewarding properties of nicotine depend upon β2 nAChR signaling associated with GABAergic neuronal populations whereas β2 signaling associated with the aversive motivational effects of nicotine depend upon DAergic neuronal transmission (Grieder et al., 2012, 2019). In terms of neurodevelopmental implications, this issue is further complicated by changes in nAChR distributions within specific neural circuits as a function of age and the hormonal impacts of normal brain development (Melroy-Greif et al., 2016), by which nicotine produces heterogeneous effects on nAChR expression patterns following adolescent exposure. For example, increased α4β2 and α7 subunit expression was reported in rats exposed to 2–6 mg/kg/day nicotine during periadolescent and adolescent periods, which were most pronounced in the midbrain, hippocampus and cortex (Abreu-Villaca et al., 2003; Doura et al., 2008). In addition, increased subunit expression patterns are more pronounced following adolescent vs. adult nicotine exposure at lower relative doses and persists for a longer period of time (Abreu-Villaca et al., 2003). These effects are also more pronounced in the mesolimbic circuitry (VTA and NAc) in adolescents vs. adults, further demonstrating the importance of DAergic transmission events as a potential pathological biomarker for the effects of adolescent nicotine exposure.

In terms of the effects of adolescent smoking behaviours on mesolimbic function, human imaging studies have found strong effects of adolescent nicotine exposure on activation dynamics within the striatum. For example, Garrison et al. (2017) reported that adolescent smokers displayed abnormally elevated pre-vs. post-treatment potentiation in reward anticipation-related activity states associated with monetary reward value, in the NAc, insula, and PFC regions, suggesting a dysregulation in motivational processing mechanisms in nicotine-dependent adolescents. Similarly, David et al. (2005) reported abnormally potentiated activation patterns in several brain regions, including the ventral striatum, in response to smoking-related associative cues in smokers vs. non-smoking adults. Finally, Flannery et al. (2019) reported an aberrant functional relationship in response to positive feedback cues in human smokers, between the habenula and striatum. During the performance of this motion prediction task (which provided subjects with both positive negative feedback input), chronic smokers showed less positive feedback responsivity in the bilateral NAc, but increased sensitivity to negative feedback responsivity in the left insula, suggesting a functional imbalance in the processing of affectively relevant information within this circuit. Thus, several imaging reports would suggest abnormal affective neural processing states, particularly in adolescent smokers. However, beyond these observational human imaging studies, numerous pre-clinical studies have reported a variety of

molecular and pharmacological alterations following adolescent or adult nicotine exposure, directly within the mesocorticolimbic circuitry.

Mesolimbic mechanisms underlying the effects of adolescent nicotine exposure on mood and anxiety phenotypes.

As discussed previously, mesolimbic signaling through VTA DA neurons and their output D1 and D2 receptor substrates in the NAc, are critical for both the acute and chronic behavioural effects of nicotine (Laviolette and van der Kooy, 2003; Laviolette et al., 2008). However, the effects of adolescent nicotine exposure on mesolimbic DA signaling and how this may differ from nicotine exposure in the mature, adult brain, is less understood. Using a rodent model of adolescent nicotine exposure, Hudson et al. (2020) combined neuronal electrophysiology, molecular protein analyses and behavioural pharmacology to examine the potential effects of adolescent nicotine on mood and anxiety-like symptoms and associated neural biomarkers directly in the shell region of the NAc. Separate experimental cohorts received their first nicotine exposures during either adolescence or adulthood, providing the opportunity to directly assay the effects of nicotine exposure during adolescence vs. the mature, adult brain. Follow up behavioural, molecular and electrophysiological assays then took place in early adulthood for adolescent treated cohorts, or mid-adulthood for the cohorts treated in early adulthood. In Fig. 1, a simplified schematic summarizes the major neuronal and molecular phenotypes observed in the NAc, associated with adolescent nicotine exposure.

Behaviourally, rats treated with chronic nicotine during adolescence displayed a variety of depressive and anxiety-like states when tested in early adulthood, including decreased times in bright environments measured in a light-dark box test, decreased centre-zone time in the open field test, deficits in social cognition/memory, increased immobility in the forced swim test and decreased sucrose preference. In terms of molecular biomarker analyses, this behavioural phenotype was accompanied with a profound upregulation of the extracellular-signal-related kinase 1–2 (ERK 1–2) and the protein-kinase B (Akt) and glycogen-synthase-kinase-3 (GSK-3) signaling pathways directly in the NASh. In contrast, the study reported a large decrease in the expression of the DA D1R with no significant changes in D2R levels. Interestingly, these molecular adaptations were completely absent following adulthood exposure, demonstrating the temporal specificity of nicotine exposure on the immature, adolescent brain. Furthermore, following adolescent nicotine exposure, these accumbal molecular adaptations persisted into young adulthood.

Importantly, all of these molecular biomarkers have been associated with mood and anxiety disorders in clinical populations. For example, Cannon et al. (2009), using PET imaging, reported significant reductions in D1R expression levels in the striatal regions of patients diagnosed with major depressive disorder. Similar findings were reported by Dougherty et al. (2006), who found significantly reduced D1R expression in striatal regions of patients diagnosed with MDD combined with co-occurring anger attacks. The functional roles of ERK 1–2 signaling in human mood and anxiety disorders are not well understood. **However, significantly reduced levels of ERK 1–2 expression have been reported in post-mortem hippocampal and frontal cortical tissue samples from suicide cases** (Dwivedi et al., 2001; Yuan et al., 2010). In addition, pre-clinical studies have reported various functional mechanisms by which ERK 1–2 signaling may by disturbed in mood and anxiety disorders. For example, MAP-kinase/ERK inhibitors can induce depressive-like behavioural symptoms in mice (Duman et al., 2007) and acute stress induced by forced swimming can strongly activate ERK 1–2 signaling in various mesocorticolimbic structures including the PFC and NAc (Morello et al., 2017).

As noted previously, neuronal activity patterns in the NAc are strongly correlated with the rewarding and aversive stimulus properties of acute nicotine and chronic nicotine exposure induces strong sensitization of the mesolimbic DA system and increased sensitivity of VTA DA neurons to nicotine exposure (Sun and Laviolette, 2014; Tan et al., 2009). A critical question is how exposure to chronic nicotine during a neurodevelopmentally sensitive period like adolescence might modulate these neuronal signatures. Interestingly, analyses of neural oscillatory patterns directly in the NAc shell following adolescent nicotine exposure (Hudson et al., 2020) revealed profound decreases in the spontaneous

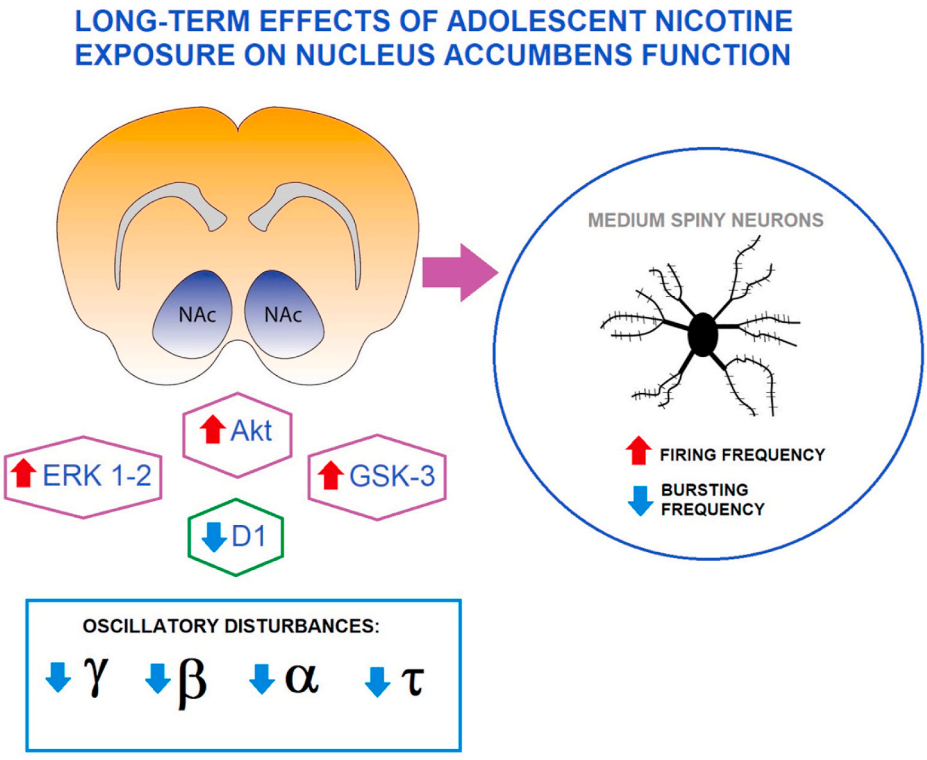

Fig. 1. Schematic summary showing the major long-term neuronal and molecular phenotypes associated with adolescent nicotine exposure in the nucleus accumbens (summarized from Hudson et al., 2020). Adolescent (but not adult) exposure to nicotine induces strong upregulation of several anxiety/mood related molecular biomarkers including ERK 1–2, Akt and GSK-3. In contrast, there is a selective downregulation of the DA D1R. In vivo neuronal electrophysiology revealed strongly increased firing frequency and bursting levels in medium spiny neurons and associated local field potential recordings revealed profound decreases in α, β, τ and γ band oscillation states. These molecular and neuronal phenotypes were associated with depressive and anxiety-like behavioural abnormalities in early adulthood.

levels τ, α, β and γ−band oscillatory states, which were accompanied by hyperactive medium spiny neuron (MSN) spontaneous activity and depressed bursting rates in nicotine vs. vehicle treated experimental cohorts. Several of these oscillatory signatures have been reported in mood and anxiety disorder populations. For example, Oathes et al. (2008) reported that patients with generalized anxiety disorder (GAD) displayed higher global levels of γ band oscillation states measured in EEG and that the EEG γ band was a reliable monitor for changes in pathological states of worrying among patients. Park et al. (2007) used spontaneous EEG recordings to examine if MDD patients might display disturbances in information processing transmission among different cortical regions while at rest. They estimated EEG synchronization while recording in a resting condition as a proxy for functional connectivity between multiple recording sites and compared α, β, δ, τ and γ oscillation patterns. They reported that MDD patients (relative to healthy controls) displayed significant decreases in the δ and α bandwidths, suggesting that MDD patients had significant abnormalities in information processing across multiple cortical regions. Furthermore, these aberrations were estimable by the likelihood of band synchronization recorded from cortical EEG recordings (Park et al., 2007). While these clinical studies were limited to correlational analyses, they provide interesting corollaries to oscillatory phenotypes observed in pre-clinical rodent studies, particularly following adolescent nicotine exposure (Hudson et al., 2020, Fig. 1) and provide potential biomarker targets for future translational studies aimed at elucidating their functional role in increasing the risk for mood or anxiety disorders following adolescent nicotine exposure.

In addition to D1R and ERK 1–2 signaling, a large body of clinical and pre-clinical evidence points to the importance of the Akt-GSK-3 signaling pathway as a critical pathological marker for mood and anxiety-related disorders. Indeed, lithium, one of the earliest identified pharmacotherapeutics for the treatment of depression and mania-related symptoms, was demonstrated to act as a potent GSK-3 inhibitor (Freland and Beaulieu, 2012; Shorter, 2009; Sutton and Rushlow, 2011), an effect which is believed to underlie its diverse therapeutic properties. Not surprisingly, disturbances in the Akt-GSK-3 signaling pathway are an established phenotype in anxiety and mood disorders (Matsuda et al., 2019). For example, Engali et al. (2014) reported a correlation between different Akt2 gene variants and personality traits related to anxiety and depression disorders. Inkster et al. (2009) reported correlations between GSK3β gene variants and grey matter volume differences in the hippocampus and bilateral superior temporal gyri in MDD patients. Given the known role of GSK-3 in regulating cellular processes and homeostasis, the authors speculated that this association may relate to GSK-3 dependent aberrations in neocortical, glial, or neuronal growth or survival factors. The functional relationships between GSK-3 and DA D1R transmission are not well understood. However, Wang et al. (2017) reported that, in cell culture assays and *in vivo* analyses, the D1R and GSK-3β physically interacted in cell culture cells and brain tissue samples. This functional interaction was found to occur at the S(417)PALS(421) motif in the C-terminus of D1R and experimental inhibition of the GSK-3β isoform was shown to impair D1R activation along with a decrease in D1R-GSK-3β interactions. In addition, inhibiting GSK-3β in rat PFC samples caused disruptions in D1R activation. Interestingly, using an NMDA antagonist rodent model of schizophrenia, these authors reported decreased levels of GSK-3β activity concomitant with impaired D1R activation in the PFC. Such a mechanism may be similar to intra-NAc effects reported following adolescent nicotine exposure, as high levels of GSK-3 phosphorylation would be indicative of less constitutively active GSK-3β, which may have caused corresponding disruption in the expression levels of the D1R. Future studies are required to more fully investigate this important functional question.

Although the aforementioned clinical studies were limited to correlational analyses, Hudson et al. (2020) reported for the first time that pharmacologically reversing nicotine-induced dysregulation of GSK-3 signaling directly in the NAc, was sufficient to reverse many of the anxiety and depressive-like behavioural phenotypes observed in later adulthood. In addition, reversal of overactive GSK-3 signaling directly in the NAc was able to reverse neuronal hyperactivity in NAc MSN neuronal populations and selectively reverse high-γ band aberrations, demonstrating a functional role for nicotine-induced GSK-3 abnormalities in anxiety and depressive-like phenotypes. More importantly, these pre-clinical findings suggest that there may be considerable plasticity in the long-term effects of adolescent nicotine exposure which might be reversible with the appropriate, targeted pharmacological interventions.

The effects of adolescent nicotine exposure on prefrontal cortical function: Implications for increased mood and anxiety disorder vulnerability.

The development of the frontal cortex, particularly during adolescence, is of critical importance for the maturation of adaptive executive control, emotion regulation, cognitive flexibility and regulation of sub-cortical affective processing centres. The concomitant anatomical and neurochemical maturation processes that take place during mammalian adolescence correspond to the strengthening of functional connections between cortical and sub-cortical neural circuits and hence, increased cognitive control over many higher-order functions (Luna et al., 2010; Yuan et al., 2015). In mammalian adolescent cortical development, there is a temporally dependent decline in the density of cortical grey matter, beginning in the later childhood years or early adolescence (Agoglia et al., 2017; Tau and Peterson, 2010), which corresponds to increased synaptic pruning events and increasing myelination of PFC-related pathways (Paus et al., 2008). This synaptic fine-tuning occurs in tandem with the maturation of inhibitory control mechanisms, such as GABAergic neuron populations, providing inhibitory inputs and tight regulation of excitatory outputs/inputs in the PFC region and associated sub-cortical, emotional regulation centres. These adaptive changes in the PFC help contribute to the appropriate development of cognitive and affective regulation, which involves regulation of sub-cortical DA neuron states in the VTA. Not surprisingly, early life stressors that lead to longer-term anxiety phenotypes have been shown to be related to aberrant sensitization of the mesolimbic DA system. For example, Yorgason et al. (2013), used a social isolation stressor model in rats to examine how the appearance of anxiety-related symptoms may be associated with hyperactive DAergic activity states. They reported that social isolation rearing caused long-term increases in anxiety-like behavioural phenotypes, which were accompanied by hyperactive levels of DA release, DA transporter activity, but no changes in D2 receptor states. Similarly, other psychotropic drugs may induce DAergic hyperdrive that ultimately leads to anxiety/affective dysregulation in early adulthood. Renard et al. (2017a,b) used an adolescent model of delta-9-tetrahydrocannabinol (THC; the primary psychoactive compound in cannabis) exposure in rats and reported that chronic THC exposure led to significant dysregulation of PFC neuronal activity states (characterized by hyperactive firing rates in pyramidal neurons and a loss in GABAergic inhibitory substrates). This cortical phenotype corresponded to hyperactive sub-cortical DAergic VTA activity that was reversible by restoration of GABAergic inhibition in the PFC. Similarly, this same protocol was reported to induce hyperactive DAergic states in the VTA that persisted into adulthood and were associated with long-term disturbances in affective behaviours, increased anxiety, social cognition deficits and learning and memory impairments (Renard et al., 2017a,b). Thus, considerable evidence has underscored the vulnerability of the DAergic system during adolescent neurodevelopment and how extrinsic drug insults (including cannabis and nicotine) during these vulnerable periods may pre-dispose individuals to long-term neuropsychiatric symptoms.

Beyond the role of DA, clinical and pre-clinical evidence demonstrates that both acute and chronic nicotine exposure can potently regulate neurotransmitter release and activity dynamics in frontal cortical regions (Couey et al., 2007; Goriounova and Mansvelder, 2012; Jobson et al., 2019) including glutamate and acetylcholine release

dynamics (Counotte et al., 2011; Verhoog et al., 2016). For example, Rubinstein et al. (2011) reported that even in adolescent 'light' smokers, smoking cues versus neutral cues induced stronger activation in medial orbital cortex relative to non-smoking subjects. Galván et al. (2011), using fMRI combined with a stop-signal procedure, reported that in the late adolescent period, smokers did not differ from non-smokers on task-related PFC activity during a response inhibition task. However, the degree of tobacco dependence was negatively associated with PFC activation patterns during inhibition behaviours, suggesting that chronic smoking either directly impacts normal PFC function, or that low inhibition-related cortical phenotypes may pre-dispose individuals to heavy smoking behaviours. These results are particularly interesting in terms of anxiety-related disorders as clinical anxiety symptoms have been associated with abnormal response inhibition behaviours (Grillon et al., 2017). In addition, heightened anxiety levels are strongly associated with attenuated inhibitory response control when measured in stop-signal tasks (Roxburgh et al., 2019), further suggesting that adolescent nicotine exposure may lead to dysregulation in normal frontal cortical inhibitory/excitatory balance.

Pre-clinical studies have similarly reported profound and enduring effects of adolescent nicotine exposure on neurochemical and functional phenotypes in the PFC. For example, Counotte et al. (2009), using a rodent model of chronic adolescent nicotine exposure during post-natal days 34–43 vs. post-adolescent controls (post-natal days 60–69), reported that when tested in adulthood, nicotine exposure selectively during adolescence induced significant and enduring cognitive deficits in attentional performance and increments in impulsive action, while these phenotypes were absent in rats treated post-adolescence. Interestingly, these effects were associated with increased evoked release of DA specifically in the PFC, but not NAc, suggesting a long-lasting hyper-DAergic drive in the PFC following adolescent nicotine exposure, consistent with subsequent reports (Jobson et al., 2019). Iñiguez et al. (2009) **reported that adolescent nicotine exposure during post-natal days 30–44, caused dose-related behavioural effects associated with depressive-like phenotypes, including loss of reward sensitivity and increased depressive-like and anxiety-like phenotypes enduring into adulthood that were reversible by fluoxetine or buprion. Interestingly, these deleterious neurodevelopmental effects were selective to adolescent nicotine exposure as exposure to nicotine during adulthood did not induce these phenotypes. However, what specific molecular and neuronal dysregulation mechanisms in the mesocorticolimbic circuitry may underlie these cognitive and affective dysregulation phenotypes following adolescent nicotine exposure?**

To address these questions, Jobson et al. (2019) used a similar rodent model of chronic adolescent nicotine exposure combined with an integrative combination of behavioural pharmacology, *ex vivo* molecular tissue analyses and *in vivo* neuronal electrophysiological recordings to identify specific mesocorticolimbic phenotypes underlying the effects of adolescent nicotine exposure. In Fig. 2, a simplified schematic showing the major neuronal and molecular phenotypes observed in the PFC following adolescent nicotine exposure is presented. Control cohorts received nicotine exposure during adulthood to selectively compare the effects of neurodevelopmental vs. mature brain nicotine exposure windows. Behaviourally, rats treated with nicotine during adolescence displayed a wide range of anxiety and depressive-like behavioural phenotypes when tested in early adulthood. Nicotine treated rats spent significantly less time in light environments when tested in the light-dark box anxiety test. Similarly, nicotine exposure during adolescent led to decreased open exploration patterns when tested in the open field test. Nicotine treated cohorts displayed social anxiety-like behaviours when tested in a social interaction and had social memory deficits when required to recall interactions with previous conspecifics. In terms of depressive-like phenotypes, nicotine treated rats displayed significantly greater immobility when tested in a forced swim test and a significantly reduced sucrose preference index, both of which are

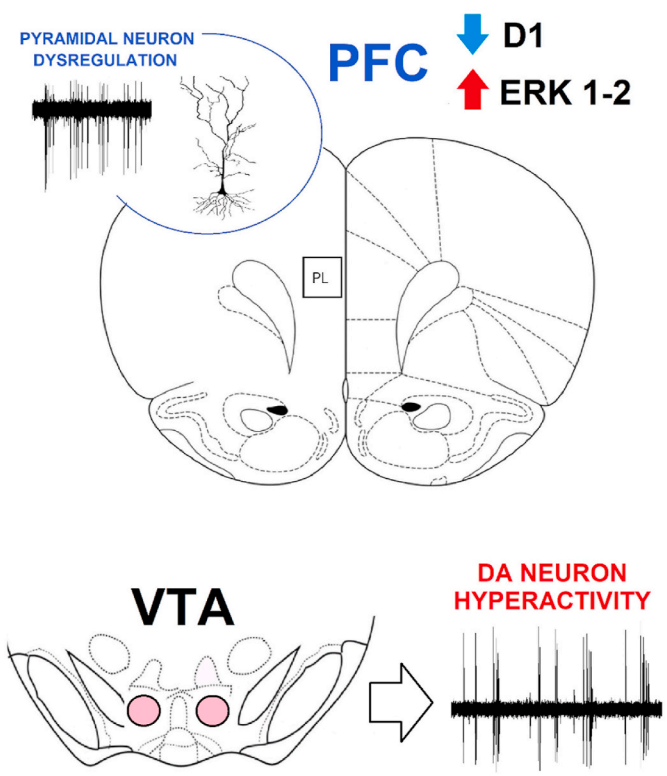

Fig. 2. Schematic summary showing the major long-term neuronal and molecular phenotypes associated with adolescent nicotine exposure in the PFC and VTA (summarized from Jobson et al., 2019). Adolescent nicotine exposure selectively increases pyramidal neuron firing frequency and bursting levels relative to vehicle control cohorts, an effect persisting into early adulthood. In addition, molecular analyses revealed a profound upregulation of ERK 1–2 phosphorylation states and a concomitant decrease in D1R expression levels. Simultaneous recordings performed in the VTA revealed strongly elevated firing frequency and bursting rate increases relative to vehicle controls. These effects were absent following adulthood nicotine exposure and were correlated with depressive and anxiety-related behavioural abnormalities when tested in early adulthood.

commonly used translational models for depressive-like symptomology. Finally, nicotine treated cohorts were tested in a sub-threshold fear memory paradigm to determine if adolescent nicotine exposure may pre-dispose the subject to abnormal sensitivity to fear-provoking stimuli. In this paradigm, a low, sub-threshold level of foot shock is used with an associative cue, and freezing behaviours are assayed 24 h after the conditioning phase. **Normally**, rats will not develop an associative fear memory to these low levels of foot shock. However, in states of affective dysregulation or potentiation of fear processing neural centres such as the BLA or PFC, rats will show hypersensitivity to these normally non-salient fear stimuli (Lauzon et al., 2009; Laviolette and Grace, 2006). Remarkably, nicotine exposure during adolescence led to an enduring hypersensitivity to normally non-salient fear-related conditioning events. No such effects were observed following exposure to nicotine during adulthood, further underscoring the unique vulnerability of the adolescent brain to nicotine exposure.

Standard fear conditioning paradigms (using supra-threshold foot shock stimulation as a conditioning cue) are generally not considered translational models of mood and anxiety disorders. However, the ability to assay for sensitivity to normally sub-threshold aversive cues and how these events may create associative memories, can serve as an effective pre-clinical proxy for negative bias schemas, wherein individuals with anxiety or mood disorders will experience normally innocuous events as highly aversive, relative to healthy individuals (Urban et al., 2018). For

example, while healthy individuals generally recall more positive vs. negative associative memories, individuals with MDD are more likely to display a cognitive negativity bias, focusing on and recalling disproportionately more aversive rather than positive memories (Gaddy and Ingram, 2014). While the neurobiological mechanisms by which smoking may potentiate negative biases in habitual smokers are not understood, some evidence suggests that chronic smoking may increase general sensitivity levels to anxiety-provoking events (Leyro et al., 2008) and that anxiety sensitivity may serve as a moderating variable in the capacity to successfully quit smoking (Langdon et al., 2016). Thus, future studies using pre-clinical models of fear/aversion sensitivity may be a useful tool for exploring the neurobiological underpinnings of this intriguing interrelationship.

In addition to the enduring behavioural phenotypes described above, Jobson et al. (2019) reported several molecular and neuronal phenotypes directly in the PFC and in the VTA. First, adolescent nicotine exposure led to a profound decrease in the expression levels of the D1R receptor and no concomitant effect in D2R levels (Fig. 2). This selective effect on D1R expression was similar to those observed in the NAc shell region following adolescent nicotine exposure (Hudson et al., 2020; Fig. 1) and consistent with the reported decrease in D1R levels in depressive disorders (Dougherty et al., 2006; Cannon et al., 2009). In addition, the apparent lack of a modulatory influence on D2R levels was consistent with previous findings in the NAc shell (Hudson et al., 2020) and in clinical studies demonstrating no apparent dysregulation of D2R levels in mood disorders (Klimke et al., 1999; Parsey et al., 2001; Montgomery et al., 2007). The underlying reasons for this selectivity in D1R adaptations (and apparent lack of effects on D2R substrates) following adolescent nicotine exposure are not currently understood. Nor is it clear why a hyperactive DAergic drive from the VTA to the NAc or PFC might selectively induce downregulation of D1R substrates but leave D2R systems relatively intact. This effect is particularly intriguing given that both D1 and D2 transmission in the NAc is critical for modulating the rewarding and aversive stimulus properties of nicotine in adult rats (Laviolette and van der Kooy, 2003; Laviolette et al., 2008). Thus, future studies are needed to address mechanistically how targeting the D1R system selectively may reverse and/or ameliorate the effects of adolescent nicotine on long-term anxiety and mood related phenotypes.

Concomitant with D1R adaptations, Jobson et al. (2019) reported a significant increase in basal phosphorylation levels of ERK 1–2, directly in the PFC, following adolescent nicotine exposure (Fig. 2). As noted previously, the ERK 1–2 pathway is importantly associated with mood and anxiety-related symptoms (Ailing et al., 2008; Shen et al., 2004; Wang et al., 2010) and similar hyper-phosphorylation of ERK 1–2 was reported in the NAc shell region following adolescent nicotine exposure (Hudson et al., 2020). Interestingly, co-analyses of post-mortem PFC tissue samples from MDD patients with rodent PFC tissue using transcriptomic comparisons, identified multiple convergent genetic markers as candidate biomarkers linked to the etiology of MDD. Interestingly, 80% of these biomarkers were linked to variants in ERK-MAP kinase signaling pathways (Malki et al., 2015). While the independent role of ERK 1–2 phosphorylation as a mechanism underlying adolescent nicotine-induced anxiety and depressive phenotypes is not currently understood, future studies are required to determine if alterations in this pathway may be functionally linked to the developmental pathophysiology of these symptoms, or if these adaptations might be coincidental to the upstream alterations in specific receptors, such as the D1R, that is associated with adolescent nicotine-related pathologies. In the striatum at least, Hudson et al. (2020) reported that pharmacological inhibition of ERK 1–2 phosphorylation states was capable of reversing nicotine-induced behavioural disturbances in a small sub-set of tests, but was largely ineffective in directly reversing nicotine-induced behavioural, molecular or neuronal disturbances induced by adolescent nicotine, particularly in comparison to the highly potent therapeutic effects of GSK-3 inhibition.

Beyond alterations in DA receptor populations, adolescent nicotine exposure also has profound effects on the expression levels of specific nAChR subunits within discrete PFC sub-regions, selectively following exposure to nicotine during adolescent neurodevelopment. For example, Counotte et al. (2009) examined the effects of adolescent nicotine exposure in rats on the temporal expression patterns of specific nAChRs in distinct PFC sub-regions, both acutely and long-term, and what these adaptations may cause in terms of PFC neuronal activity states. Specifically, they reported that adolescent nicotine exposure induced a significant upregulation of nAChRs containing the α4 or β2 subunits, just 24 h after the last injection. Interestingly, nicotine exposure in adulthood had no effects on these expression patterns. The observed potentiation was relatively transient and had dissipated after 5 weeks. In addition, this alteration in nAChR expression levels was correlated with a 34% increase in the amplitude of nicotine-induced inhibitory postsynaptic currents in layers II/III PFC pyramidal neurons. While adaptations in nAChR levels returned to baseline levels, there were longer term changes in the glutamatergic signaling system. For example, reduced functional activity of the mGluR2 in PFC synapses was correlated with impaired attentional performance following adolescent nicotine exposure (Counotte et al., 2011). However, pharmacological stimulation of PFC mGluR2s was reported to improve attention performance in the adolescent nicotine exposed cohorts, underscoring the possibility that these neurodevelopmental pathologies may be plastic in nature and potentially reversible with appropriate pharmacological interventions (Counotte et al., 2011), similar to effects observed in the NAc (Hudson et al., 2020). Thus, nicotine acting directly on its native receptor substrates is capable of altering excitatory/inhibitory balance within the PFC which may in turn modulate excitatory vs. inhibitory neuronal balance. This dysregulation of excitatory/inhibitory function in the PFC following adolescent nicotine is consistent with the findings of Jobson et al. (2019), who found profound alterations in the spontaneous activity rates of presumptive PFC pyramidal neurons, indicating a potential loss of inhibitory regulation following adolescent, but not adult nicotine exposure. Future studies are required to more closely examine how modulation of nAChR expression patterns in the PFC may in turn regulate levels of glutamatergic vs. GABAergic activity states within specific PFC subregions and how this may modulate inputs or outputs with other mesocorticolimbic structures.

Is dopamine dysregulation a final common pathway for nicotine induced pathophysiology to the developing adolescent brain?

Despite a growing body of clinical evidence demonstrating strong associations between smoking behaviours and increased vulnerability for mood and anxiety disorders, there is still a limited amount of evidence illuminating the neurobiological mechanisms behind this effect. This review highlighted several proposed neuronal and molecular mechanisms to account for the effects of adolescent nicotine on increased neuropsychiatric risk, particularly in terms of anxiety and mood disorders. Nevertheless, the common thread revealed by virtually all clinical and pre-clinical research on this topic revolves around DA. Specifically, how neurodevelopmental insults to the developing DAergic signaling pathways within the mesocorticolimbic circuitry may predispose the individual to increased risks for anxiety and mood disorders. The adolescent DAergic system shows dramatically heightened sensitivity to the acute effects of nicotine, particularly in terms of DA signaling in the striatum (Trauth et al., 2001). Thus, it may be intuitive to assume that a process of DAergic sensitization that is aberrantly accelerated by extrinsic nicotine stimulation, specifically during adolescence, is the primary culprit in nicotine induced pathophysiology. In addition, VTA DA neurons show spontaneously faster activity rates in the adolescent vs. adult brain (McCutcheon et al., 2012). Recordings from VTA DA neurons sampled during adolescence showed strongly increased spontaneous levels of firing frequency and bursting activity, similar to the persistent effects on VTA DA activity patterns observed following selective adolescent nicotine exposure (Jobson et al., 2019; Counotte et al., 2012). Interestingly, these effects were concomitant

with elevated levels of phosphorylated ERK 1–2 in the VTA vs. adult samples, similar to effects observed in the NAc in adolescent rats treated chronically with nicotine during adolescence (Hudson et al., 2020).

However, such a DAergic 'sensitization' mechanism is not necessarily sufficient to explain why long-term nicotine exposure may increase the risk of mood and anxiety disorders. As previously described, many studies have found that the mature, adult mammalian brain appears largely immune to the long-term effects of nicotine, at least in terms of increasing neuropsychiatric risk. However, DAergic sensitization is still powerfully demonstrated following nicotine exposure in mature mammalian brains. For example, Tan et al. (2009) exposed adult rats to chronic nicotine **(9 mg/kg per day)** or saline vehicle (via osmotic pump implants for 14 days). Following nicotine exposure, they reported powerful sensitization of the mesolimbic DA system such that VTA DA neurons showed reduced spontaneous firing activity whilst presumptive VTA GABAergic neurons showed strongly potentiated baseline activity. In contrast, VTA DA neurons showed a dramatic sensitized response to subsequent nicotine administration in terms of nicotine-induced DA neuron firing and bursting activity. In addition, whereas treatment with DA receptor antagonists had no effect on nicotine reward effects in vehicle controls, and in fact potentiated nicotine reward processing, in chronic nicotine treated cohorts, this same DA receptor blockade completely blocked the rewarding properties of nicotine, even switching normally rewarding doses of nicotine into highly aversive conditioning cues (Tan et al., 2009). Given that chronic nicotine exposure during adulthood has thus far failed to induce increased vulnerability to mood or anxiety-related phenotypes (at least in pre-clinical studies), this may suggest that other factors, beyond DAergic sensitization, are likely to be involved in the effects of adolescent nicotine on these risk factors. As discussed in this review, these pathways may involve multiple neurotransmitter systems and their associated molecular signaling pathways, such as GABA, glutamate, ERK-1-2, Akt, GSK-3 and others, functionally interacting among multiple mesocorticolimbic structures.

Nevertheless, there are clear adaptations in the mesocorticolimbic DA signaling system unique to adolescent nicotine exposure that suggest common or shared mechanisms among these pathways. Notably, the selective loss of D1R expression and hyper-phosphorylation of the ERK 1–2 pathways in both the NAc and PFC, both of which are absent following adulthood exposure, are both indicative of aberrant mesocorticolimbic DA transmission following adolescent nicotine exposure which persists into early adulthood. Similarly, dysregulation of Akt-GSK-3 signaling pathways in the striatum, a biomarker that is strongly linked to mood and anxiety disorders is an interesting target for future research studies both clinically and pre-clinically.

Beyond nicotine related sensitization phenomena, nicotine differentially modulates DAergic transmission during the process of dependence and withdrawal from nicotine very differently in the adolescent vs. adult brain. In the adult rat brain, the aversive effects of nicotine withdrawal are mediated through D1R and D2R signaling directly in the NAc (Laviolette et al., 2008). However, Natividad et al. (2010) reported that decreased DAergic signaling in states of nicotine withdrawal were significantly greater in adolescent vs. adults, indicating differential sensitivity of the mesolimbic pathway to nicotine-induced withdrawal during distinct neurodevelopmental windows. A possible explanation for the increased vulnerability to nicotine exposure during adolescence may relate to the immaturity of inhibitory mechanisms in regions such as the VTA or the PFC, such as GABAergic terminals density and/or interneuron populations which, in the mature brain, may be better able to buffer the highly excitatory effects of nicotine on cationic nAChR's located within these sensitive neural regions. Thus, future research questions should address how the cyclical nature of nicotine dependence and withdrawal during chronic smoking behaviours may differentially impact the immature DAergic system during adolescence and how this may set the stage for longer-term pathological impacts on mesocorticolimbic function, to which the mature, adult brain may be immune.

In addition to increased vulnerability to mood and anxiety-related disorders, the ability of adolescent nicotine exposure to induce such profound and long-lasting alterations on DAergic transmission may have important implications for co-morbid drug addictions, particularly given the evidence for a persistent hyper-DAergic state within the mesocorticolimbic circuitry (Counotte et al., 2009; Hudson et al., 2020; Jobson et al., 2019). Indeed, there is evidence for increased co-substance dependence, including alcohol and cannabis use, among smokers diagnosed with depression or anxiety symptoms (McCrabb et al., 2019). Causal relationships amongst multiple dependencies and co-occurring mood or anxiety disorders are exceedingly difficult to disentangle in clinical analyses. However, pre-clinical research approaches, which offer temporal and experimental control over specific drugs of interest and behavioural outcomes, can offer an effective empirical approach to these complex issues.

1.3. Future directions

Given the increasing rates of adolescent smoking behaviour and dependence, particularly with the exponential rise in popularity and accessibility of electronic cigarette delivery systems, there is an urgent need to better understand the neurobiological mechanisms underlying the increased risk of neuropsychiatric disorders following adolescent nicotine exposure. In particular, understanding the pathophysiological sequelae that may set up the adolescent brain for anxiety and mood disorders following chronic nicotine use may inform the development of more effective intervention or treatment strategies for these comorbidities. Several critical research gaps exist in the current clinical and pre-clinical literature in terms of smoking and mood and anxiety disorders. Notably, few studies have comprehensively examined sex differences either in terms of differential sensitivity to the neurobiological effects of adolescent nicotine use nor in terms of the relative increased risks for the development of mood and anxiety disorders. This is particularly germane given that females in general experience a greater prevalence of both mood and anxiety disorders (Angst and Dobler-Mikola, 1985; Cyranowski et al., 2000; Ford and Erlinger, 2004; McLean et al., 2011). In the United States, current smoking levels have declined from ~21% (nearly 21 of every 100 adults) in 2005 to ~14% (nearly 14 of every 100 adults) in 2018. Nevertheless, smoking rates among males and females are relatively stable and similar, with ~16% of males vs. ~12% of females (Centres for Disease Control, 2019). Nevertheless, women experience greater difficulty quitting nicotine products and are less likely to respond positively to smoking intervention treatments (Cepeda-Benito et al., 2004; Torres et al., 2016). This raises the possibility that the adolescent female brain may be more susceptible to smoking related mood and anxiety disorders and this is suggested in both clinical and pre-clinical studies (O'Dell and Torres., 2014). Future studies are required to examine the confluence between clinical and pre-clinical evidence in order to mechanistically identify the specific sex-specific factors that may underlie these differential risk profiles.

Finally, there remains an urgent need to identify a wider range of specific neuronal, molecular and genetic biomarkers that link the effects of nicotine exposure directly on the adolescent brain and how these factors differ from the effects of nicotine on the mature brain. Elucidation of these biomarkers have the promise of providing better prognostic identification of individuals/populations who may be at greatest risk of smoking-related neuropsychiatric disorders in later life and further, may allow for the identification of more effective interventions aimed at preventing or reversing these neuroplastic adaptations induced by adolescent nicotine exposure.

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