



Age-dependent effects of tobacco smoke and nicotine on cognition and the brain: A systematic review of the human and animal literature comparing adolescents and adults

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ABSTRACT

Cigarette smoking is often initiated during adolescence and an earlier age of onset is associated with worse health outcomes later in life. Paradoxically, the transition towards adulthood also marks the potential for recovery, as the majority of adolescents are able to quit smoking when adulthood emerges. This systematic review aimed to evaluate the evidence from both human and animal studies for the differential impact of adolescent versus adult repeated and long-term tobacco and nicotine exposure on cognitive and brain outcomes. The limited human studies and more extensive yet heterogeneous animal studies, provide preliminary evidence of heightened fear learning, anxiety-related behaviour, reward processing, nicotinic acetylcholinergic receptors expression, dopamine expression and serotonin functioning after adolescent compared to adult exposure. Effects of nicotine or tobacco use on impulsivity were comparable across age groups. These findings provide novel insights into the mechanisms underlying adolescents' vulnerability to tobacco and nicotine. Future research is needed to translate animal to human findings, with a focus on directly linking a broader spectrum of brain and behavioural outcomes.

1. Introduction

Tobacco smoking carries the highest substance-attributable mortality rate and is estimated to be responsible for over seven million deaths worldwide each year (Peacock et al., 2018; World Health Organisation Factsheet, 2021). The high prevalence of smoking initiated in adolescence and the association between earlier age of onset and heightened risk of later dependence (Kendler et al., 2013; Reitsma et al., 2021) renders understanding the effects of tobacco and its constituents on both the adolescent and adult brain of utmost importance. Subsequently, the purpose of this systematic review was to investigate age-dependent effects of tobacco and nicotine use on cognition and the brain.

Across adolescence, significant changes in brain development occur with the maturation of reward-related regions preceding the development of prefrontal regions relevant for inhibitory control (Baker et al., 2015; Casey et al., 2005). This imbalance between heightened reward sensitivity and suboptimal inhibitory control is suggested to render

adolescents more prone to engage in risky behaviour such as smoking as compared to adults (Lydon et al., 2014). Importantly, during this critical period of development, the neuromodulatory and neurotoxic effects of nicotine may more profoundly impact the structure, function and connectivity of the adolescent brain, and place adolescents at heightened risk of developing cognitive problems (Counotte et al., 2009) and addictive behaviours (Conrod and Nikolaou, 2016; Nock et al., 2017).

Although adolescence marks a time of significant vulnerability to addiction, evidence of resilience is also apparent. The majority of adolescents who engage in risky behaviours such as smoking have the ability to reduce their use as they approach adulthood without the need for formal intervention (O'Loughlin et al., 2014). This natural reduction or so-called 'maturing' out of smoking may be related to the high level of neural plasticity. The heightened plasticity specifically found during adolescence is reflected in enhanced behavioural flexibility and recovery from brain trauma compared to adults (Carroll et al., 2004). This suggests that aspects of brain development and plasticity concur to

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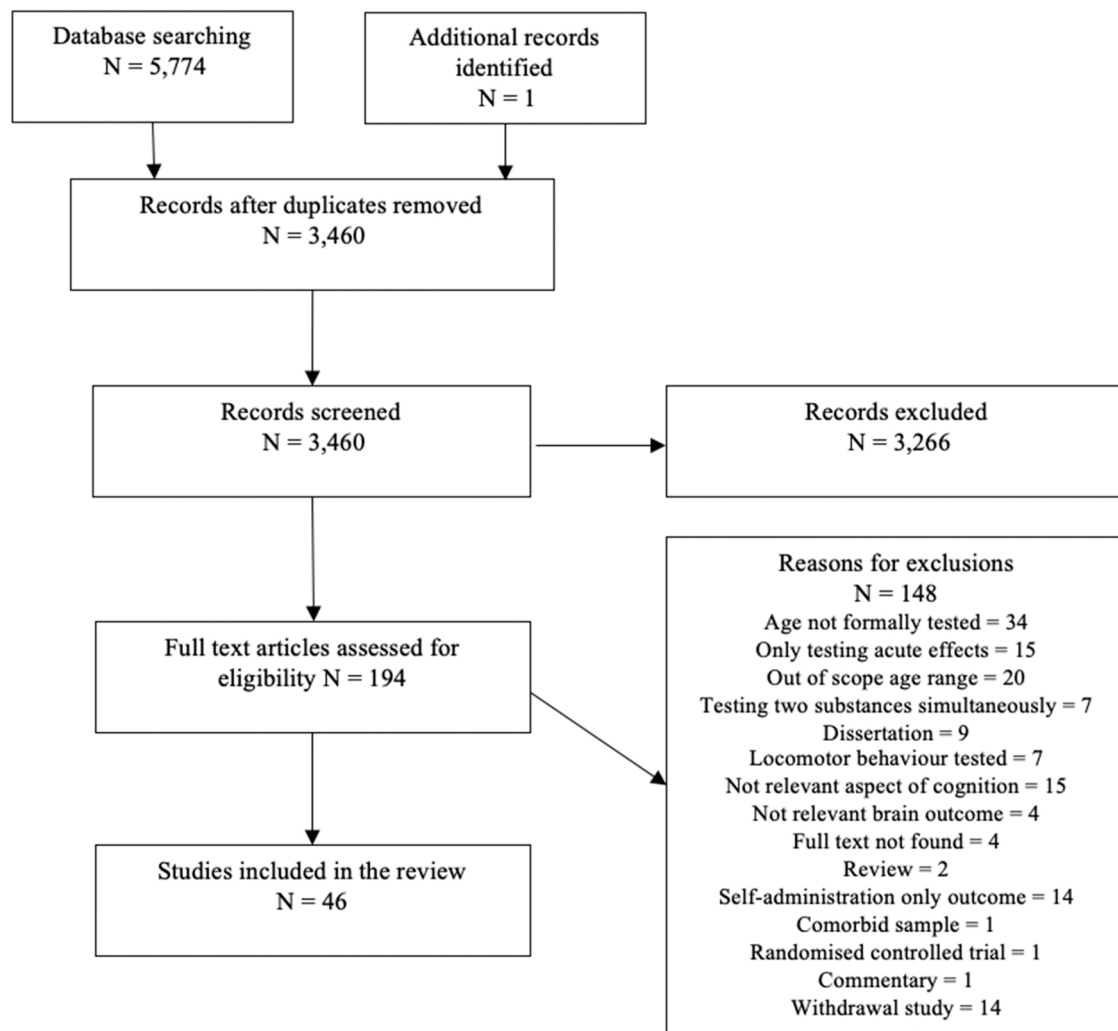


Fig. 1. PRISMA flow diagram detailing the screening process.

provide both increased risk and resilience to addiction during adolescence compared to adulthood. This critically highlights the importance of unravelling how drugs of abuse, such as nicotine, differentially impact the brain during adolescence and adulthood.

While the majority of reviews to date have investigated the impact of tobacco smoke and nicotine on cognition and the brain specifically during adulthood (Brody, 2006; Ceballos, 2006; England et al., 2015; Heishman et al., 2010; Swan and Lessov-Schlaggar, 2007; Valentine and Sofuoglu, 2018; Waisman Campos et al., 2016) and to a lesser extent during adolescence (Dwyer et al., 2009; England et al., 2015; Gould, 2010), only two reviews have addressed how effects may differ between adolescence and adulthood (Leslie, 2020; Yuan et al., 2015). These narrative reviews by Leslie and colleagues point to increased nicotine reward sensitivity, dopamine release and activity of the nicotinic acetylcholine receptors (nAChRs), but reduced nicotine aversion during adolescence as compared to adulthood (Leslie, 2020). The current review will extend previous narrative work by systematically reviewing all human and animal evidence for age differences in the effects of tobacco smoke and nicotine on cognition and the brain, with a focus on the effects of repeated and long-term exposure. This review also includes a broader focus on cognition found to play a role in addictive behaviour such as craving and impulsivity and a more extensive look into the underlying brain mechanisms. An in-depth integration of the outcomes across both the human and rodent findings is provided, along with current knowledge gaps and potential future directions that may prove fruitful.

2. Method

2.1. Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for the current systematic review (Moher et al., 2009). Initial searches were conducted in Medline, PsycInfo, EMBASE, Web of Science Core Collection and Scopus during December 2021 with terms related to tobacco, nicotine, cognition, adolescence/adulthood (see Appendix for full search strategy and syntax).

2.2. Study selection and extraction

Two authors (KCP and LK) performed a blinded review of all search results to determine whether the retrieved studies met the inclusion criteria. In the first phase, only titles and abstracts were screened and the articles which did not meet the inclusion criteria were excluded. Following this, the full texts of the remaining articles were reviewed and the articles that did not meet the inclusion criteria were excluded.

The inclusion criteria were: 1) human samples including both adolescents younger than 18 and adults older than 18, and animal samples including adolescent [Post Natal Day (PND) 25–42 for rats and mice] and adult (PND 65 < for rats and mice) animals; 2) repeated or long-term tobacco or nicotine exposure as the independent variable (i.e., single exposure studies were excluded) and cognitive, reward-related, or

Table 1

Characteristics and findings of rodent studies on age-dependent effects of tobacco and nicotine on cognition. Note: Studies are listed in order of appearance in the text. Only analyses assessing differences between adolescents and adults in the effect of tobacco and/or nicotine on cognitive outcomes are listed. Abbreviations: BLA Basolateral amygdala; BNST Bed nucleus of the stria terminalis; CeA Central nucleus of the amygdala; CPP Conditioned place preference; CTA Conditioned taste aversion; CSE Cigarette smoke extract; DA Dopamine; DS Dorsal striatum; EPM Elevated plus maze; FST Forced swim test; HC Hippocampus; HYP Hypothalamus; IL Infralimbic; i.p. Intraperitoneal; L-D box Light-Dark box; mPFC medial prefrontal cortex; NAc Nucleus Accumbens; nAChR Nicotinic acetylcholine receptors; OFT Open field test; PFC Pre-frontal cortex; PND Postnatal day; s.c. subcutaneous; ? Unknown; VTA Ventral Tegmental Area.

Author	Sample	Characteristics of tobacco/nicotine exposure	Outcomes	Design	Result
Dannenhoffer and Spear (2016)	Male Sprague–Dawley rats, N = 75. N = 40–50 Adolescents PND 22, N = 40–50 Adults PND 67. Adolescents (conditioning PND 25–33) Adults (conditioning PND 70–78)	s.c. injection of 0.0, 0.2, 0.4, or 0.8 mg/kg nicotine (free base weight) or saline alternated daily, for 9 days (4 injections in total; Adolescents PND 26, 28, 30, 32; Adults PND 71, 73, 75, 77); tested following day (Adolescents; PND 34; Adults; PND 79). s.c injection of 0.0, 0.2, 0.4, or 0.8 mg/kg nicotine (free base weight) paired (4 injections in total; Adolescents PND 26, 28, 30, 32; Adults PND 71, 73, 75, 77) with a supersaccharin solution (3% sucrose and 0.125% saccharin in water). Ten minutes later, 100 g bottles of supersaccharin for 30 min; Baseline intake 2d compared with intake on 10d test. (Adolescents PND 34; Adults PND 79)	CPP CTA	Age X Dose Age X Dose	CPP: At low dose (0.2 mg/kg) Adolescents ↑ CPP vs adults and age-matched controls CTA: Adults ↑ CTA vs adolescents at all doses. Adolescents ↑ vs age-matched controls. Adults ↑ vs age-matched controls.
Wilmouth and Spear (2004)	Sprague–Dawley rats; N = ? Adolescents PND 28, N = ? Adults PND 60 Adolescents (conditioning PND 28–33). Adults (conditioning PND 60–65)	Presented with paired (Adolescents 0.0015%, Adults 0.003%) or unpaired solutions alternated daily, 6 days (3 paired solutions in total; Adolescents PND 28–33; Adult PND 60–65); preference tested following day (Adolescents PND 34; Adults PND 66).	CTA	Age X Dose	CTA during conditioning: Adolescents and adults comparable. CTA during testing: Adults ↑ CTA vs adolescents.
Shram et al. (2006)	Male Wistar rats; N = 48 Peri adolescents PND 28, N = 48 Adults PND 60 – 63 Peri-adolescents (conditioning PND 30–37); Adults (conditioning PND 62–72)	s.c injection of 0.2, 0.4, or 0.8 mg/kg nicotine (free base weight) or saline alternated daily, 8 days (4 injections in total; Peri adolescents PND 30, 32, 34 & 36 (counterbalanced); Adults PND 63, 65, 67, 69 (counterbalanced); preference tested following day (Adolescents; PND 38; Adults; PND 70–73)	CPP	Age X Dose	CPP: At high dose (0.8 mg/kg) Peri-adolescents ↑ CPP vs adults, low doses and age-matched controls. No effect in adults.
	Male Wistar rats; N = 48 Peri-adolescents PND 30, N = 48 Adults PND 62 – 65 Peri-adolescents (conditioning PND 31–35) Adults (conditioning PND 62–66)	s.c injection of 0.2, 0.4, or 0.8 mg/kg nicotine (free base weight) or saline daily on 4 consecutive days (4 injections in total; Peri adolescents; PND 31–34; Adults; PND (62–65)-(66–69); tested the following day (Peri adolescents; PND 35; Adults; PND 67–70). Note: extinction testing the following 3 days after testing.	CTA	Age X Dose	Test day: Adults ↑ CTA (0.4 mg/kg) vs age-matched controls. No effect for Peri-Adolescents. Test + Extinction days: Adults ↑ CTA (0.4 or 0.8 mg/kg) compared to age-matched controls. No effect for Peri-adolescents.
Ahsan et al. (2014)	Male Sprague–Dawley rats, N = ? Adolescent PND 21, N = ? PND 56 Adolescents (conditioning PND 28–33) Adults (conditioning PND 63–68)	i.p or s.c injection of 0, 0.05, 0.1, 0.2 or 0.4 mg/kg nicotine (free base weight) or saline, alternated daily, 6 days (3 injections in total; Adolescents PND 29, 31 & 33; Adults PND 63, 66 & 68); tested the following day (Adolescents PND 34; Adults PND 69).	CPP	Age X Dose	Adolescents ↑ CPP (0.1 and 0.2 mg/kg) vs adults and age-matched controls, Adults ↑ CPP (0.6 mg/kg) vs adolescents and age-matched controls.
Kota et al. (2011)	Male ICR mice; N = ? Adolescent PND 28 – 34, N = ? Adult PND 70 + Adolescents (conditioning PND 29–31) Adults (conditioning PND 71–73)	s.c injection of 0.5 mg/kg nicotine (free base weight) or saline daily on 3 consecutive days (3 injections in total; Adolescents PND 29, 30 & 31; Adults PND 71, 72 & 73); tested following day (Adolescents PND 32; Adults PND 74). <i>Acquisition:</i> subset injected/conditioned (0.5 mg/kg) nicotine (free base weight) for 1, 2 or 3 days (Adolescents PND 29, 30 & 31; Adults PND 71, 72 & 73); tested following day (Adolescents PND 32; Adults PND 74). <i>Extinction:</i> extinction testing every following 24 h after testing (until no preference observed). (Adolescents PND 33, 34, 35; Adults PND 75, 76, 77) <i>Reinstatement:</i> after extinguishment of preference, mice were injected 0.1 mg/	CPP	Age X Dose	Adolescents ↑ CPP vs adults at dose 0.05 and 0.1 mg/kg. Adolescents ↑ CPP vs age-matched controls at dose 0.05, 0.1 and 0.5 mg/kg. Adults ↑ CPP vs age-matched controls at dose 0.5 mg/kg. <i>Acquisition</i> Both Adolescents and Adults ↑ CPP vs age-matched controls after 3 days of conditioning/injection, but not after 1 or 2 days. <i>Extinction</i> 72 h after last injection/conditioning, Adolescents ↑ CPP vs age-matched controls, while preference was extinct for adults <i>Reinstatement</i> Adolescents showed recovering CPP after 0.1 mg/kg injection on day 9, adults no recovery.

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Table 1 (continued)

Author	Sample	Characteristics of tobacco/nicotine exposure	Outcomes	Design	Result
Torres et al. (2008)	Male Wistar rats, N = 7 – 14 Adolescents PND 28, N = 7 – 14 Adults PND 60 Adolescents (conditioning PND 34–41) Adults (conditioning PND 66–73)	kg nicotine (free base weight) and re-evaluated for preference under same test day protocol. s.c injection of 0.0, 0.2, 0.4, 0.6, 0.8 or 1.2 mg/kg nicotine (free base weight) or 0, 0.5, 1.0 or 2.0 mg/kg D-amphetamine (salt weight) alternated daily with saline, 8 consecutive days (4 injections in total; Adolescents PND 35, 37, 39 & 41; Adults PND 67, 69, 71 & 73); tested the following day (Adolescents PND 42; Adults PND 74).	CPP	Age X Dose	Adolescents ↑ CPP at doses 0.2, 0.4 and 0.6 mg/kg nicotine compared to age-matched controls, while Adults ↑ CPP at 0.2 mg/kg. Adolescents and Adults show significant differences at doses 0.4, 0.6 and 1.2 mg/kg.
Torres et al. (2009)	Female Wistar rats, N = ? Adolescents PND 28 – 43, N = ? Adults PND 60 – 75 Adolescents (conditioning PND 34–42) Adults (conditioning PND 66–74)	s.c injection of 0.0, 0.2, 0.4, 0.6, 0.8, 1.2 or 1.8 mg/kg nicotine (free base weight) alternated daily with saline, for 8 consecutive days (4 injections in total; Adolescents PND 35, 37, 39 & 41; Adults PND 67, 69, 71 & 73); tested 24 hr or 48 hr after last dose (Adolescents PND 43; Adults PND 75).	CPP	Age X Dose X Sex	Adolescents ↑ CPP vs adults and age-matched controls at dose 0.6 mg/kg.
Vastola et al. (2002)	Male and female Sprague–Dawley rats; N = 28 Adolescents PND 28, N = 28 Adults PND 58. Adolescents (conditioning PND 28–39) Adult (conditioning PND 58–69)	s.c injection of 0.6 mg/kg nicotine (free base weight) or saline alternated daily, 8 days (4 injections in total; Adolescents PND 33, 35, 37 & 39; Adults PND 63, 65, 67 & 69); tested the following day (Adolescents; PND 40; Adults; PND 70).	CPP	Dose X Age X Sex	Adolescents ↑ CPP vs adults and age-matched controls at dose 0.6 mg/kg. No effect for adults.
Belluzzi et al. (2004)	Male Sprague–Dawley rats, <i>Acute (1-trial)</i> N = 32 early Adolescents PND 27 – 30, N = 32 late Adolescents PND 38 – 41, N = 48 Adults PND 90 – 94 Early Adolescents PND 27 (conditioning PND 28–29) Late Adolescents (conditioning PND 39–40) Adults (conditioning PND 91–92). <i>Repeated (4-trial)</i> N = 32 late Adolescents PND 38 – 47, N = 48 Adults PND 90 – 99. Late Adolescents (conditioning PND 39–47) Adults (conditioning PND 91–99).	<i>Acute (1-trial)</i> s.c injection of 0.125, 0.25 or 0.5 mg/kg nicotine (free base weight) or saline alternated daily, 2 days (1 injection in total; (Early Adolescents PND 28; Late Adolescents PND 39; Adults; PND 91); tested the following day (Early Adolescents PND 30; Late Adolescents PND 41; Adults; PND 93). <i>Repeated (4-trial)</i> s.c injection of 0.125, 0.25 or 0.5 mg/kg nicotine (free base weight) or saline alternated daily, 8 days (4 injections in total; (Late Adolescents PND 40, 42, 44 & 46; Adults; PND 92, 94, 96 & 98); tested the following day (Late Adolescents PND 48; Adults; PND 100).	CPP	Age X Dose	<i>Acute (1-trial)</i> Early Adolescents ↑ CPP at dose 0.5 mg/kg, while no effect for late Adolescents or Adults. No age x dose interaction effects. <i>Repeated (4-trial)</i> No effect of nicotine in either age groups. No age x dose interaction effects.
Kota et al. (2008)	Female ICR mice, N = 36 Adolescents PND 28, N = 36 Adults PND 70 Adolescents (conditioning PND 28–36) Adults (conditioning PND 70–78)	s.c injection of 0.1, 0.5, 0.7 or 1.0 mg/kg nicotine (free base weight) or saline daily (5 h apart) on 3 consecutive days (3 injections in total; Adolescents PND 33–35; Adults PND 75–77); tested following day (Adolescents PND 36; Adults PND 78).	CPP	Age X Dose	Adolescents show ↑ CPP than age-matched controls at dose 0.5 mg/kg. No differences in adult-exposed vs age-matched controls. Adults show ↑ CPP than age-matched controls at doses 0.7 and 1.0 mg/kg. No differences in adolescent-exposed vs age-matched controls. No age x dose interaction effects.
Kota et al. (2009)	Male ICR mice, N = 48 Early Adolescents PND 28 – 34, N = 48 Middle Adolescents PND 35 – 48 PND, N = 48 late Adolescents PND 49 – 58, N = 48 Adults PND 70 + Early & late Adolescents (conditioning PND 70–73) Adults (conditioning PND 120–123).	Early Adolescents pre-treatment (intermittent): s.c. injection of 0.1, 0.5, mg/kg nicotine (free base weight) or saline 2x daily every 3 days (8 total injections; PND 27, 30, 33, 36); tested 7 weeks later (PND 74) Early Adolescents pre-treatment (frequent): s.c. injection of 0.1 and 0.5 mg/kg nicotine (free base weight) 1x daily for 14 consecutive days (14 total injections; PND 27–33); tested 7 weeks later (PND 74) Late Adolescents & adults pre-treatment: s.c. injection of 0.5 mg/kg nicotine (free base weight) or saline 1x daily for 14 consecutive days (14 total injections; Late Adolescents PND 50–56; Adults PND 74–80); tested 3 weeks later (Late Adolescents PND 74); tested 7 weeks later (Adults PND 124) s.c injection of 0.5 mg/kg of nicotine (free base weight) or saline 2x daily for 7 consecutive days (14 total injections;	CPP nAChR function in VS, PFC, thalamus, and HC	Age X Dose	Early Adolescents show ↑ CPP than age-matched controls at doses 0.05 and 0.1 and 0.5 mg/kg, while middle and late adolescents and adults show ↑ CPP than age-matched controls at dose 0.5 mg/kg. No age x dose interaction effects. Pre-treated early Adolescents (0.5 mg/kg) show ↑ CPP than age-matched controls in adulthood. Pre-treated adults and pre-treated late adolescents no effect of nicotine. All regions: Adolescents ↑ vs adults and age-matched controls.

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Table 1 (continued)

Author	Sample	Characteristics of tobacco/nicotine exposure	Outcomes	Design	Result
Torrella et al. (2004)	Male and female Sprague – Dawley rats; N = 14–24 Adolescents PND 30 – 39, N = 14–24 Adults PND 60 – 69	Early Adolescents PND 27–33; Adults PND 74–80; sacrificed after 7 weeks (Early Adolescents PND 70; Adults PND 120)	CPP	Age X Dose	Adolescents ↑ CPP compared to age-matched controls, while no effect for adults. No age x dose interaction effects.
Marusich et al. (2017)	Male Sprague – Dawley rats, N = 42 Adolescents PND 21 – 23, N = 40 Adults PND 60 +	s.c injection of 0.2, 0.4 or 0.8 mg/kg nicotine (free base weight) or saline alternated daily, 8 consecutive days (4 injections in total; Adolescents PND 29, 31, 33 & 35; Adults PND 68, 70, 72 & 74); tested the following day (Adolescents PND 36; Adults PND 75).	CPP	Age X Dose	Adolescents ↑ CPP than adults regardless of nicotine exposure, but no CPP for both adolescents and adults vs age-matched controls.
Adriani et al. (2006)	Sprague – Dawley rats, N = 10 Adolescents PND 34 – 43 N = 10 Adults PND 60 – 69). Adolescents (conditioning PND 79–84) Adults (conditioning PND 105–110)	<i>Pre-treatment</i> s.c injection 0.4 mg/kg nicotine (free base weight) or saline 1x daily for 10 consecutive days (Adolescents PND 34–43; Adults PND-60–69). <i>Conditioning</i> (5 weeks later) Injections of 0, 0.3 or 0.6 mg/kg or saline, alternated daily, 6 consecutive days (3 injections in total; Adolescents 80,82 & 84; Adults; PND 106, 108 & 110), tested the following day (Adolescents PND 85; Adults PND 111).	CPP	Age X Dose X Pre-treatment	Adolescents ↑ CPP at dose 0.3 mg/kg vs age-matched controls. No effect of nicotine in adults. Adults and Adolescents ↑ CPP at dose 0.6 mg/kg independent from age of pre-treatment.
Xue et al. (2020)	Male and female Wistar rats; N = 32 Adolescents PND 40–59, N = 20 Adults PND 75	s.c injection of 0.03, 0.1, 0.3 mg/kg nicotine (free base weight) or saline 1x daily for 4 days (4 injections in total; Adolescents (males) PND 49–52 (females) PND 50–54; Adults (males) PND 92–95 (females) PND 136–139). Tested 15 min later (Adolescents (males) PND 52 (females) PND 54; Adults (males) PND 95 (females) PND 139).	Reward thresholds and response latencies	Age X Treatment X Sex	Reward threshold: Adults and adolescents ↓ vs age-matched controls. No interaction between age and treatment. Adolescent females ↓ vs adolescent males. Response latencies: Adults and adolescents ↓ vs age-matched controls. No interaction between age and treatment.
Jobson et al. (2019)	Male Sprague–Dawley rats; N = 20 Adolescents PND 35, N = 20 Adults PND 65	s.c injection of 0.4 mg/kg of nicotine (salt weight) or phosphate buffered saline 3 × daily for 10 consecutive days (Adolescents; PND 35–44; Adults; PND 65–74); 30d abstinence (OFT, FST, L-D box; Adolescents PND 75; Adults PND 105). 30–31d abstinence (Fear conditioning; 30d Conditioning PND 75; 31d Testing PND 76)	Anxiety; FST, L-D box, OFT	Age X Treatment	FST: Immobility Adolescents ↑ vs age-matched controls. Adults no difference vs age-matched controls. No significant age X treatment interaction. Swimming time Adolescents ↓ vs age-matched controls. Adults no difference vs age-matched controls. L-D box: Light environment Adolescents ↓ vs age-matched controls. Dark environment Adolescents ↑ vs age-matched controls. No significant age x treatment interaction. No effect in adult exposed vs age-matched controls.
Smith et al. (2006)	Male and female Long Evans rats; N = 65 Adolescents PND 28, N = 56 Adults PND 85	Nicotine (free base weight) dose low (1 mg/kg/day) or high (2 mg/kg/day) via osmotic mini pumps over 15 days (Adolescents PND 28–42; Adults PND 85–99); 30d abstinence (OFT; Adolescents PND 72; Adults PND 129). 31d abstinence (Fear conditioning (contextual) 32d abstinence Adolescents PND 74; Adults PND 131, Fear conditioning (cued) 33d abstinence: Adolescents PND 75; Adults PND 132, Cued Extinction 42d	Fear conditioning; context	Age X Treatment	OFT: Inner chamber zone Adolescents ↓ vs age-matched controls. Outer chamber zone: Adolescents ↑ vs adults and age-matched controls. Freezing: Adolescents ↑ vs age-matched controls. Adults ↓ vs age-matched controls. No age x treatment interaction.
			Anxiety; OFT	Treatment Age X Dose	Center duration (low and high dose) Adolescents ↓ vs adults and age-matched controls. Adolescents high dose ↓ vs age-matched controls
Smith et al. (2006)	Male and female Long Evans rats; N = 65 Adolescents PND 28, N = 56 Adults PND 85	Nicotine (free base weight) dose low (1 mg/kg/day) or high (2 mg/kg/day) via osmotic mini pumps over 15 days (Adolescents PND 28–42; Adults PND 85–99); 30d abstinence (OFT; Adolescents PND 72; Adults PND 129). 31d abstinence (Fear conditioning (contextual) 32d abstinence Adolescents PND 74; Adults PND 131, Fear conditioning (cued) 33d abstinence: Adolescents PND 75; Adults PND 132, Cued Extinction 42d	Fear conditioning; cued and contextual	Treatment Age X Dose	Contextual fear conditioning: day 2 Adults ↑ vs adolescents regardless of nicotine exposure. Comparison to age-matched controls not shown. Cued fear conditioning: day 3 Adolescents ↑ vs age-matched

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Table 1 (continued)

Author	Sample	Characteristics of tobacco/nicotine exposure	Outcomes	Design	Result
		abstinence; Adolescents PND 81; Adults PND 138)			controls. No differences adults vs age-matched controls. Adults ↑ vs adolescents regardless of nicotine exposure. Cued extinction (freezing): day 9 Adolescents ↑ vs age-matched controls. No differences adults vs age-matched controls. Adolescents ↓ vs adults regardless of nicotine exposure.
Holliday et al. (2016)	Male C57BL/6 J mice; N = 30 Adolescent PND 32, N = 30 Adults PND 54	Nicotine (12.6 mg/kg/day, free base weight) or saline for 12 days via osmotic pumps (Adolescents PND 32–44; Adults PND 54–66). 30d abstinence. FST 24 h and 30d abstinence; Adolescents PND 33 or 74; Adults PND 67 or 96). EPM & Fear conditioning 30d abstinence; Adolescents PND 74; Adults PND 96)	Anxiety; EPM, FST	Age X Drug	EPM: time spent on open arms: Adults ↑ vs adolescents and age-matched controls. No effects of nicotine in adolescents. FST: Time immobile (24-hour abstinence)- Adolescents ↑ vs age-matched controls. No age X drug interaction. (30-day abstinence)- Adolescents ↑ vs adults and age-matched controls. Latency to immobility (24-hour abstinence)- no effect of nicotine for either age group and no age x drug interaction. (30-day abstinence) Adolescents ↓ vs adults and age-matched controls.
			Fear Conditioning; Contextual and Cued	Age X Drug	Contextual learning (freezing): Adolescents ↓ vs adults and age-matched controls. No differences between exposed adults and age-matched controls. Cued learning (freezing): No differences between exposed and age-matched controls for either age group. No age x drug interaction.
Kutlu et al. (2018)	Male C57BL/6 J mice; N = 24–28 Preadolescent PND 23, N = 32–36 Late adolescent PND 38, N = 32 Adult PND 53	i.p injection of nicotine (0.045, 0.09, 0.18, or 0.36 mg/kg, free base weight) prior to subsequent extinction or spontaneous recovery sessions across 5 days (Preadolescent PND 23–27; Late adolescent; PND 38–42; Adult; PND 53–57). 5 sessions in total over 5 days.	Fear conditioning; Contextual	Age X Drug X Trial	Test day: no effect of nicotine or age x drug interaction. Extinction of contextual fear response (freezing): Adults ↑ (all doses) vs age-matched controls. Late adolescents ↑ (0.36, 0.18, and 0.09 mg/kg) vs age-matched controls, Pre-Adolescents- all doses no effect. Spontaneous recovery of contextual fear memory: Pre- and Late adolescents < Adults. Adults ↑ (0.36 mg/kg) vs age-matched controls. No differences pre or late adolescents vs age-matched controls.
Burton and Fletcher (2012)	Male and female Sprague Dawley Rats; N = 22 Adolescents PND 42, N = 23 Adults PND 70 <	s.c injection of 0.15 and 0.3 mg/kg nicotine (salt weight) or saline 1x daily for 12 days prior to daily sessions (Adolescents PND (42–50):(54–64); Adults PND (70 <):(82–?)	Impulsive action	Age X Treatment	Premature responding: both age groups ↑ vs age-matched controls. No significant age x treatment interaction.
Adriani et al. (2004)	Male and Female Outbred CD-1 strain mice; N = 14 Pre-adolescents PND 24, N = 14 Mid-adolescents PND 37, N = 14 Post-adolescents PND 50	2 h/day, 12days, (10 mg/l) nicotine (free base weight) or water (Pre-adolescents PND 24–35; Mid-adolescents PND 37–48; Post-adolescents PND 50–61); no abstinence, tested on last day of treatment (Pre-adolescents PND 35; Mid-adolescents PND 48; Post-adolescents PND 61).	Anxiety; EPM	Age X Dose	Time spent in the open arms: Pre-adolescents ↑ vs age-matched controls, mid-adolescents ↓ vs age-matched controls. Post-adolescents no differences vs age-matched controls. No significant Age x Dose interaction.
	Male and Female Outbred CD-1 strain mice; N = 10 adolescents PND 35, N = 10 Adult PND 70	i.p injection of 0, 0.03, 0.10, 0.30 mg/kg nicotine (free base weight) 1x daily for 10 consecutive days (10 total injections; Adolescents PND 35–44; Adults PND 70–79); no abstinence, tested on last day of treatment (Adolescents PND 44; Adults PND 79)	Anxiety; EPM	Age X Dose	Time spent/entries in the open arms: Adolescents ↓ vs adults and age-matched controls at dose 0.1 mg/kg. Adults ↑ vs adolescents and age-matched controls at dose 0.1 mg/kg.
		i.p injection of 0, 0.03, 0.10, 0.30 nicotine (free base weight) 1x daily for 10 consecutive days (10 total injections;	AMPA GluR2/3 subunits in striatum and HC	Age X Sex X Dose	Striatum: All doses Adolescents ↓ vs adults and age-matched controls. Adults ↑ vs age-matched

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Table 1 (continued)

Author	Sample	Characteristics of tobacco/nicotine exposure	Outcomes	Design	Result
		Adolescents PND 35–44; Adults PND 70–79; sacrificed after 60d Adolescents PND 104; Adults PND 139).			controls. HC: All doses Adolescents ↓ vs adults and age-matched controls. Adults no effect. Striatum: no age differences. Females across both ages ↓ vs age-matched controls. No effect for males. HC: No age or sex differences.
Acri et al. (1995)	Male Sprague-Dawley rats; N = 16 Adolescents PND 39–42, N = 16 Adults PND 67–74	Nicotine (12 mg/kg/day; free base weight) or saline (0.9% NaCl) for 10 days via osmotic pumps (Adolescents PND (39–42): (49–52); Adults PND (67–74):(77–84). Tested on day 1, 6, 9 of treatment and after 24 hr, 3d, 6d abstinence. (Adolescents PND 43,48,51,53,55 & 58; Adults PND 74, 79,82, 84, 86 & 89)	ASR	Drug X Age X Time	ASR amplitudes: day 1 and day 6 Adults ↑ vs age-matched controls. Significant difference in the effect of NIC on both age groups.
Elliott et al. (2004)	Male and female Sprague-Dawley rats; N = 80 Adolescent PND 30, N = 80 Adult PND 60	s.c injection of 0.1, 0.5, or 1.0 mg/kg of nicotine (free base weight) or saline 1x daily for 5 consecutive days (5 total injections; Adolescents PND 30–34; Adults PND 60–64); Tested on 2nd treatment day (Adolescents PND 31, Adults PND 61)	EPM	Age X Gender X Treatment	Percentage of time in open arms: Female adolescents, male and female adults ↓ vs age-matched control groups. Adolescent males ↑ vs age-matched controls. No formal reporting on interaction effect. Visual inspection of data suggests age x treatment interaction effect. Percentage of open arm entries: Adolescents ↑ vs Adults and age-matched controls. Closed arm entries: no main effects for gender or age or interactions. Active lever presses: Adults ↑ vs adolescents and age-matched controls.
Funk et al. (2016)	Male <i>Fos-lacZ</i> rats; N = 43 Adolescent PND 28, N = 43 Adult PND 68	2 h/day, 12days, 0.03 mg/kg/infusion nicotine (salt base weight) or saline (Adolescents PND 40–51; Adults PND 80–91); 24 hr, 7d, 14d and 28d abstinence (Adolescents PND 52, 59, 66 & 80; Adults PND 92, 99, 106 & 120)	Craving	Age X Withdrawal Day	FosB in ventral mPFC, OFC, NAc core and shell, CeA and BLA: No age differences. No effect of nicotine.
	Male <i>Fos-lacZ</i> rats; N = 10–12 Adolescents PND 28, N = 10 Adults PND 68	Sacrificed after 1d or 14d abstinence (Adolescents PND 52 or 66; Adults PND 92 or 106).	FosB expression in mPFC, and amygdala	Age X Withdrawal Day	FosB in the dorsal mPFC- Day 1 and 14 after nicotine: Adults ↑ vs adolescents and age-matched controls.

brain outcomes as the dependent variables; 3) statistical comparisons of adolescents and adults on cognitive and/or brain outcomes; 4) nicotine administration measures *during* adolescence or adulthood, not retrospectively (e.g., adults reporting back on adolescence); 5) only primary quantitative data collection (no case studies, or review papers); 6) focus on tobacco or nicotine exposure in samples without comorbidities or (modelled) genetic vulnerabilities (e.g. individuals or rodent models of psychosis); 7) written in English; 8) studies published in a peer-reviewed journal before December 12, 2021 (see Fig. 1 for a detailed screening process). Unpublished work which had not undergone peer-review was excluded to ensure only high-quality articles were included.

2.3. Measures used

In humans, we defined cognition as any construct that falls within the boundary of standard neuropsychology testing, but also included more broad aspects of cognition such as craving and impulsivity, as they have repeatedly been shown to play a role in addictive behaviour (for a review see De Wit, 2009). Brain-based studies investigating aspects of cognition were also included. In rodents, we defined cognition as learning, memory and attention, based on a seminal review (Rodríguez and Wetsel, 2006). Further, due to the high comorbidity between nicotine addiction and several anxiety-related disorders (Fluharty et al., 2016), anxiety was included as a secondary outcome. Rodent studies

investigating locomotor activity were excluded because although behavioural sensitisation is considered to reflect neurobiological changes that may underlie certain aspects of addictive behaviour (Robinson and Berridge, 1993), the translational relevance for addictive behaviour and human addiction remains unclear (Robinson and Berridge, 2008; Vanderschuren and Pierce, 2010). Across both human and rodent studies, nicotine or tobacco withdrawal studies were excluded, unless they included relevant brain-related or cognitive outcomes. Finally, within the studies that were included, peripheral findings that did not relate to cognition were not described.

Across both humans and rodents there is great disparity in the period which is identified as adolescence. Based on rodent cognitive developmental milestones, adolescence has been defined more conservatively as being from PND28–42 (Spear, 2000), or more liberally with adolescence being considered as PND21–59 (Tirelli et al., 2003). More recently, the boundary of early adolescence has been disputed with a more liberal approach of PND21 considered to be the norm (McCormick and Mathews, 2010). The week between PND21–28 has also been described as the juvenile period, with PND21 identified as the lower boundary for early adolescence (Burke and Miczek, 2014; Doremus-Fitzwater and Spear, 2016). Several studies have selected PND25 as the boundary for early adolescence (Morales et al., 2014; Rajendran and Spear, 2004). Following a more conservative approach, it was decided to characterise the boundaries of adolescence between PND28 to PND42, but lower the

Table 2

Characteristics and findings of rodent studies on age-dependent effects of tobacco and nicotine on the brain. Note: Studies are listed in order of appearance in the text. Only analyses assessing differences between adolescents and adults in the effect of tobacco and/or nicotine on the brain are listed. Abbreviations: AC Adenylyl cyclase; BLA Basolateral amygdala; BNST Bed nucleus of the stria terminalis; CEA Central nucleus of the amygdala; CSE Cigarette smoke extract; DA Dopamine; DS Dorsal striatum; GABA Gamma aminobutyric acid; Glu Glutamate; HC Hippocampus; HYP Hypothalamus; ICR Institute of Cancer Research; IL Infralimbic; i.p. Intraperitoneal; mGluR5 Metabotropic glutamate receptor subtype 5; mPFC medial prefrontal cortex; NAc Nucleus Accumbens; nAChR Nicotinic acetylcholine receptors; PFC Pre-frontal cortex; PND Postnatal day; PVTh Paraventricular nucleus of the thalamus; PVN Hypothalamic paraventricular nucleus; SC superior colliculus; s.c subcutaneous; ? Unknown; VS Ventral Striatum; VTA Ventral Tegmental Area; $\alpha 4\beta 2$ alpha4beta2.

Author	Sample	Characteristics of tobacco/ nicotine exposure	Outcomes	Design	Result
Yang et al. (2021)	Male Sprague-Dawley rats: N = 4 Adolescents PND 33–35, N = 4 Adults PND 83–85.	s.c. injection of 0.5 mg/kg/day nicotine (salt weight) or saline 1x daily for 7 consecutive days (7 total injections; Adolescents PND (33–35):(39–41); Adults PND (83–85):(89–91)). Sacrificed after final injection (Adolescents PND 39–41; Adults PND 89–91).	mGluR5 expression in the NAc GABA neurons.	Age X Treatment	Basal expression of mGluR5 in whole NAc lysates: no differences between adolescents and adults, and no effect of nicotine in either group. Membrane expression of mGluR5 in GABA medium spiny neurons: Adults ↑ vs adolescents and age- matched controls.
Smith et al. (2015)	Male Long-Evans rats; N = 160; N = 80 Adolescents PND 35, N = 80 Adults PND 80	s.c. injection of 0.5 mg/kg nicotine (free base weight) or saline 1x daily for 2 or 7 days (2 or 7 total injections; Adolescents PND 35-(37 or 40); Adults PND 80-(82–86) Following days (3d or 8d) s.c injection before testing in OF. Sacrificed after 24 h. (Adolescents PND 38–41; Adults PND 83–87)	DRD1, DRD2, DRD3 and D3nf splice variant mRNA expression	Age X Drug	DRD1 mRNA expression in NAc shell & core, olfactory tubule/ islands of Calleja & DS: Adolescents ↑ vs adults and age-matched controls. Adults ↓ vs age-matched controls. DRD2 expression in striatum, NAc shell & core, DS, olfactory tubule/ islands of calleja: regardless of nicotine exposure adolescents ↑ vs adults. DRD3 & D3nf expression in olfactory tubule/islands of calleja: regardless of nicotine exposure adolescents ↑ vs adults. DRD2, DRD3, D3nf & DRD3:D3nf ratio mRNA in striatum, NAc shell & core, DS, olfactory tubule/islands of calleja: No Age x Drug interaction.
Dao et al. (2011)	Male Sprague-Dawley rats; N = 14–16 Early Adolescents PND 28, N = 14–16 Late Adolescents PND 37, N = 14–16 Adults PND 86.	i.v injections of 30 µg/kg/0.1 ml nicotine (salt weight) or saline 2x daily for 4 consecutive days (8 total injections; Early Adolescents PND 28–31; Late- adolescents PND 37–40; Adults PND 86–89). c-fos; Sacrificed after 30 min (Early adolescents PND 31; Late adolescents PND 40; Adults PND 89) 5-HT and DA; Sacrificed after 24 hr (Early adolescents PND 32; Late adolescents PND 41; Adults PND 90)	c-fos mRNA expression in NAc, PFC, BLA and DS	Age X Pretreatment	c-fos in NAc shell: Adolescents ↑ vs adults and age-matched controls. c- fos in PFC and DS no age differences. c-fos in BLA: Adolescents ↑ vs age-matched controls. Adults ↑ vs age-matched controls – no significant age x pretreatment interaction.
			5-HT markers in NAc, PFC, BLA and DS	Age X Pretreatment	SERT binding in PFC, BLA and DS: Adolescents ↑ vs adults and age- matched controls. No age differences in NAc. 5-HT levels in BLA: Adolescents ↑ vs adults and age-matched controls. No age differences in PFC, NAc or DS. 5-HIAA: No age differences in PFC, NAc, DS or BLA. DA markers in NAc: Adults and adolescents ↑ vs age-matched controls. No Age x Pretreatment interaction effects. PFC, BLA or DS: no age differences.
Keser et al. (2013)	Male and female adult Sprague Dawley rats; N = 34 Adolescents PND 35, N = 24 Adults PND 98. Note: Each age group split into minimum, median and maximum preference drinkers based on voluntary consumption. Minimum and maximum rats used in experiment.	Free choice paradigm: 24 h/day, 2 weeks, 10 mg/L nicotine (salt weight), remaining period, 20 mg/L. Adolescents total 12w, Adults total 6w (Adolescents PND 35–119; Adults PND 84–126). Sacrificed immediately after (Adolescents PND 119; Adults PND 126)	NO activity in the frontal cortex, HC, and amygdala	Age X Sex X Preference	Maximum preferring adolescent rats ↑ vs maximum preferring adult rats. Age at onset did not affect nicotine consumption in minimum preferring groups NOx levels in amygdala: Adults ↑ vs adolescents, male adults ↓ vs age- matched controls. Female adults and adolescents no difference vs age-matched controls. Frontal cortex: min and max preference adolescents ↑ vs adults and age-matched controls. HC: no age differences and no differences vs age-matched controls.

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Table 2 (continued)

Author	Sample	Characteristics of tobacco/ nicotine exposure	Outcomes	Design	Result
Cano et al. (2020)	Male Sprague Dawley; N = 45 Adolescents PND 30–32, N = 36 Adults PND 89–91	Passive i.v injections of 0.5 mg/kg nicotine (free base weight) or aqueous CSE (Nicotine concentration 150 ug/ml) or saline in an operant chamber programmed to deliver one injection per minute for 15 min 3x daily (total 1.5 mg/kg/day of nicotine) for 10 consecutive days (Adolescents PND (30–32): (40–42), Adults PND (89–91): (99–101). Sacrificed after 1 h (Adolescents PND 40–42; Adults PND 99–101)	nAChR upregulation-subregions of the striatum, the limbic system, and the medial habenula and interpeduncular nucleus	Age X Drug	$\alpha 4\beta 2$ nAChR binding in medial amygdala and substantia nigra NIC (+/- CSE): Adolescents \uparrow vs adults and age-matched controls. NAC, caudate-putamen and hypothalamus- no age differences. Regulation of $\alpha 3\beta 4$ nAChR in medial habenula and interpeduncular nucleus- no effects of age. $\alpha 7$ binding in hypothalamus and (Central, basolateral & medial) amygdala NIC (+/- CSE): Adolescents \uparrow vs adults and age-matched controls.
Doura et al. (2008)	Male Sprague-Dawley rat; N = 16 Adolescents PND 29, N = 16 Adults PND 70–90	Nicotine (6 mg/kg/day; free base weight) or saline for 14 consecutive days via osmotic minipumps (Adolescents PND 29–42; Adults PND (70–90): (83–103). Sacrificed immediately after (Adolescents PND 42; Adults PND 83–103)	nAChRs expression	Age X Treatment	$\alpha 4\beta 2$ * average regulation across 38 regions: Adults \uparrow vs adolescents and age-matched controls. $\alpha 4\beta 2$ * regulation in 35 of the 38 regions, including the cerebral cortex, and in many forebrain regions and HC: Adults \uparrow vs adolescents and age-matched controls. Global $\alpha 4\beta 2$ * binding: no significant age x treatment interaction. $\alpha 7$ regulation in 20 regions: Adults \uparrow vs adolescents and age-matched controls. $\alpha 7$ regulation in frontal cortex (inner laminae) and visual cortex (inner laminae): Adolescents \uparrow vs adults and age-matched controls. Bed nucleus stria terminalis, anterior hypothalamus, dentate gyrus, HC: Adolescents \downarrow vs adults and age-matched controls. Global $\alpha 7$ binding: no significant age x treatment interaction. $\alpha 6$ * regulation in 15 regions: Adolescents \downarrow vs adults and age-matched controls. $\alpha 6$ * regulation in caudal striatum, medial habenula, VTA, substantia nigra, ventral lateral geniculate: Adolescents \downarrow vs adults and age-matched controls. Optic nerve: Adolescents \uparrow vs adults and age-matched controls. Global $\alpha 6$ * binding: no significant age x treatment interaction.
Hoegberg et al. (2015)	Female and Male Sprague-Dawley rats; N = 27 Early Adolescents PND 28, N = 29 Late Adolescents PND 42, N = 34 Adults PND 84	Nicotine (6 mg/kg/day; free base weight) or saline for 14 (7 for early adolescents) consecutive days via osmotic minipumps (Early adolescents PND 28–34; Late-adolescents PND 42–55; Adults PND 84–96). Sacrificed immediately after (Early adolescents PND 34; Late-adolescents PND 55; Adults PND 96)	nAChR upregulation in cerebral cortex	Age X Sex X Treatment	$\alpha 4\beta 2$ * and nAChRs in the cerebral cortex: All nicotine exposed male rats \uparrow vs age-matched controls. Adult and late adolescent exposed females \uparrow vs age-matched controls. No effect of NIC in early adolescent rats. Age x Treatment interaction. $\alpha 4\beta 2$ * PND42 Late adolescent females \uparrow vs late adolescent males. PND28 early adolescent males \uparrow vs early adolescent females. Binding of [3 H]EB-labeled nAChRs in the cerebral cortex: All nicotine exposed male rats \uparrow vs age-matched controls. Adult and late adolescent exposed females \uparrow vs age-matched controls. No effect of NIC in early adolescent rats. No age x treatment interaction. $\alpha 5$ -containing nAChRs in the cerebral cortex: no age x treatment interaction.
Levin et al. (2007)	Male Sprague-Dawley albino rats; N = 13 Adolescents PND 32, N = 13 Adults PND 64	?h/day, 4 weeks, 0.03 mg/kg/infusion nicotine (free base weight) or saline (Adolescents PND (38–44):(68–74); Adults	$\alpha 4\beta 2$ nAChR binding in midbrain, striatum, HC	ANCOVA with Age (controlled for nicotine self-admin)	$\alpha 4\beta 2$ in Midbrain and striatum: Adolescents \uparrow vs adults and age-matched controls. Hippocampus: no age effects.

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Table 2 (continued)

Author	Sample	Characteristics of tobacco/nicotine exposure	Outcomes	Design	Result
Trauth et al. (1999)	Male and female Sprague–Dawley rats; N = 24–48 Adolescents PND 30, N = 24–48 Adults PND 90.	PND (68–74):(98–104). Sacrificed 24 hr after. (Adolescents PND 69–75; Adults PND 99–105). Nicotine (initial dose 6 mg/kg/day; salt weight; Adolescents 3–4 mg/kg/day; Adults 5 mg/kg/day) for 17 consecutive days via osmotic minipumps (Adolescents PND 30–47; Adults PND 90–107). Tested on day 1 and 14 of treatment and after 0 h, 5d, 15d, 4w abstinence (PND 45, 50, 60, 75, 105, 120 & 135)	$\alpha 4\beta 2$ nAChR in the midbrain, cerebral cortex, and HC	Age X Treatment x Gender x Region	Adolescents $\alpha 4\beta 2$ in midbrain (0 h \uparrow 5d \uparrow 15d \uparrow 4w males \uparrow females \downarrow vs controls, but \uparrow vs adults), cerebral cortex (0 h \uparrow 5d \uparrow 15d \uparrow 4w \uparrow vs controls, no differences vs adults), HC (0 h \uparrow vs controls, but \downarrow vs adults 5d \uparrow 15d \downarrow 4w males \uparrow females \downarrow) vs adults and age-matched controls (unless otherwise stated).
Counotte et al. (2012)	Male Wister rats; N = 20 Adolescents PND 34, N = 20 Adults PND 60.	s.c injection of 0.4 mg/kg nicotine (salt weight) or saline 3 \times daily for 10 days (Adolescents PND 34–43; Adults PND 60–69). 1d (Adolescents PND 44; Adults PND 70) and 5w abstinence (Adolescents PND 78; Adults PND 104)	nAChR expression in mPFC and occipital cortex	Age X Time X Region x Treatment	^3H -Epi-binding in mPFC: 1d adolescents \uparrow vs adults and age-matched controls, 5 wk = no age effects. Regulation of $\alpha 4\beta 2$ * nAChRs in mPFC: 1d=Adolescents \uparrow vs adults and age-matched controls, 5 wk= no age effects. Regulation of $\alpha 7$ nAChRs in mPFC and occipital cortex = no age effects.
McDonald et al. (2007)	Male Long–Evans rats; N = 19 Adolescents PND 29, N = 19 Adults PND 80	Nicotine (initial 2.0 mg/kg/day; free base weight) or saline for 14 consecutive days via osmotic minipumps (Adolescents PND 29–43; Adults PND 80–94). The final dose rates for adolescent and adult pre-treated animals were 0.95 and 2.0 mg/kg/day. 30d after dosing rats performed an open field test with nicotine challenge (1 \times i.p injection of 0.18 mg/kg nicotine; free base weight) Sacrificed after 7d (Adolescents PND 80; Adults PND 131)	Total dendritic length and branch number in NAc	Age X Treatment	Medium spiny neuron dendritic length in NAc: Adolescents \uparrow vs adults and age-matched controls. Medium spiny neuron branch number in NAc: Adolescents \uparrow vs age-matched controls. No effect in adults. No age x dose interaction. Large aspiny neurons branching and dendritic length: no effect of nicotine and no age x dose interaction.
Bergstrom et al. (2008)	Male Long-Evans hooded rats; N = 19 Adolescents PND 29, N = 19 Adults PND 80	Nicotine bitartrate (2 mg/kg/day; free base weight) or saline with sodium tartrate for 14 consecutive days via osmotic pumps (Adolescents PND 29–43; Adults PND 80–94). 30d after dosing rats performed an open field test with nicotine challenge (1 \times i.p injection of 0.18 mg/kg nicotine; free base weight) Sacrificed after 7d (Adolescents PND 80; Adults PND 131)	Pyramidal neurons from Layer V of the PL cortex	Age X Pre-Treatment X Cell type	Total basilar length of complex cells in pyramidal neurons from PL cortex: Adolescents \uparrow vs age-matched controls. No effect in adults. Total basilar length/branch number of simple cells in pyramidal neurons from PL cortex: Adults \uparrow vs adolescents and age-matched controls. Total apical length or branch number of simple or complex pyramidal neurons: no age differences.
Bergstrom et al. (2010)	Male Sprague–Dawley rats; N = 13 Adolescents PND 32, N = 11 Adults PND 60	s.c injection of 0.5 mg/kg nicotine (free base weight) or saline 3x week for 2 weeks (six total injections; Adolescents PND 32–43, Adults PND 60–71). Sacrificed after 20d (Adolescents PND 63, Adults PND 91).	Dendritic morphology of neurons located in the right and left BLA and IL cortex	Age X Pretreatment X Hemisphere	BLA basilar dendrites: Adults \uparrow dendritic length in the right hemisphere only vs adolescents and age-matched controls. Adolescents no alteration in dendritic morphology. Complexity of Apical Tree principal neurons: both adults and adolescents \downarrow vs age-matched controls. Dendritic morphology of pyramidal neurons from the IL: no effect in adults or adolescents.
Alajaji et al. (2016)	Male ICR mice; N = 8 Early adolescent PND 28, N = 8 Adult PND 70	s.c injection of nicotine (0.5 mg/kg; free base weight) or saline (2 injections/ day) for 7 days (Early Adolescents PND 28–34; Adults PND 70–76) and the NAc was collected 24 h after the last nicotine injection (Early Adolescents PND 35; Adults PND 77).	DeltaFosB expression	Age X Treatment	DeltaFosB expression in NAc: Early Adolescents \uparrow vs adults and age-matched controls.
Cao et al. (2007)	Male Sprague–Dawley rats; N = 14–26 Adolescents PND 27, N = 14–26 Adults PND 90	i.v. injections of 30 $\mu\text{g/kg/100}$ μl nicotine (free base weight), 16 $\mu\text{g/kg/100}$ μl acetaldehyde,	c-fos mRNA expression in the CeA, NAc, SC, PVTh, PVN and BNST	Age X Drug X Brain area	c-fos NIC or ACE: No effect of age in levels of c-fos expressed in the BNST, CeA, NAc, and the SC. As no

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Table 2 (continued)

Author	Sample	Characteristics of tobacco/nicotine exposure	Outcomes	Design	Result
Doura et al. (2010)	Male Sprague–Dawley rats; N = 18 Adolescents PND 28–30; N = 18 Adult PND 60–70	saline or a combination of acetaldehyde and nicotine x 2 for 1d (Adolescents PND 27; Adults PND 90). Placed into locomotion boxes immediately after and monitored for 30 min. Sacrificed after this (Adolescents PND 27; Adults PND 90). Nicotine (6 mg/kg/day; free base weight) or saline for 14 consecutive days via osmotic minipumps (Adolescents PND (28–30):(42–44) Adults PND (60–70):(74–84)). Sacrificed immediately after (Adolescents PND 42–44; Adults PND 74–84) or after a 30-day withdrawal period (Adolescents PND 72–74; Adults PND 104–114).	Gene expression in the VTA	Age X Treatment	age effect ages were combined. Effect of nicotine on both age groups. c-fos in PVTh: NIC (+/-ACE): Adolescents ↑ vs adults and age-matched controls. c-fos in PVN: NIC (+/-ACE): Adults ↑ vs adolescents and age-matched controls. Transient response: 80 adolescent-specific genes and 171 adult-specific genes, 11 across age groups. Persistent response genes: 62 adolescent-specific genes, 33 adult-specific genes and 9 across age groups. Late response genes: 532 adolescent-specific genes, 101 adult-specific genes and 352 across age groups.
Slotkin et al. (2008)	Male and female Sprague–Dawley rats: N = >= 24 Adolescents PND 30 N = >= 24 Adults PND 90	Nicotine (6 mg/kg; free base weight) or saline for 17.5 consecutive days via osmotic minipumps (Adolescents PND 30–47; Adults PND 90–107). Adults tested 3d, 13d, 23d and 73d abstinence. Adolescents tested 58d, 68d, 78d and 128d abstinence. (PND 105, 110, 120, 130 & 180)	AC cell signalling	Age X Treatment X Region	Basal AC in cerebellum, brain stem and cerebral cortex: (PND 105–110) Adults ↑ vs age-matched controls. (PND 120–180) Adolescents ↓ vs adults and age-matched controls. AC response to Forskolin in cerebellum, brain stem and cerebral cortex: (PND 105–110) Adults ↑ vs age-matched controls. (PND 130–180) Adolescents ↑ vs adults and age-matched controls.

boundary to PND25 in order to capture the beginning of early adolescence.

3. Results

3.1. Study search

Our study search resulted in 3460 studies once duplicates were removed. After an initial review of titles and abstracts, 3266 studies were excluded. A full-text review was then conducted on 194 studies, resulting in the exclusion of 148 studies (see flow diagram in Fig. 1). Finally, 5 human studies and 41 rodent studies were included. Study characteristics and findings of the included articles were reported according to PRISMA practices. The studies are detailed in Table 1 (Rodents and cognitive outcomes), Table 2 (Rodents and brain-based outcomes) and Table 3 (Humans). Of note, most studies were performed using male rodents, unless explicitly mentioned the discussed results pertain to the male sex.

3.2. Animal studies: cognitive outcomes

3.2.1. Learning and memory

Impairments in learning and memory have frequently been established as both a precursor and result of addiction (Goodman and Packard, 2016; Torregrossa et al., 2011). Several paradigms exist that tap into aspects of learning and memory, enabling an understanding of how these cognitive processes contribute to the development and maintenance of addiction.

3.2.2. Conditioned aversion or preference studies

Heightened reward sensitivity and reduced sensitivity to the aversive effects of tobacco and nicotine are suggested to place adolescents at increased risk of escalating their use of cigarettes compared to adults (Lydon-Staley and Geier, 2018; Wilmouth and Spear, 2004). The rewarding and aversive effects of nicotine can be investigated with

conditioning paradigms, including conditioned taste aversion (CTA) and conditioned place preference (CPP). In the CTA paradigm, nicotine administration is repeatedly paired with an appetitive solution such as saccharin. The resulting reduction in consumption of the appetitive solution provides an index of nicotine aversion.

Three studies investigated taste aversion with consistent findings (Dannenhoffer and Spear, 2016; Shram et al., 2006; Wilmouth and Spear, 2004). Paired injections of nicotine and a sucrose + saccharin solution led to CTA at all doses in both adolescent- and adult-exposed rats compared to their respective age-matched controls (Dannenhoffer and Spear, 2016). Although both age groups displayed CTA, the aversion was weaker in the adolescent-exposed rats compared to adult-exposed rats. Similarly, adult rats showed significantly greater CTA compared to adolescent-exposed rats when tested 24 h post access to nicotine (Wilmouth and Spear, 2004). Furthermore, no significant CTA was found in peri-adolescent rats, when compared to age-matched controls when preference was tested 24 h post-dosing (Shram et al., 2006). By contrast, adult rats showed significant CTA compared to age-matched controls, which persisted following three days of extinction (Shram et al., 2006).

In sum, adolescent-exposed rats appear to be less sensitive to the aversive properties of both low and high dose nicotine compared to adult-exposed rats. Also, exposure during adulthood appears to heighten sensitivity to the aversive properties of nicotine and this continues after nicotine cessation. This suggests adolescents are more tolerant to the aversive properties of nicotine which could place them at heightened vulnerability to escalating their cigarette use (Jensen et al., 2015). In the context of tobacco dependence, lower aversive reactions to nicotine have been correlated with a higher risk of the development of habitual tobacco use (Sartor et al., 2010). Although the findings suggest there are age effects in the sensitivity of the aversion to nicotine, there are several factors that may also influence these effects. In particular, the effects of the deprivation of food and/or water (Anderson et al., 2010) and isolated housing environments (Smith et al., 1998) have been found to differ between age groups (Anderson et al., 2010) and may confound age

Table 3

Characteristics and findings of human studies on age-dependent effects of tobacco and nicotine on cognition and the brain. Note: Studies are listed in order of appearance in the text. Only analyses assessing differences between adolescents and adults in the effect of tobacco and/or nicotine on brain or cognitive outcomes are listed. Abbreviations: DLPFC Dorsal lateral prefrontal cortex; DV = Dependent variable; FTND Fagerstrom Test for Nicotine Dependence; IV = Independent variable; M age = mean age; mPFC medial prefrontal cortex; PPI Psychophysiological Interaction.

Author	Outcomes	Sample (N, Age)	Measurement of cigarette use	Design	Result
Lydon-Staley and Geier (2018)	Sensation seeking, impulse control	N = 5080, Age 12–33 yrs.	Cigarette-Smoking: reported whether smoked every day for 30 days or did not and whether smoked at any time during past 30 days or not at all. Odds ratio (OR) of any smoking in the past 30 days were the following: at 12.5 years (OR=0.16), 18 years (OR=0.84), 22.54 years (OR=0.68), 27.91 years (OR=0.90) and at 32.41 years (OR=0.71). The odds of daily smoking were the following: years 12.67 (OR=0.03) and at 23.40 years (OR=0.53).	Multivariate time-varying effect modelling: predictors (sensation-seeking, impulse control) and daily cigarette smoking as outcome (as functions of continuous age). Control: sex and race/ethnicity	Sensation seeking and daily smoking or any smoking in the previous 30 days: Strongest association during adolescence relative to adulthood. Impulse control and any smoking or daily smoking: significant across adolescence and young adulthood, although the association was strongest in the late-20 s and early 30 s
Reynolds (2004)	Delay discounting	N = 73; N = 19 adolescents (14–16 yrs), N = 54 adults (19–21 yrs)	Reported cigarettes per day and years since onset of use. Non-smoking group: reported never having smoked. Adolescent smokers: average of 6.77 cigarettes per day, started smoking an average of 2 years prior to participation. Adult smokers consumed an average of 21 cigarettes per day and had smoked for an average of 5 years. N = 19 adolescent smokers, N = 25 adult smokers, N = 29 adult non-smokers.	Cross-sectional. Age x Cigarette consumption	Delay discounting young adult smokers ↑ vs adolescent smokers and young adult non-smokers.
Brook et al. (2004)	Memory, Concentration, Learning.	N = 975, Five waves; T1 M age = 5.57 yrs, T2 M age = 14.05 yrs, T3 M age = 16.26 yrs, T4 M age = 22.28 yrs, T5 M age = 26.99 yrs.	Frequency of tobacco use in childhood (T1-T2), during late adolescence (T2-T3), during the early 20 s (T3-T4) and during the late 20 s (T4-T5). Ever smoked daily, length of time during which the individual smoked daily, specific age periods during which the individual smoked daily. The percentage of participants who were daily tobacco users during the waves was the following: Prior to T2 10.28% (n = 77), T2-T3 20.03% (n = 150), T3-T4 36.32% (n = 272) and T4-T5 34.98% (n = 262).	Logistic regression analysis: DV= Health Problems IV = daily use of tobacco during at least one period. Control: gender, age, level of education, personal income. Longitudinal: Measurement of health problems (T5) and tobacco use history (T1-T5).	Daily smoking during adolescence into young adulthood predicts increased memory, learning and concentration deficits in adulthood when compared to daily smoking during childhood and early adolescence.
Do and Galván (2015)	Craving and brain activity	N = 80; N = 39 Adolescents (13–18 yrs), N = 41 Adult (25–30 yrs)	Cigarettes per day, last cigarette smoked before scan, smoking duration. Smoking status: verified by CO in breath and qualifying urinary cotinine levels. Baseline smoking: recorded daily smoking consumption and administered the FTND to measure nicotine dependence. Participants were classified as non-smokers (<5 cigarettes in lifetime); Adults N = 21, Adolescents N = 19 or smokers (daily smoking ≥6 months; ≥5 cigarettes/day); Adults N = 20, Adolescents = 20.	Behavioural: Label × age group × smoking group Control: SES, ethnicity, and gender. Neuroimaging: Group level, a priori region of interest analyses was conducted in anatomically defined bilateral amygdala, striatum, insula and DLPFC. PPI Analysis: Functional connectivity during the graphic vs non-graphic labels contrast. Three seed regions: bilateral amygdala, bilateral insula, and bilateral ventral striatum.	Behavioural: Baseline craving no age differences. Reduction from baseline craving when viewing the graphic labels adolescents ↓ vs adults. Craving in response to graphic vs non-graphic = no age differences. Neuroimaging: Graphic > non-graphic: Activation in the right amygdala: adult smokers ↑ vs adolescent smokers. Non-graphic > Graphic: Activation in the left putamen: adolescent smokers ↑ vs adult smokers. Activity in the Bilateral amygdala, bilateral putamen, right caudate, bilateral insula and bilateral DLPFC- no age differences for both contrasts. Functional connectivity: Graphic > non-graphic: Positive FC between the bilateral amygdala and right NAc- adolescent

(continued on next page)

Table 3 (continued)

Author	Outcomes	Sample (N, Age)	Measurement of cigarette use	Design	Result
Do and Galván (2016)	Craving and brain activity	N = 78; N = 39 Adolescents (13–18 yrs), N = 39 Adults (25–30 yrs)	Cigarettes smoked per day, smoking duration, and nicotine dependence via the FTND. Participants were classified as non-smokers (<5 cigarettes in lifetime); Adult N = 19, Adolescent N = 19 or smokers (daily smoking ≥6 months; ≥5 cigarettes/day); Adult N = 20, Adolescent = 20.	Behavioural: Age group x Smoking group Control: Socioeconomic status, gender, hours since last cigarette, smoking duration, cigarettes per day, and revised dependence scores. Neuroimaging: voxel wise analysis two ROIs NAc and DLPFC.	smokers ↑ vs adult smokers. Graphic > non-graphic: Positive FC between the bilateral amygdala and left parietal lobe, between the bilateral insula and left mPFC and between the bilateral insula and left caudate adolescent smokers ↑ vs adult smokers. Graphic > non-graphic: Positive FC between the bilateral insula and right putamen, and between the bilateral insula and left caudate- adult smokers ↑ vs adolescent smokers. Negative FC between the bilateral putamen and right insula adult smokers ↑ vs adolescent smokers. Behavioural: Craving (prescan and change in craving level)- no age differences. Neuroimaging: Smoking > neutral contrast: NAc Activation in adolescent smokers ↑ vs adult smokers. Smoking > neutral contrast: DLPFC activation- no age differences Adolescent smokers: NAc mediated the association between craving and subsequent desire to smoke. Craving ↑ associated with functional coupling between cortical and striatal regions.

effects in the sensitivity to the aversion of nicotine (Dannenhoffer and Spear, 2016). Whilst one study deprived food and water in a CTA procedure to increase motivation for the tastant (Shram et al., 2006), a second study provided free access to food and water to minimise stress to the rodents (Dannenhoffer and Spear, 2016) and across both studies adolescents were found to show attenuated aversive sensitivity to nicotine, indicating evidence of age effects rather than differences due to housing or training conditions. There is also evidence to suggest there are sex effects in the motivation for nicotine in an operant setting, with adult females showing heightened motivation for nicotine compared to their adult male counterparts (Chaudhri et al., 2005). Although one study investigated both male and female rats and found consistent findings across sexes (Wilmouth and Spear, 2004) two more recent studies only included male rats (Dannenhoffer and Spear, 2016; Shram et al., 2006). The three studies to date have also only tested sensitivity to the aversive properties of nicotine after 1 day of abstinence. Taken together, future studies should include CTA procedures that test the effects of social housing environments, should include samples of male and female rodents, and should evaluate whether the attenuated sensitivity to the aversive properties is found after extended abstinence periods.

The rewarding effects of nicotine can be measured with the CPP paradigm. In the CPP paradigm, nicotine is repeatedly administered prior to placement of the animal in one compartment, and saline is administered prior to placement in a distinct compartment. CPP is assessed during test days by recording the amount of time the rodents stay in the compartment paired with nicotine relative to saline. Thirteen studies investigated CPP, with relatively consistent findings (Adriani et al., 2006; Ahsan et al., 2014; Belluzzi et al., 2004; Dannenhoffer and Spear, 2016; Kota et al., 2008; Kota et al., 2009; Kota et al., 2011; Marusich et al., 2017; Shram et al., 2006; Torrella et al., 2004; Torres et al., 2008; Torres et al., 2009; Vastola et al., 2002). Seven of the 13 studies showed an interaction effect between age and sensitivity to

nicotine induced CPP. Across the seven studies, increased CPP was found in adolescent-exposed rats and mice as compared to adult-exposed and their relative age-matched controls when tested the following day after conditioning (Ahsan et al., 2014; Dannenhoffer and Spear, 2016; Kota et al., 2011; Shram et al., 2006; Torres et al., 2008; Torres et al., 2009; Vastola et al., 2002). This effect was consistent across a large range of doses (0.05–1.2 mg/kg) and conditioning days (3–8 days). Only one of the seven studies found evidence of elevated CPP in adult-exposed male Sprague-Dawley rats after six days of conditioning with 0.6 mg/kg nicotine compared to all other groups tested (Ahsan et al., 2014).

There were also four studies that found increased CPP in adolescent-exposed rats and mice as compared to age-matched controls, but the effects were too small to result in significant age-related differences (Belluzzi et al., 2004; Kota et al., 2008, 2009; Tirelli et al., 2004; Torrella et al., 2004). The majority of these studies included fewer conditioning days compared to the seven studies which did find a significant difference between age groups, which may explain the differing findings. However, two studies found conflicting findings at higher doses of nicotine. Kota et al. (2008) found increased CPP in adult mice exposed to 0.7 and 1.0 mg/kg of nicotine compared to age-matched controls, whilst no differences were present in adolescent-exposed mice compared to age-matched controls at these doses (Kota et al., 2008). In another study, the same research group observed increased CPP in early, mid and late adolescent and adult mice after exposure to 0.5 mg/kg of nicotine compared to their age-matched control groups (Kota et al., 2009). One further study suggested there is an age effect in the level of experienced reward to nicotine, but this was not nicotine-induced, as nicotine exposure did not induce CPP for either age group compared to their age-matched controls (Marusich et al., 2017).

A final set of studies took yet a different approach, by pre-exposing rodents to nicotine during adolescence or adulthood followed by the CPP conditioning procedure in adulthood (Adriani et al., 2006; Kota et al., 2009). Increased CPP was present in rats that were exposed to

nicotine during adolescence (Adriani et al., 2006) and mice that were exposed to nicotine during early adolescence (Kota et al., 2009), both at low doses (0.03–0.05 mg/kg) and relative to their age-matched controls. By contrast, no differences were found between adult-exposed rats and age-matched controls. Although, when exposed to a slightly higher dose of nicotine (0.06 mg/kg) both adolescent and adult rats displayed increased CPP, independent of pre-treatment or age variables (Adriani et al., 2006). A final study investigated the long-term effects of nicotine on CPP, with a similar pattern of findings (Kota et al., 2007). After five days (72 h post conditioning) of extinction testing, significant CPP was displayed in adolescent exposed mice compared to age-matched controls, whilst preference was extinct for adult exposed mice. After seven days, adolescent-exposed mice showed reinstatement of CPP whereas adult-exposed mice did not.

Taken together, the findings suggest that during adolescence, and particularly so during early adolescence, the rewarding effects of nicotine are heightened, even when exposed to a low dose of nicotine, and regardless of whether exposure takes place immediately or after a period of pre-exposure. Moreover, these effects appear to be sustained long-term with heightened CPP still found up to two months after nicotine cessation in adolescent exposed rodents and increased reinstatement of CPP after a single dose of nicotine. Together with lower sensitivity to the aversive properties of nicotine in adolescent-exposed rodents, this may increase the risk of the development and maintenance of addiction when smoking is initiated during early adolescence. These findings suggest adolescent rodents may retain nicotine-paired cues and contextual signs for a longer period than adults, resulting in the risk of increased nicotine-seeking (Kota et al., 2011). This was demonstrated by Ahsan and colleagues (2014) who observed that adolescent-exposed rats had increased CPP compared to adult-exposed rats and acquired and maintained nicotine self-administration whereas adult-exposed rats did not (Ahsan et al., 2014). Combined with lower sensitivity to the aversive properties of nicotine in adolescent-exposed rodents, this may increase the risk of the development and maintenance of addiction when smoking is initiated during early adolescence. Interestingly, two of the 13 studies investigated CPP and CTA within the same study enabling an understanding of how the two effects interact. Across both studies increased CPP and reduced nicotine aversion was present in (peri)adolescent-exposed rats as compared to adult-exposed rats (Shram et al., 2006; Dannenhoffer and Spear, 2016). Taken together, these studies suggest that the reward-aversion balance may be shifted towards reduced nicotine aversion and heightened rewarding effects of nicotine during adolescence. Future studies should investigate the relationship between these two effects further, including the potential underlying mechanisms that could be driving the association and whether the shift in reward-aversion balances translates to higher risk of subsequent dependence.

3.2.3. Reward threshold

Alongside CPP paradigms, the rewarding effects of nicotine can be investigated with intracranial self-stimulation procedures. Intracranial self-stimulation (ICSS) is an operant behavioural paradigm in which rodents learn to deliver small electrical pulses to specific brain regions involved in reward processing (Xue et al., 2020). It provides insight into the rewarding effects of nicotine as changes in reward thresholds can be investigated. Administration of nicotine has been found to reduce ICSS thresholds (Kenny and Markou, 2006), which indicates increased reward value (Xue et al., 2020).

One study investigated reward thresholds and response latencies with ICSS in rats (Xue et al., 2020). Response latencies have been shown to reflect psychomotor performance (Igari et al., 2014). After determining the individual reward threshold (i.e., the midpoint between stimulation intensities that supported responding and failed to support responding), nicotine was administered for four consecutive days with varying doses (0.03, 0.1, 0.3 mg/kg) per day. Nicotine reduced the brain reward threshold and response latencies of both adolescent and adult

rats 15 min after exposure, suggesting increased reward value of nicotine across both age groups. Whilst there were no age interaction effects in reward threshold or response latencies, adolescent females were found to be more sensitive to the effects of nicotine than adolescent male rats, and there was a non-significant trend of increased sensitivity in adolescent females compared to adult females. These findings contradict the findings from the CPP studies, as they suggest there is increased reward value of nicotine when exposure takes place during both adolescence and adulthood. The conflicting findings could be due to the methodology used, as CPP provides a measure of the rewarding effects of contextual cues associated with nicotine use on a behavioural level, whereas ICSS procedures provide insight into the state of the reward system and psychomotor performance in the presence of nicotine (Tzschentke, 1998). Future studies should include measures of reward threshold to establish whether the current findings can be replicated. If so, this may provide evidence that whilst both age groups are sensitive to the acute effect of nicotine on the reward system, adolescents are uniquely sensitive to the rewarding effects of contextual cues associated with nicotine both in the short and long-term. Although the sex effects did not reach significance in the current study, this should be explored further, particularly as sex differences have been found in the rewarding effects of nicotine (Lenoir et al., 2015).

3.2.4. Fear conditioning and retention

Classical/Pavlovian fear conditioning (FC) paradigms are associative learning tasks, whereby rodents learn to associate a neutral conditioned stimulus (CS+, e.g., tone), with an aversive unconditioned stimulus (US, e.g., foot shock) in a certain context. By repeated pairings, both the discrete cue and the context will be associated with the aversive stimulus, and when presented can elicit a conditioned response (CR) in the rodents such as freezing behaviour. The degree of freezing behaviour displayed in response to exposure to the discrete cue or the context is subsequently determined as a measure of cued or contextual fear conditioning, respectively. Both forms of fear conditioning involve different processes implicating both overlapping and separate brain regions. Whilst the amygdala is implicated in both forms of fear conditioning (Kim and Jung, 2006), cued fear conditioning involves links from thalamic and cortical inputs to the lateral amygdala (Sachella et al., 2021), whilst context fear conditioning involves circuits within the hippocampus which send contextual representations to the amygdala (Gilmartin and Helmstetter, 2010; Kim and Cho, 2020). Conditioned behavioural responses are also present in individuals suffering from substance use disorders, such as cue-induced drug-seeking behaviour, highlighting the relevance of FC paradigms. Further, the network of brain structures found to be involved in FC and extinction processes overlap with the regions implicated in the development and maintenance of addiction (Milad et al., 2007; Konova et al., 2019; Salloum et al., 2007).

Three studies investigated the effects of nicotine on fear conditioning, with mixed findings (Holliday et al., 2016; Jobson et al., 2019; Smith et al., 2006). All three studies investigated the long-term effects of nicotine exposure by testing rodents on fear conditioning after 30 days of abstinence. Across two studies, nicotine exposure resulted in increased freezing behaviour in adolescent-exposed rats only relative to their age matched controls during both a contextual (Jobson et al., 2019), and cued fear conditioning test (Smith et al., 2006). In the first study adult-exposed rats spent significantly less time freezing during a contextual fear conditioning test compared to age-matched controls (Jobson et al., 2019), whereas, in the second study there was no effect of nicotine on adult-exposed rats during a cued fear conditioning test (Smith et al., 2006). Additionally, Smith and colleagues tested contextual fear learning whereby adults were found to show higher levels of freezing regardless of nicotine exposure. However, a direct comparison to age-matched controls was not shown. In contrast, in a third study, exposure to nicotine resulted in reduced levels of freezing during a contextual fear conditioning test in adolescent-exposed mice only,

compared to all other groups when tested 30 days post-dosing (Holliday et al., 2016). This latter study did not reveal a nicotine effect in adult-exposed mice. Holliday and colleagues also tested cued fear conditioning and found no age differences between nicotine-exposed mice on levels of freezing, nor were there differences between nicotine-exposed rats and their age-matched controls in either age group.

Two studies investigated fear extinction (Kutlu et al., 2018; Smith et al., 2006). In one study fear conditioning was followed by a fear expression test and subsequently extinction sessions that were preceded by nicotine injections (Kutlu et al., 2018). In adults, nicotine impaired fear extinction, which was not apparent in adolescents. By contrast, none of the doses of nicotine affected the levels of freezing during contextual fear extinction sessions in early adolescent rats. Late adolescent mice only exhibited increased freezing at the three highest doses of nicotine (0.36, 0.18, and 0.09 mg/kg) relative to their age-matched controls. In a second study, a different design was followed which included fear conditioning sessions, and subsequently context- and cue-induced expression of fear were assessed separately (Smith et al., 2006). In subsequent trials the authors investigated cued extinction, by investigating the response to the tone. This study revealed greater freezing behaviour (higher latency to move) by the low nicotine exposed adolescents in this test, although they were not different from vehicle-treated adolescent rats on day three. These findings suggest a more persistent expression of cued fear.

In sum, the effects of age on fear conditioning are mixed, with two studies showing lower levels of freezing in adolescence regardless of nicotine exposure (Smith et al., 2006; Holliday et al., 2016). Of the three studies to investigate more prolonged exposure and more long-term effects of this exposure, two studies showed nicotine increased freezing to context (Jobson et al., 2019) and cues (Smith et al., 2006) in adolescence, while one study showed decreased freezing to context and no effect of nicotine on levels of freezing to cues (Holliday et al., 2016). In adult-exposed rats, one study showed a nicotine-induced decrease in freezing to context (Jobson et al., 2019), whilst two studies suggested no effect of nicotine on freezing levels to cues (Smith et al., 2006; Holliday et al., 2016) or context (Holliday et al., 2016). Across the two studies which showed nicotine-induced increased freezing in adolescence, both studies included rats and similar low doses of nicotine. The study which showed nicotine-induced reduced freezing in adolescence included mice (as opposed to rats), which may explain the apparent contrast in findings across studies. Although a larger dose was administered in this study, direct comparisons between rats and mice are hampered by species differences in nicotine metabolism (Matta et al., 2007). Strain-dependent effects have been found to modulate the effect of nicotine on fear conditioning (Portugal et al., 2012), suggesting that in addition to effects of age, fear conditioning is also subject to genetic variability. Taken together, the findings suggest that adolescents are more sensitive to the effects of nicotine on cued and context fear conditioning, compared to when exposure takes place during adulthood. However, the direction of these effects warrants further investigation. While several groups have attempted to delineate the underlying brain mechanisms that may play a role in the effect of nicotine on fear behaviour, brain and behavioural measures have been investigated in separate samples (Holliday et al., 2016). Future studies that investigate brain-behaviour associations in the same sample of rodents will be critical to shed light on causal relationships.

The findings from the two studies investigating fear extinction were conflicting; one shows that acute nicotine treatment impairs extinction of the expression of contextual fear conditioning in adults and late adolescent rats (Kutlu et al., 2018), whilst the other shows more persistent conditioned freezing behaviour in mice that were exposed to nicotine during adolescence (Smith et al., 2006). The conflicting findings across studies could be due to the type of fear extinction that was tested, with Kutlu and colleagues investigating extinction of contextual fear conditioning, whilst Smith and colleagues investigated extinction of

cue-induced fear conditioning. As previously described the two forms of conditioning involve distinct processes (Kim and Cho, 2020; Sachtell et al., 2021), although extinction appears to predominantly involve the prefrontal cortex (Kutlu et al., 2018). These studies used different species (rats and mice) and the age of the rodents during treatment and testing varied considerably across studies. Specifically, Smith and colleagues tested male and female Long Evans rats after 42 days of abstinence, whilst Kutlu and colleagues tested male C57BL/6 J mice on the same day of exposure. Overall, these studies suggest age-dependent differences in the effects of nicotine on the expression of conditioned fear as measured through freezing behaviour across age groups. To understand the direction of this effect, further studies incorporating the same methodology will play a key role.

3.2.5. Impulsivity

Impulsivity is described as a predisposition to act rapidly and respond without adequate thought of the negative consequences to both internal and/or external stimuli, which may hamper long-term goals (Moeller et al., 2001). Many facets of impulsivity have been characterised, with the two major subtypes falling under the category of poor inhibitory control over motor responses or poor decision making due to acting on impulse (Winstanley et al., 2006). Not surprisingly, impulsivity is considered a core impairment underlying addictive behaviours (see Lee et al., 2019 for a systematic meta-review).

One study investigated impulsive action with the two-choice serial reaction time test (2-CSRTT) (Burton and Fletcher, 2012). This test has been widely used to investigate impulsive action, which reflects a failure to withhold an inappropriate response to a prepotent stimulus (Winstanley et al., 2006). Although nicotine exposure significantly increased premature responding in adolescents and adults as compared to age-matched controls, no age-related differences in nicotine-induced premature responding were found, nor were there differences in accuracy or reinforcer latencies. This suggests that both adolescents and adults are sensitive to the effects of nicotine on impulsive action. However, it should be noted that the adolescent animals were tested during late adolescence (PNDs 52–56), and some of the effects of nicotine are known to be more substantial during early to mid-adolescence (Adriani et al., 2002; Burton and Fletcher, 2012; Dao et al., 2011), which could explain the lack of differences observed between the age groups. For example, early adolescent mice showed a selective vulnerability to oral nicotine self-administration when compared to middle and late adolescent mice (Adriani et al., 2002). Moreover, early adolescent exposure to nicotine has unique effects on limbic functioning (Dao et al., 2011). Future studies should investigate the effects of nicotine on impulsive action including a sample of early to mid-adolescent rodents to determine whether nicotine effects on impulsivity may be age-dependent.

3.3. Other behavioural outcomes

3.3.1. Anxiety

Nicotine addiction is associated with high comorbidity of several anxiety-related disorders (Fluharty et al., 2016). Multiple paradigms exist to measure anxiety-related behaviour in rodents. One of the most widely used is the open field test (OFT), which is based on the innate tendency of animals stay close to perimeter walls and avoid open spaces and bright lights. Anxiety is indexed by time spent in the centre zone relative to the peripheral zone (Ohl, 2003). Another commonly applied paradigm is the elevated plus maze (EPM) which assumes that rodents tend to approach dark enclosed spaces and avoid open areas, due to an unconditioned fear of heights and open spaces. Anxiety behaviour is indexed by the amount of time spent on the open arms relative to the closed arms (Handley and Mithani, 1984). The light/dark (LD) test is based on the conflict between approach and avoidance behaviour. Rodents have the tendency to explore novel environments, whilst showing aversion to bright-lit spaces. Indices of anxiety therefore include the

time spent in the light compartments relative to the dark compartment and transitions between them (Bourin and Hascoët, 2003). Additionally, in acoustic startle (AS) paradigms rodents are exposed to an intense and sudden startling stimulus, such as a light flash or loud noise. This gives rise to an unconditioned reflex in the form of a startle response which provides an objective measure of anxiety (Koch and Schnitzler, 1997). The forced swim test (FST) involves forcing rodents to swim in a cylinder from which there is no escape. Although the forced swim test is widely considered to measure depression-like behaviours and is widely used to screen for the effectiveness of antidepressants (Yankelevitch-Yahav et al., 2015), it has been proposed that the escape-directed behaviours and reduced immobility during the test are driven by anxiety (Anyan and Amir, 2018). The amount of time spent showing active (climbing and swimming) or passive (immobility) behaviour is scored, where the score for active behaviour provides an index of anxiety (Anyan and Amir, 2018).

Six studies investigated anxiety-related behaviour using one or a combination of the anxiety paradigms described above, with relatively consistent results (Acri et al., 1995; Adriani et al., 2004; Elliott et al., 2004; Jobson et al., 2019; Smith et al., 2006; Holliday et al., 2016). Five of the six studies showed an interaction effect between age and sensitivity to nicotine-induced anxiety (Adriani et al., 2004; Elliott et al., 2004; Jobson et al., 2019; Smith et al., 2006; Holliday et al., 2016). Across the two studies using the OFT and three studies using the EPM, increased anxiety-related behaviour was displayed in adolescent-exposed rodents compared to adult-exposed and their relative age-matched controls (Adriani et al., 2004; Elliott et al., 2004; Jobson et al., 2019; Smith et al., 2006; Holliday et al., 2016). This effect was consistent across a large range of doses (0.03–12.6 mg/kg), length of exposures (5–12 days) and paradigms.

There were also two studies using the EPM and one study using the L-D box, in which nicotine exposure increased anxiety-related behaviour in adolescent-exposed rodents relative to age-matched controls, but the comparison between age groups did not reach significance (Adriani et al., 2004; Elliott et al., 2004; Jobson et al., 2019). Although, in one of the studies using the EPM, nicotine exposure reduced anxiety-related behaviour in adolescent-exposed males whereas increased anxiety-related behaviour was displayed in adolescent-exposed females relative to their age-matched controls (Elliott et al., 2004). Within the same study by Adriani and colleagues (2004), mice that self-administered nicotine during mid-adolescence showed increased anxiety compared to age-matched controls, while reduced anxiety was observed in mice that self-administered nicotine in pre-adolescence and no effect of nicotine self-administration in post-adolescent mice was found. This suggests that, even though the overall age effect did not reach significance, nicotine selectively enhances anxiety during mid-adolescence. Although, in one study no effect of nicotine during adolescence was found when using the EPM and a sample of mice (Holliday et al., 2016), and two studies using the FST found nicotine exposure during adolescence reduced anxiety-related behaviour 24-hour post dosing (Holliday et al., 2016; Jobson et al., 2019) and 30 days later (Holliday et al., 2016). Additionally, two studies using the EPM suggested nicotine exposure during adulthood reduced anxiety-related behaviour (Adriani et al., 2004; Holliday et al., 2016), whilst another using the AS suggested nicotine exposure increased anxiety-related behaviour during adulthood (Acri et al., 1995).

Across studies, both acute and long-term effects of nicotine appear to increase anxiety-related behaviour in rodents exposed to nicotine during adolescence, particularly when this exposure takes place during mid-adolescence, highlighting potential vulnerability periods within adolescence. There may also be sex differences in these effects (Elliott et al., 2004), although Smith and Colleagues did not find sex effects (Smith et al., 2006). The differing findings across studies could be due to the type of rat strain used, as there is evidence to suggest the two rat strains differ in their responses to nicotine in a sex-dependent manner (Faraday et al., 2005). Nevertheless, the evidence suggesting that

exposure to nicotine during adolescence increases the risk of anxiety-related behaviour both in the short-term and into adulthood is convincing. The anxiogenic effects of nicotine were observed using different anxiety tests, however, age-specific effects were most consistent for the OFT and EPM. Although, two studies investigating anxiety-related behaviour with the FST observed reduced anxiety-related behaviour after adolescent nicotine exposure. This may suggest adolescents are uniquely sensitive to the effects of nicotine on selective aspects of anxiety-related behaviour (Radhakrishnan and Gulia, 2018). It should be noted one study only measured the time animals were immobile (Holliday et al., 2016), whilst the other also measured escape directed behaviours, such as number of climbs and swimming time (Jobson et al., 2019). It will be important for future studies to include measures of escape directed behaviour so to capture anxiety-related behaviour to a larger extent (Anyan and Amir, 2018). Taken together, it appears exposure to nicotine during adolescence may lead to anxiety, which is known to be a drug-vulnerable phenotype in adulthood. Evidence for this claim has been found in a study by Adriani and colleagues (2003) who found exposure to nicotine during adolescence increased the vulnerability of developing nicotine addiction compared to when a similar exposure took place in adulthood (Adriani and Laviola, 2004). More recently, there has been a focus on unravelling the neurobiological mechanisms which may show adaptations after adolescent nicotine exposure and subsequently increase the risk of anxiety-related behaviour in later life (Jobson et al., 2019). Adolescent exposure has selectively been found to result in hyperactivity of DA in the ventral tegmental area and PFC neuronal activity states (Jobson et al., 2019). Key future directions will involve investigating whether mid-adolescence is a specific vulnerability period in adolescence, examining whether there are sex effects in this association and to further delineate the underlying brain mechanisms that may be contributing to the increased risk of anxiety-related behaviour after mid-adolescent nicotine exposure.

3.3.2. Craving

Drug craving plays a central role in addiction. While the definition of craving is often disputed, there is consensus about craving being a neurocognitive emotional-motivational response to a vast array of cues, which can range from internal and external environments, and particularly to drug-related stimuli (Ekhtiari and Paulus, 2016). Smoking-related stimuli have repeatedly been shown to induce craving on a physiological, neural and subjective level (Betts et al., 2021; Cui et al., 2012; Lin et al., 2020), which has also been associated with the severity of nicotine addiction (Lin et al., 2020; Vollstädt-Klein et al., 2011).

One study investigated nicotine craving in rodents (Funk et al., 2016). Funk and colleagues (2016) used standard self-administration chambers equipped with a house light and both active and inactive levers. Rats were trained to self-administer nicotine. Active lever presses were reinforced with a nicotine infusion and a concurrent auditory (2900HZ, 1 s) and visual (light, 30 s) cue. The rats were subsequently tested for cue-evoked responding in extinction (non-reinforced) sessions after one, seven, 14, and 28 days of withdrawal. Active lever presses during extinction testing were operationalised as a measure of cue-induced drug-seeking behaviour and thus indicative of craving (Venniro et al., 2016). Both age groups showed cue-induced drug-seeking behaviour that increased with longer withdrawal duration. This effect was more pronounced in adult-exposed rats compared to adolescent-exposed rats. This suggests withdrawal-induced craving is higher when exposed to nicotine during adulthood. Interestingly, within the same study, incubated nicotine seeking on withdrawal day 14 was associated with increased neuronal activity in the amygdala, NAc, mPFC and OFC across both age groups. Moreover, inactivation of nicotine-cue-activated Fos-expressing neurons in the central nucleus of the amygdala resulted in decreased incubation of nicotine seeking in adult-exposed rats. This suggests a causal role of the central nucleus of

the amygdala in the incubation of nicotine craving in adult rats. However, as the current findings are based on the outcomes of one study, future replication studies are required to corroborate the findings.

3.4. Animal studies: brain outcomes

3.4.1. Neurotransmitter systems: glutamate

Glutamate is the brain's main excitatory neurotransmitter. Evidence suggests the glutamatergic system plays a critical role in the incentive motivational properties of nicotine, alongside several other aspects of nicotine addiction (Liechti and Markou, 2008). The actions of glutamate are mediated by metabotropic (mGluR) and ionotropic (iGluR) glutamate receptors (Kew and Kemp, 2005). In particular, the mGluR5 receptor regulates synaptic plasticity of several mesocorticolimbic regions (Niu et al., 2020). Drug-evoked changes in synaptic plasticity have frequently been reported in regions including the nucleus accumbens (NAc) and are suggested to contribute to the aetiology of addiction (Lüscher and Malenka, 2011).

Two studies investigated levels of glutamate receptors (Adriani et al., 2004; Yang et al., 2021). After seven days of exposure to nicotine (0.5 mg/kg/day), membrane expression of mGluR5 in NAc GABA medium spiny neurons was higher in adult rats compared to adolescents and relative to the respective age-matched controls (Yang et al., 2021). Another study reported reduced levels of GluR2/3 subunits in the striatum and hippocampus of adolescent mice compared to all other groups 60 days post nicotine dosing (Adriani et al., 2004). In the striatum, nicotine increased levels of GluR2/3 subunits in adults relative to age-matched controls, but there was no effect of nicotine on GluR2/3 levels in the hippocampus. Overall, it appears that both adolescents and adults are sensitive to the effects of nicotine on levels of glutamate receptors, but there are subtle regional differences across the age groups. Nicotine-induced age-dependent differences in mGluR5 expression are specifically observed on the NAc membrane, and adults are more sensitive to the effects of nicotine on glutamate expression. In contrast, nicotine-induced reductions in levels of GluR2/3 subunits in the striatum and hippocampus appear to be more prominent in adolescent-exposed mice, suggesting increased sensitivity to nicotine modulation of GluR2/3 in adolescence compared to in adulthood. Across studies, the brain region and type of glutamate subunit investigated varied, which hampers the comparison of findings across studies. Nevertheless, the findings suggest there are differing adaptations of neural mechanisms depending on whether exposure takes place during adolescence or adulthood, which may result in opposing effects on the risk of the development of nicotine addiction (Adriani et al., 2004). In terms of GluR2/3 modulation, adolescent animals showed increased sensitivity compared to adults. There is accumulating evidence to suggest that mGluR2/3 subunits play a critical role in different aspects of nicotine addiction. In fact, mGluR2/3 has in recent years been proposed as a potential therapeutic target for smoking cessation (see Cross et al., 2018 for a review). This may suggest that nicotine exposure during adolescence could increase the risk of nicotine addiction due to the increased sensitivity of the modulation of this subtype of glutamate receptor. It will be important for future studies to address this and to evaluate how the modulation of glutamatergic neurotransmission is altered across the brain regions of the mesolimbic dopaminergic pathway, with the inclusion of more subtypes of glutamate receptors.

3.4.2. Dopamine

Dopamine (DA) is a neurotransmitter known to play a critical role in the reinforcing effects of drugs of abuse, such as nicotine, and has been suggested to trigger the neurobiological changes associated with addiction (Volkow et al., 2007). The mesolimbic dopaminergic system consists of DA neurons in the midbrain, including the ventral tegmental area (VTA), that project to the prefrontal cortex (PFC) and striatal regions, including the NAc. DA mediates its actions via DA receptors, including the DRD1 (D1 and D5) and DRD2 (D2, D3 and D4) subtypes,

which are abundantly expressed in these regions.

Two studies investigated nicotine-induced changes in DA levels (Dao et al., 2011) and receptor-related mRNA expression (Smith et al., 2015). Daily injections with nicotine resulted in increased DRD1 mRNA expression in the NAc shell and core, olfactory tubule, islands of Calleja, and dorsal striatum of adolescent nicotine exposed rats compared to their adult counterparts and age-matched controls (Smith et al., 2015). No age-related differences in DRD2, DRD3, D3nf mRNA or DRD3:D3nf mRNA ratio were observed. DRD1 antagonists have previously been found to reduce the development of conditioned place preference for nicotine (Acquas et al., 1989), which suggests the nicotine-induced enhanced DRD1 mRNA expression present during adolescence may relate to the elevated reinforcement value of nicotine found in this age group (Ostadali et al., 2004).

A second study investigated DA levels in the PFC, NAc, BLA and DS in rats 24 h after receiving two daily doses of nicotine across four consecutive days (Dao et al., 2011). Nicotine enhanced DA levels in the NAc, although this effect was not age-dependent and no age-related differences were found in the PFC, BLA or DS. Integrating the two studies, while nicotine exposure increased DRD1 mRNA expression in different regions in adolescence, it increased DA levels in the NAc regardless of age. The NAc appears to be sensitive to the effects of nicotine, more so than other regions of the limbic system. Both studies investigated the effects of nicotine 24 h after the last dosing. For future studies, it would be insightful to investigate longer withdrawal periods to establish the long-term effects of nicotine on levels of DA and DA receptor-related mRNAs.

3.4.3. Serotonergic function

5-hydroxytryptamine (5HT) or serotonin is a neurotransmitter that is known to contribute to the maintenance of synaptic plasticity (Crispino et al., 2020), and both reinforcement and incentive motivational processes (Roiser et al., 2006). The serotonergic system is of critical importance not only for the establishment of drug-use associated behaviours but also for the development and maintenance of addiction (see Müller and Homberg, 2015 for a review).

One study investigated serotonergic function after nicotine exposure (Dao et al., 2011).

This study investigated 5-HT levels in the PFC, NAc, BLA and DS in rats 24 h after receiving two daily doses of nicotine across four consecutive days (Dao et al., 2011). 5-HT levels in the BLA were increased in adolescent-exposed rats compared to adult-exposed rats and age-matched controls, whilst no age differences were found in the PFC, DS or NAc. Increased regional serotonin transporter (SERT) binding in the PFC, BLA and DS was also observed in adolescent-exposed rats compared to adult-exposed and age-matched controls, but not within the NAc. This suggests that exposure to nicotine in adolescence affects normative 5-HT function by inducing changes in 5-HT levels within the limbic system in the short term, however, this is dependent on the brain region in question. The release of 5-HT has previously been found to mediate the nicotine enhancement of initial drug-self administration in adolescence (Larsson et al., 1990), placing adolescents at increased vulnerability to engage in risky behaviour such as drug-taking. In future studies it will be important to establish the role of serotonergic neurotransmission across the different brain regions and to evaluate the long-term effects of nicotine on both serotonin functioning and subsequent vulnerability to risky behaviours.

3.4.4. Nitric oxide

The nitric system has been shown to play a pivotal role in addiction (Uzay and Oglesby, 2001). Inhibition of nitric oxide (NO) synthase has previously been found to attenuate signs of withdrawal from nicotine (Malin et al., 1998).

One study investigated levels of nitric oxide metabolites in the frontal cortex, hippocampus and amygdala of rats given free access to nicotine (10 mg/L) across six weeks for adult-exposed rats or 12 weeks

for adolescent-exposed rats (Keser et al., 2013). Higher levels of nitric oxide were found in the frontal cortex of adolescent-exposed compared to adult-exposed rats and relative to age-matched controls (Keser et al., 2013). Conversely, in the amygdala levels of nitric oxide were generally higher in adult rats regardless of nicotine exposure, and there were no effects of nicotine on nitric oxide levels in either age group. Further, no differences in levels of nitric oxide metabolites were found in the hippocampus between adolescent and adult exposed rats relative to age-matched controls. This suggests adolescent nicotine exposure has lasting effects on NO synthesis specifically in the frontal cortex. However, these findings should be treated with caution as the duration of exposure to nicotine varied across age groups, which could explain the observed differences. Future studies incorporating a similar length of nicotine exposure across age groups will help to elucidate whether the differences found are due to age effects or length of exposure.

3.4.5. Nicotinic acetylcholinergic receptors (nAChRs)

Nicotine acts on nAChRs comprised of hetero- or homo-complexes of β and α subunits. Exposure to nicotine has repeatedly been shown to increase levels of nAChRs (Moretti et al., 2010), particularly the $\alpha 4\beta 2$ and $\alpha 7$ subtypes which are suggested to contribute to nicotine-induced reward and reinforcement (Albuquerque et al., 2009).

Seven studies investigated the effect of tobacco smoke and/or nicotine exposure on levels of nAChRs binding, showing mixed results (Cano et al., 2020; Counotte et al., 2012; Doura et al., 2008; Hoegberg et al., 2015; Kota et al., 2009; Levin et al., 2007; Trauth et al., 1999).

Ten days of exposure to cigarette smoke extract and nicotine led to the upregulation of $\alpha 4\beta 2$ binding in the medial amygdala and substantia nigra (SN) in adolescent exposed rats compared to all other groups tested (Cano et al., 2020). In contrast, more prolonged 14-day exposure to a higher dose of nicotine (6 mg/kg/day) resulted in the upregulation of $\alpha 4\beta 2$ * binding in 35 brain regions, including the forebrain regions and hippocampus and cerebral cortex in adult exposed rats compared to all other groups tested (Doura et al., 2008). A similar treatment regime also led to the upregulation of $\alpha 4\beta 2$ * binding in the cerebral cortex in a sample of late-adolescent and adult female rats compared to early-adolescent rats and relative to age-matched controls, as well as upregulation in early, late and adult-exposed male rats relative to their age-matched controls (Hoegberg et al., 2015). By contrast, four weeks of exposure to a low concentration of nicotine (0.03 mg/kg) increased $\alpha 4\beta 2$ * binding in the midbrain and striatum of adolescent-exposed rats as compared to all other groups, and no effects of nicotine were found in the hippocampus nor were there age-related differences (Levin et al., 2007). Overall, these findings suggest that prolonged exposure to nicotine, specifically across late adolescence and adulthood, leads to increased $\alpha 4\beta 2$ * nAChR binding across several brain regions.

For $\alpha 7$ binding, a selective upregulation was observed in the hypothalamus for adolescent nicotine exposure (Cano et al., 2020), while Doura et al. (2008) reported a selective downregulation of $\alpha 7$ binding in the anterior hypothalamus, along with in the bed nucleus stria terminalis, dentate gyrus and hippocampus in adolescent-exposed rats (Doura et al., 2008). These contrasting findings may be related to the differences in dose and route of administration: Cano et al. (2020) administered nicotine intravenously (1.5 mg/kg) while Doura et al. (2008) delivered nicotine via osmotic pumps (6 mg/kg). A previous study has shown that the regulation of nicotinic acetylcholine receptors depends on the temporal pattern of nicotine exposure (Semenova et al., 2018). As such, it is conceivable that the different treatment regimes may explain the differing findings. Further, $\alpha 7$ binding was higher in the basolateral, central, and medial amygdala (Cano et al., 2020), and frontal visual cortices (Doura et al., 2008) of adolescent-exposed rats compared to all other groups tested.

Downregulation of $\alpha 6$ * was found in the caudal striatum, medial habenula, VTA, SN and lateral geniculate of adolescent exposed rats compared to all other groups tested (Doura et al., 2008). Whilst no effects of age or nicotine in the regulation of $\alpha 3\beta 4$ nAChR binding in the

amygdala and hippocampus (Cano et al., 2020) or $\alpha 5$ -containing nAChRs in the cerebral cortex were apparent (Hoegberg et al., 2015). Overall, these findings suggest upregulation of nAChR binding is dependent on the length and age of first exposure to nicotine and is specific to certain receptor subtypes of nAChRs and brain regions.

Whilst the stated studies provide evidence of differential regulation of nAChRs binding immediately after nicotine exposure, it is important to establish whether these effects are persistent. Three studies investigated the regulation of nAChRs binding four (Trauth et al., 1999), five (Counotte et al., 2012) and seven weeks after cessation of nicotine exposure (Kota et al., 2009). ^3H -Epi-binding in the mPFC was found to be upregulated 24 h after the last of 10 injections of nicotine in adolescent-exposed rats compared to adult-exposed and relative to age-matched controls (Counotte et al., 2012). Interestingly, five weeks later there was no longer an age-dependent effect of nicotine treatment in the mPFC. These findings were mirrored by the acute upregulation of $\alpha 4\beta 2$ * binding in the mPFC of adolescent rats, which also diminished five weeks later. No age effects were found in $\alpha 7$ binding in the mPFC or occipital cortex 24 h or five weeks after nicotine dosing. NACHR functioning in the ventral striatum, PFC, thalamus, and hippocampus was found to be elevated seven weeks after adolescent mice had been exposed to nicotine for seven days when compared to mice exposed to nicotine in adulthood and relative to age-matched controls (Kota et al., 2009).

Similarly, fourteen days of nicotine exposure increased $\alpha 4\beta 2$ * binding in the hippocampus of adolescent-exposed rats compared to age-matched controls when tested immediately after exposure, although compared to adult-exposed rats binding was reduced (Trauth et al., 1999). When the same rats were tested 5 days after exposure adolescent-exposed rats showed increased binding, whereas 15 days later they showed reduced binding compared to all other groups tested. Four weeks after nicotine dosing, adolescent-exposed males showed increased binding whereas adolescent-exposed females showed reduced binding compared to all other groups tested. Nicotine exposure also increased $\alpha 4\beta 2$ * binding in the midbrain and cerebral cortex in adolescent-exposed rats compared to all other groups when tested immediately, one, five and 15 days after treatment with nicotine. However, when tested at 4 weeks upregulation was found in the midbrain of adolescent-exposed male rats, whereas downregulation was found in adolescent-exposed female rats. And, both males and female nicotine-exposed rats were found to show increased binding compared to adult-exposed rats. Also, when the rats were tested at 4 weeks after nicotine treatment increased $\alpha 4\beta 2$ * binding was present in the cerebral cortex of adolescent-exposed rats compared to their age-matched controls.

This provided mixed findings for the effects of nicotine exposure during adolescence; whilst effects are acute in the mPFC, elevated nAChR functioning in several reward-related brain regions were present well into adulthood. The $\alpha 4\beta 2$ receptor has been found to contribute to both nicotine-induced reward and reinforcement (Albuquerque et al., 2009). Across studies, both adolescent and adult exposure to nicotine (Trauth et al., 1999; Levin et al., 2007; Kota et al., 2009) or CSE (Cano et al., 2020) induced the upregulation of $\alpha 4\beta 2$ binding in several reward-related regions immediately after dosing. One study included a sample of early and late adolescent rats and found increased binding in late adolescent exposed rats compared to early adolescent exposed rats (Hoegberg et al., 2015). This suggests late adolescent rats are more sensitive to the effects of nicotine on $\alpha 4\beta 2$ binding. When investigating the effect of abstinence on $\alpha 4\beta 2$ binding, altered binding was found in the hippocampus, midbrain, and cerebral cortex up to 15 days after last exposure (Trauth et al., 1999). After 4 weeks, sex differences emerge in adolescent specific sensitivity to the effects of nicotine on $\alpha 4\beta 2$ binding (Trauth et al., 1999). Taken together, whilst the effects of dosing appear to lead to widespread changes across late adolescence and adulthood, the long-term effects appear to be more pronounced in adolescent-exposed rodents. It should be noted that receptor

functionality is not assessed with the current study designs. When receptors are continually stimulated the nAChRs desensitize (Buccafusco et al., 2009), which opens the possibility that the differences observed across age groups could be related to the rate of desensitization. Future studies will need to address this issue. Several studies have started to evaluate the functional consequences of the up/down regulation observed in $\alpha 4\beta 2$ binding. For example, Counotte and colleagues observed nicotine-induced increased $\alpha 4\beta 2$ binding and increased GABAergic transmission in the mPFC, suggesting the change in regulation of nAChRs may initiate a cascade of events which lead to long-term adaptations on a systems level (Counotte et al., 2012) resulting in increased sensitivity in adolescents (Schramm-Sapota et al., 2009). In line with this, Kota et al. (2009) observed enhanced sensitivity to the rewarding effects of nicotine as measured with CPP, which was correlated with long-lasting increases in nAChR binding (Kota et al., 2009). Future studies investigating the functional consequences of adolescent nicotine induced nAChR upregulation will play a critical role in understanding the increased sensitivity to nicotine in adolescence.

There were limited studies that investigated other acetylcholine receptor subtypes, which highlights an area for future research. Of particular interest in this respect is the $\alpha 7$ subtype, based on its role played in nicotine reward and reinforcement (Albuquerque et al., 2009). Across two studies, $\alpha 7$ binding was altered after adolescent exposure in several reward-related regions when tested after last dosing of nicotine (Doura et al., 2008) and CSE (Cao et al., 2020), although effects did not persist in the mPFC or occipital cortex (Counotte et al., 2012). The upregulation was found within regions which play a role in mediating the shift to negative reinforcement, which is characteristic of nicotine dependence (Antolin-Fontes et al., 2015). Future studies should investigate other subtypes such as $\alpha 7$ and administer CSE over nicotine alone as upregulation was elevated compared to nicotine treatment (Cano et al., 2020). Together, the findings suggest that tobacco and its constituents dysregulate nAChR binding both in the short and long-term, but the level of dysregulation is dependent on the age and length of exposure, the specific brain region and receptor subtype.

3.5. Neuromodulatory & neurodevelopmental processes

3.5.1. Structural plasticity

Repeated exposure to drugs of abuse, including nicotine, has consistently been shown to alter the dendritic morphology of several neurons located in brain regions associated with reward and incentive motivation, such as the NAc, and regions involved with inhibitory control, including the PFC (Robinson and Kolb, 2004). These modifications extend well past drug exposure, which suggests they may be associated with symptoms characteristic of addiction, such as maladaptive decision-making, craving and lack of inhibitory control (DePoy and Gourley, 2015).

Three studies investigated aspects of dendritic remodelling (McDonald et al., 2007; Bergstrom et al., 2008, 2010). McDonald and colleagues (2007) administered nicotine to rats, followed with an openfield test and nicotine challenge 30 days after chronic dosing, and rats were subsequently sacrificed after 7 days abstinence (McDonald et al., 2007). Adolescent-exposed rats were found to have greater total dendritic length of medium spiny neurons compared to all other groups tested. Nicotine increased the branch number of medium spiny neurons in adolescent exposed rats only compared to their age-matched controls. Adults generally possessed significantly more branches on medium spiny neurons regardless of nicotine exposure. The total dendritic length and branch length of large aspiny neurons did not differ after nicotine exposure in both age groups, and there were no differences between pre-treated age groups. A second study with a similar treatment regime found nicotine increased the total basilar length of complex pyramidal neurons in layer V of the prelimbic cortex of adolescent-exposed rats compared to age-matched controls, whereas there was no effect of nicotine on adult-exposed rats (Bergstrom et al., 2008). The total basilar

length and branch numbers of simple pyramidal neurons were found to be increased in adult-exposed rats only, compared to all other groups tested. By contrast, no effects of nicotine were found on the total apical length or branch number of simple or complex pyramidal neurons, nor were there age effects on these measures.

Extending abstinence to 20 days in a subsequent study in rats exposed to nicotine during adulthood, basilar dendrites in the right hemisphere of the basolateral amygdala had a greater total length and bifurcations relative to the left hemisphere and compared to rats exposed to nicotine during adolescence and relative to age-matched controls (Bergstrom et al., 2010). The complexity of the apical tree of principal neurons in the basolateral amygdala was reduced in both rats exposed to nicotine during adolescence or adulthood, relative to age-matched controls. No differences in dendritic morphology of pyramidal neurons in the infralimbic cortex were found in both age groups, as compared to age-matched controls.

Taken together, these findings suggest that nicotine-induced dendritic remodelling within brain regions of the corticolimbic system is both neuron subtype-specific and age-dependent. Specifically, exposure to nicotine during adolescence resulted in higher plasticity of the medium spiny neurons of the NAc (McDonald et al., 2007) and complex cells found in pyramidal neurons of the prelimbic cortex (Bergstrom et al., 2008) suggesting greater nicotine-induced structural plasticity during adolescence. These findings were consistent when tested after seven days of abstinence. Although, when abstinence was extended to 20 days, there were no effects of nicotine on dendritic morphology of pyramidal neurons in the infralimbic cortex (Bergstrom et al., 2010). Across studies, both the route and length of nicotine exposure, as well as the brain region of interest differed, which may explain the conflicting findings. Nevertheless, there appears to be maladaptive rewiring across the mesolimbic dopamine pathway when exposure to nicotine takes place during adolescence. The evidence suggests that medium spiny neurons with increased dendritic length show heightened sensitivity to dopamine-dependent modulation of glutamatergic signalling (Hernández-Echeagaray et al., 2004) and have been associated with increased behavioural activity during subsequent nicotine challenges (McDonald et al., 2007). Adult nicotine exposure also increased plasticity of the simple pyramidal neurons of the prelimbic cortex (Bergstrom et al., 2008), and basilar dendrites of the basolateral amygdala (Bergstrom et al., 2010), which was consistent across both seven and 20 days of abstinence. Taken together, these data suggest there is elevated nicotine-induced neuroplasticity across both age groups. The development of the amygdala has been suggested to extend into young adulthood (Koshibu et al., 2004), which may explain why changes were evident in this region in rodents exposed to nicotine during adulthood. Across the studies, nicotine-induced structural plasticity was altered across age groups, but this was both region and cell-dependent. Future studies will need to address this, particularly when investigating the mPFC, as different cortices were found to show differential changes after nicotine exposure. Whilst evidence of the functional consequences of dendritic remodelling is emerging (McDonald et al., 2007), it will be important to establish how nicotine-induced neuroplasticity within these regions effects behaviour.

3.5.2. Transcription factors

Transcription factors are proteins that control gene expression levels by binding to the promoter region of target genes. Several transcription factors including cAMP response element-binding proteins (CREB) and fos family proteins have been implicated in aspects of the addiction phenotype (Nestler, 2012). C-fos, fosB and deltafosB are immediate early genes and are considered an indirect marker of brain activity (Gallo et al., 2018). Cigarette smoking has consistently been found to induce c-fos expression in several brain regions including the striatum, hippocampus, amygdala, and VTA, all known to play a role in nicotine reinforcement (Sherafat et al., 2021).

Four studies investigated fos expression with mixed findings (Alajaji

et al., 2016; Cao et al., 2007; Dao et al., 2011; Funk et al., 2016). Cao and colleagues (2007) found increased c-fos expression in the paraventricular nucleus of the thalamus in nicotine (+/- acetaldehyde) adolescent-exposed rats compared to their adult counterparts and age-matched controls when tested 30 min after dosing. Whereas, in the hypothalamic paraventricular nucleus elevated c-fos expression was present in the adult-exposed rats compared to all other groups tested. No age differences were found in the bed nucleus of the stria terminalis, central nucleus of the amygdala, NAc or superior colliculus. As no age effects were found, age groups were combined, and a significant effect of nicotine was found on c-fos expression within these regions.

Testing 30 min after the last dosage of a four day exposure paradigm, adolescent rats did show elevated levels of c-fos expression in the NAc shell compared to their adult counterparts and relative to age-matched controls (Dao et al., 2011). No age differences in c-fos expression in the PFC or basolateral amygdala were found. However, nicotine exposure did increase c-fos expression in the basolateral amygdala of both age groups compared to age-matched controls. Testing one day after a more prolonged seven day exposure increased levels of deltafosB expression in the NAc of early adolescent-exposed mice compared to all other groups tested (Alajaji et al., 2016). This suggests nicotine induces fos expression in the NAc in rodents specifically exposed to nicotine during adolescence, but only when this exposure is prolonged. In contrast, 12 days of self-administration did not result in age-related differences in the NAc core or shell, and no differences were found in the ventral mPFC, OFC, and central and basolateral amygdala of male rats when tested both one and 14 days after the last day of access to nicotine (Funk et al., 2016). Age-related differences were present in the dorsal mPFC with adult-exposed rats showing elevated fosB expression, compared to adolescent-exposed rats and relative to age-matched controls (Funk et al., 2016).

It appears nicotine's effects on fos expression are complex and both age and region-dependent. The conflicting findings could be partly due to the mode of administration, length of exposure, or specific brain regions that were analysed. Across two studies, chronic nicotine exposure during early adolescence (PND28 <) resulted in elevated c-fos (Dao et al., 2011) and deltafos-B (Alajaji et al., 2016) expression in the NAc when tested 24 h after last dosing. By contrast, no effect was found when dosing commenced on PND 40. This suggests early adolescents show increased sensitivity to the effects of nicotine on gene transcription in the NAc. Future studies should include rodents at varying stages of development i.e., early to late adolescence to capture whether nicotine-induced gene transcription alterations take place during selective vulnerability periods. The functional consequences of elevated fos expression have been investigated in several studies, with elevated deltafos-B associated with enhanced CPP after early adolescent nicotine exposure (Alajaji et al., 2016). Deltafos-B is degraded after 1–2 months which suggests it may initiate a cascade of events rather than maintain drug dependence. It is plausible that deltafos-B alters the expression of target genes known to play a role in addiction, such as the dynorphin gene, which has been shown to be involved in the rewarding effects of nicotine (Nestler, 2008). Elevated deltafos-B expression in the NAc has also been associated with incubated nicotine seeking in both adolescent and adult exposed rats (Funk et al., 2016), suggesting a role in the incubation of nicotine craving across age groups. Future studies following a similar methodology will be important to fully elucidate the effects of nicotine on fos expression as well as incorporating methods which can unravel the direction of the functional effects.

3.5.3. mRNA expression (transcriptome)

Converging evidence suggests moderate to high genetic influences on nicotine addiction with heritability rates estimated to be ~50% (Giannoulis et al., 2021). A vast amount of human and preclinical studies have been conducted to understand how drugs of abuse, such as nicotine, alter gene expression profiles, and thereby impact the development and maintenance of addiction (Zhou et al., 2014).

One study investigated mRNA expression levels in the rat VTA (Doura et al., 2010). Nicotine exposure led to changes in gene expression with distinct temporal expression patterns, which were referred to as transient (initially upregulated or downregulated but returned to baseline after 30 days abstinence), persistent (persistently upregulated or downregulated across treatment and abstinence) and late (upregulated or downregulated after 30 days abstinence) response genes. Results revealed 80 adolescent versus 171 adult transient genes, 62 adolescent versus 33 adult persistent genes, and 532 adolescent versus 101 adult-specific late genes. Pathway analyses revealed that the adolescent-specific genes formed a much more interacted network when compared to the adult-specific genes, with adolescent-specific mRNA representing genes being involved in long-term potentiation, neuronal structure and function, and several psychological disorder related pathways. Also, the effects of nicotine appear to involve predominant changes in mRNA expression in adult exposed rats, whereas more long-term changes were found in adolescent exposed rats. In sum, this suggests that adolescents are more vulnerable to the effects of nicotine on long-term changes in gene expression within the brain's reward system. Further studies are warranted to establish how the processes regulated by the implicated genes may result in changes in the adolescent brain which may persist into adulthood, increasing the risk of later drug use and dependence.

3.5.4. Adenylyl cyclase cell signalling

Adenylyl cyclase (AC) is an enzyme which mediates cell signalling, specifically being responsible for the conversion of adenosine triphosphate (ATP) into cyclic adenosine monophosphate (AMP). Nicotine has been found to induce changes in cell signalling cascades such as the AC pathway, which is a pathway that has been linked to both aspects of drug addiction and withdrawal (Abreu-Villaça et al., 2003).

One study investigated AC cell signalling (Slotkin et al., 2008). Adult nicotine exposure resulted in an immediate increase in basal AC activity in the cerebral cortex, brainstem and cerebellum compared to age-matched controls. As the immediate effects of adolescent exposure and withdrawal (PND 45–75) were not assessed, comparisons to the adult-exposed rats were not performed. The long-term effects of exposure to nicotine in adolescence resulted in larger and more widespread changes in basal AC activity within the cerebellum, brainstem, and cerebral cortex, with deficits first emerging in early adulthood. The long-term effects of nicotine in adulthood mirrored the findings for adolescent exposure, although the effects were not as pronounced and not significant compared to age-matched controls. The AC response to forskolin showed a similar pattern, with an increase in the forskolin response in the cerebellum, brainstem, and cerebral cortex of adult-exposed rats during treatment and at the onset of withdrawal, compared to age-matched controls. However, by the first week of withdrawal (PND 110), no significant differences were observed anymore. A significant, but transient increase in AC response to forskolin was found for adolescent-exposed rats compared to adult-exposed rats and age-matched controls. The long-term effects of nicotine on adult-exposed rodents mirrored the findings in adolescent-exposed rodents, although less pronounced. These findings suggest that adolescent compared to adult nicotine exposure, to a greater extent leads to long term deficits in heterologous mechanisms at several different points in the AC pathway across three different brain regions. As AC mediates cell signalling, the findings suggest exposure to nicotine during adolescence could result in long-term changes in the function of multiple neurotransmitters pathways and brain circuits relevant for the development and maintenance of nicotine addiction (Abreu-Villaça et al., 2003). A critical future direction will be to investigate whether the disruption in cell signalling found after adolescent nicotine exposure can be related to functional/ behavioural changes relevant for addiction.

3.6. Human studies

Five studies investigated the age-related effects of cigarette/tobacco smoke on several aspects of cognition including sensation seeking, impulse control, delay discounting, memory, concentration, learning, and craving. Sensation seeking is the tendency to seek intense and novel experiences and sensations (Zuckerman, 1994), and has frequently been shown to be associated with the functioning of the dopaminergic system (Norbury and Husain, 2015). Impulse control involves the ability to regulate one's behaviour to fulfil long-term goals, of which the PFC has been found to play a prominent role (Sebastian et al., 2014). High levels of sensation seeking and reduced impulse control have frequently been associated with addiction, both as a determinant and consequence of substance use (Blanchard et al., 2009; de Wit, 2009).

One study examined age-varying associations between cigarette smoking, impulse control, and sensation-seeking (Lyndon-Staley and Geier, 2018). Using data provided by the National Longitudinal Study of Adolescent to Adult Health they examined adolescents from the ages of 12–33 across three waves of data. Within the sample, the odds ratio (OR) of any smoking in the past 30 days peaked during late adolescence: at 12.5 years (OR=0.16), 18 years (OR=0.84), 22.54 years (OR=0.68), 27.91 years (OR=0.90) and at 32.41 years (OR=0.71). The odds of daily smoking were 0.03 for 12.67 years and 0.53 at 23.40 years. Moreover, this study reported the strongest association between smoking behaviours (daily cigarette smoking or any smoking in the previous 30 days) and sensation-seeking during adolescence compared to adulthood.

The association between impulse control and smoking behaviours were found to be significant across adolescence and young adulthood, although the association was strongest in the late-20 s and early 30 s. This suggests that sensation-seeking peaks during adolescence, which is in line with developmental models (Casey et al., 2011), and makes adolescents more susceptible to pursuing risky behaviours such as smoking. Whether sensation seeking is a prerequisite to initiating smoking or whether smoking increases sensation seeking during this critical age period cannot be deciphered with the statistical design. Further, the self-report scale used to measure sensation seeking was a one-item measure, limiting the validity of the findings. The findings also suggest that levels of impulse control and smoking are associated across both adolescence and adulthood but may be particularly important during young adulthood relative to adolescence. Impulse control plays a role in the initiation and maintenance of drug use across adolescence and adulthood (Perry and Carroll, 2008). However, the same holds as for the association between smoking and sensation seeking; whether smoking alters impulse control or vice versa cannot be disentangled with the methodological design.

Delay discounting provides an assessment of the extent to which the subjective value of a commodity reduces as a function of its delay in attainment. Paradigms investigating delay discounting involve measuring the tendency of individuals to select smaller immediate rewards over a delayed larger reward. Elevated delay discounting has frequently been associated with addiction severity (Amlung et al., 2017).

One study investigated age-related differences in the effects of cigarette smoking on delay discounting (Reynolds, 2004). Young adult smokers (average of 21 cigarettes per day) were found to discount more compared to both adolescent smokers (average of 7 cigarettes per day) and young-adult non-smokers, who reported no previous use of cigarettes. This suggests that cigarette use during young adulthood increases the preference for smaller immediate rewards as compared to cigarette smoking in adolescence. However, the differences across age groups could be due to the length and severity of exposure to tobacco and its constituents; adult smokers reported smoking 21 cigarettes per day for an average of five years whilst adolescent smokers reported smoking seven cigarettes per day for an average of two years prior to participation.

One study investigated the age-related effects of cigarette smoking

on several aspects of cognitive functioning including memory, concentration, and learning (Brook et al., 2004). This longitudinal study included 749 participants with five waves of data collection, whereby measurements of tobacco use history were recorded through T1 to T5, while measurements of neurobehavioural and cognitive symptoms were recorded only at T5. Specifically, the frequency and length of tobacco use in childhood (T1-T2; M age 5.57–14.05 years), late adolescence (T2-T3; M age 14.05–16.26 years), early 20 s (T3-T4; M age 16.26–22.28 years) and mid 20 s (T4-T5; M age 22.28–26.99 years) were investigated. The percentage of participants who were daily tobacco users peaked during early 20 s: prior to T2 10.28% (n = 77), T2-T3 20.03% (n = 150), T3-T4 36.32% (n = 272) and T4-T5 34.98% (n = 262). Neurobehavioural and cognitive deficits were observed at T5 that were related to daily use of tobacco during adolescence and adulthood, with a stronger association during late adolescence to young adulthood. This suggests that tobacco use during both adolescence and young adulthood impairs aspects of memory, concentration, and learning. Since the study only included self-report measures of cognitive functioning, it would be informative to include more objective task-based measures in future studies.

Smoking-related cues have repeatedly been shown to induce craving on a physiological, neural and subjective level (Betts et al., 2021; Cui et al., 2012; Lin et al., 2020), of which the extent of craving has been associated with the severity of nicotine use and dependence (Lin et al., 2020; Vollstädt-Klein et al., 2011). Two studies investigated age-related differences in cue-induced cigarette craving on both a behavioural and neural level (Do and Galván, 2015, 2016). Adolescent (smoking duration = 16 months) and adult (smoking duration = 71 months) smokers (daily smoking ≥ 6 months; ≥ 5 cigarettes/day) and non-smokers (< 5 cigarettes in lifetime) were presented with either emotionally graphic warning labels relating to smoking or non-graphic labels depicting images of neutral items and no graphic images during an fMRI paradigm and were subsequently asked to rate their desire to smoke. On a behavioural level, baseline craving ratings and craving responses to the graphic smoking-related vs non-graphic neutral warning labels were elevated in smokers compared to non-smokers but did not differ between the age groups. However, over the course of the task, adolescent smokers exhibited a greater craving reduction in response to the graphic smoking-related warning labels as compared to their adult counterparts. On a neural level, the graphic smoking-related warning labels as compared to the non-graphic neutral warning labels elicited increased activation in the right amygdala of adult smokers compared to adolescent smokers. Whereas the non-graphic neutral warning labels compared to the graphic smoking-related labels elicited greater activation in the left putamen of adolescent smokers compared to adult smokers. No age-related differences in activity were found in the bilateral amygdala, bilateral putamen, right caudate, bilateral insula or bilateral dorsolateral PFC when the graphic smoking-related warning labels were presented, compared to the non-graphic neutral warning labels.

A functional connectivity analysis was also performed to investigate changes in connectivity during the presentation of the graphic smoking-related vs non-graphic neutral warning labels. Greater positive functional connectivity was found between the bilateral amygdala and left parietal lobe and between the bilateral insula and both the left mPFC and left caudate in adolescent smokers compared to adult smokers. Further, greater positive functional connectivity was observed between the bilateral insular and right putamen in adult smokers compared to adolescent smokers. Additionally, greater negative functional connectivity was present between the bilateral putamen and right insula in adult smokers compared to adolescent smokers and non-smokers alike. Specifically, among adult smokers, craving was associated with the strengthening of connectivity between frontostriatal (striatum and DLPFC) and frontolimbic (amygdala and DLPFC) regions, such that higher levels of craving led to stronger negative connectivity between subcortical regions and DLPFC. The greater connectivity observed in

adult smokers, which was associated with levels of craving, is suggested to provide further support of greater regulatory strength of the PFC over limbic regions in adulthood (Kober et al., 2010). This effect may only have been found in adult smokers due to differences in the development of functional connectivity between limbic and frontal regions, and thus no effect and relation to craving were found in adolescent smokers.

In the same study, smokers and non-smokers performed a cigarette cue reactivity fMRI task. Initially, whole brain analyses were performed to assess the main effects of smoking-related and neutral cues, of which both cues were found to elicit activation in several frontolimbic regions. Following this, a region of interest approach was applied, focusing on the NAc and DLPFC, regions that have been implicated in craving and undergo major developmental changes during adolescence (Do and Galván, 2016). The smoking versus neutral contrast elicited greater NAc activation in adolescent smokers compared to adult smokers, although there was no difference in craving between the age groups. No age-related differences in DLPFC activation were found. Additionally, activation of the NAc mediated the association between cigarette cue-induced craving and subsequent desire to smoke post scanning specifically within the adolescent smoking group. Furthermore, increased craving in adolescent smokers was associated with functional coupling between cortical and striatal regions. Once more, these findings were not present in adult smokers. Taken together, these findings suggest that adolescent smokers are more responsive to smoking-related stimuli, whereby craving is increased and both activity and functional connectivity of reward-related regions is elevated relative to adult smokers and non-smokers. These findings support developmental models whereby there is an imbalance in the maturation of reward-related and cognitive control brain regions during adolescence (Casey et al., 2008), resulting in increased responses to drug-related stimuli. It should be noted that the adults smoked more cigarettes per day and had longer smoking histories, which may have impacted the findings.

In summary, there were five studies that investigated the age-related effects of cigarette/tobacco smoke on several aspects of cognition. The findings from one study suggests the association between smoking behaviours and sensation seeking peaks during adolescence compared to adulthood, whereas the association between smoking behaviours and impulse control are significant across both adolescence and young adulthood, with the strongest association during the late-20 s to early 30 s (Lydon-Staley and Geier, 2018). This suggests that smoking, and levels of impulse control are related, independent of age of onset. Delay discounting, which provides an index of impulsive behaviour (Amlung et al., 2017), was elevated in young-adult smokers compared to both adolescent smokers and young adult non-smokers (Reynolds, 2004). Whilst the association between smoking and sensation seeking appears to peak during adolescence, impulsive behaviour appears to peak during young-adulthood, and impulse control and smoking appear to be related independent of the age of onset. It should be noted that the two studies were both cross-sectional in design so causality cannot be deciphered. In the one longitudinal study to date, tobacco use during both adolescence and young adulthood impaired aspects of memory, concentration, and learning in adulthood. Craving was higher in human smokers compared to non-smokers but did not differ between adolescent and adult smokers (Do and Galván, 2015, 2016). Findings at the neural level suggest increased adolescent sensitivity, since the NAc mediated the association between cigarette cue-induced craving and the subsequent desire to smoke post-scanning, specifically within the adolescent smoking group.

Whilst the human studies to date provide initial evidence of increased vulnerability to the effects of smoking on aspects of cognition in adolescence, there were limited studies investigating each cognitive domain. Most studies included a cross-sectional design that limits the ability to draw conclusions on causality. This also raises an important issue when comparing adolescent and adult smokers as the length and severity of exposure to tobacco and its constituents can vary, which may drive the differences found between age groups. Whilst animal studies

can help in this regard, it is critical that human studies are also performed to improve the translational value of the findings. More so, longitudinal studies will help to establish how trajectories of use are related to changes in both cognitive and brain-based outcomes and whether adolescence are uniquely susceptible to these effects. To date, there is only one longitudinal study that has investigated whether smoking during different stages of adolescence and adulthood could predict memory and learning deficits in adulthood. Whilst informative, neurobehavioural functioning was only measured via self-report at the last timepoint. In terms of brain-based outcomes there are currently only two studies to date, that have investigated the brain-based mechanisms that may play a role in the changes in behaviour that are present after smoking in adolescence and adulthood. There was also a lack of studies investigating cognitive domains and brain-based outcomes known to play a pivotal role in the vulnerability to addiction, such as cognitive control (Cousijn et al., 2014) and social cognition (Cousijn et al., 2018), and the integrity of the underlying neural networks. Taken together, it will be key for future studies to incorporate longitudinal designs whereby adolescent and adult levels of smoking can be measured over time, and a broader spectrum of cognitive and brain-based outcomes should be investigated, to understand the complex interplay between age, smoking and cognition.

4. Discussion

This systematic review evaluated the evidence to date for age-dependent effects of tobacco smoke and nicotine on cognition and the brain. The findings provide a detailed understanding of the age-dependent effects of nicotine in processes encompassing learning, memory, and reward, and the potential underlying brain mechanisms. However, other cognitive domains remain less investigated. Through the integration of human and animal studies, preliminary evidence suggests there are aspects of risk to the effects of tobacco smoke and nicotine during adolescence specifically. There was limited evidence suggesting adolescents are more resilient to the effects of nicotine or tobacco on neurocognition. Although promising, this systematic review also shed light on the lack of studies and variability of the methodology across available studies when investigating cognitive and brain-based outcomes. Therefore, the conclusions should be treated with caution. Cognitive and brain-based outcomes were predominately investigated independently of one another, which highlights the need for future studies linking brain to behaviour. An extensive evaluation of the most consistent results is discussed below, along with prominent knowledge gaps and potential future directions.

4.1. Limbic structures: fear, learning and anxiety behaviours

Fear-related memory processes and anxiety-related behaviours were extensively studied relative to other cognitive domains. Regarding anxiety, nicotine exposure appears to consistently increase anxiety-related behaviour in adolescents, particularly when exposure takes place during mid-adolescence (Adriani et al., 2004; Elliott et al., 2004; Jobson et al., 2019; Smith et al., 2006; Holliday et al., 2016), although there were sex differences in this effect in one study (Elliott et al., 2004). These findings align with a previous review, which suggested increased anxiety-related behaviour in adolescents (Leslie, 2020), and extend findings by incorporating additional paradigms that measure different aspects of anxiety-related behaviour. The findings of the three studies to investigate the effect of nicotine on fear conditioning are somewhat more mixed. Two studies point to increased fear memory formation in adolescents after nicotine exposure (Jobson et al., 2019; Smith et al., 2006), one study points to reduced fear memory formation in adults (Jobson et al., 2019), and one suggests reduced fear memory formation in adolescents (Holliday et al., 2016).

An array of brain regions, including the amygdala, play a key role in anxiety and fear learning (Forster et al., 2012; Raber et al., 2019). This

review revealed that nicotine caused mixed effects on amygdala-related functioning. Nicotine exposure increased c-fos expression in the amygdala in both age groups (Dao et al., 2011; Cao et al., 2007), whilst no effects of nicotine were found on fosB expression in both age groups (Funk et al., 2016). Nicotine further reduced the complexity of apical tree neurons in both adolescents and adults, while increasing the total length of basilar dendrites in adults (Bergstrom et al., 2010). There were adolescent-selective effects of nicotine exposure in the up-regulation of $\alpha 4\beta 2$ binding in the medial amygdala, and $\alpha 7$ binding in the basolateral, central, and medial amygdala (Cano et al., 2020). Alterations in nAChR signalling in the amygdala have been found to modulate anxiety, with $\alpha 4\beta 2$ and $\alpha 7$ nAChRs subtypes playing the most prominent role (Kutlu and Gould, 2015). Specifically, mice with increased activity of $\alpha 4\beta 2$ * nAChRs showed increased anxiety-like behaviour (Labarca et al., 2001). The amygdala also mediates the shift to both negative reinforcement and negative emotional states during withdrawal, which play a key role in addiction (Koob and Volkow, 2010). The upregulation of both $\alpha 4\beta 2$ and $\alpha 7$ nAChRs in the amygdala in adolescents could place them at increased risk of anxiety-related disorders, and nicotine addiction. Whilst preliminary findings suggest exposure to nicotine during adolescence enhances the development of anxiety-related behaviours, potentially via the involvement of $\alpha 4\beta 2$ * and $\alpha 7$ nAChRs in the amygdala, further studies incorporating both behavioural measures of anxiety-related phenotypes as well as brain-based outcomes will be critical to corroborate these findings.

The hippocampus is also known to play a key role in fear learning and anxiety behaviours (Çalışkan and Stork, 2019). The evidence for age-dependent effects of nicotine on hippocampal functioning is mixed. Similar to the amygdala, no nicotine-induced age-related differences in levels of nitric oxide metabolites were found (Keser et al., 2013), but adolescent nicotine exposure selectively reduced levels of GluR2/3 subunits in the hippocampus (Adriani et al., 2004). Adolescent exposure also led to elevated nAChR functioning (Kota et al., 2009), specifically elevated $\alpha 4\beta 2$ * binding (Trauth et al., 1999). However, this was not replicated by another study (Levin et al., 2007), and adult exposure to nicotine also elevated $\alpha 4\beta 2$ * binding (Doura et al., 2008). Further, adolescent exposure was found to downregulate $\alpha 7$ binding (Doura et al., 2008). The nAChRs subtype $\alpha 4\beta 2$ * localised in the hippocampus is suggested to be critical for the enhancing effects of nicotine on fear learning, more so than the $\alpha 7$ subtype (Davis et al., 2007). Because exposure to nicotine during both adolescence and adulthood upregulated $\alpha 4\beta 2$ * binding, these results imply that nicotine-induced changes in nAChR levels may not explain the age differences in fear learning. However, elevated $\alpha 4\beta 2$ * binding was found in adolescent rats during both nicotine treatment and up to four weeks post-dosing (Trauth et al., 1999), whilst the adult rats were only tested immediately after nicotine dosing (Doura et al., 2008). Future studies investigating the long-term effects of nicotine in adult-exposed rats are needed to shed light on whether $\alpha 4\beta 2$ * binding is upregulated in the long-term in adults as well. Moreover, $\beta 2$ -containing nAChRs in the hippocampus have also been found to modulate the effect of nicotine on anxiety-related disorder symptomatology (Kutlu and Gould, 2015). This suggests once more that the increased anxiety-related behaviour found in adolescents after exposure to nicotine could be modulated by the upregulation of $\alpha 4\beta 2$ * binding. These preliminary findings suggest that exposure to nicotine during adolescence enhances fear learning and anxiety-related behaviours, potentially via the involvement of $\alpha 4\beta 2$ * nAChRs in the hippocampus and amygdala, and additionally the $\alpha 7$ nAChRs in the amygdala. However, further studies incorporating both behavioural measures of fear learning and extinction, anxiety-related phenotypes as well as brain-based outcomes will be critical to corroborate these findings.

Anxiety and fear conditioning paradigms are often used to assess if substances can influence (learned) avoidance behaviours, which intuitively translates well to human substance use (i.e., reduced avoidance would promote escalation of use). In humans, anxiety is seen as an

important comorbidity, being both a risk factor (Moylan et al., 2012) and consequence (Moylan et al., 2013) of smoking. Translating the discussed rodent findings to humans is difficult and to date, the role of age in the link between smoking and anxiety and avoidance behaviours has not been tested in humans. One human study touched upon general non-fear related learning and memory, reporting a stronger association between daily use of tobacco during late adolescence/young adulthood and impaired aspects of memory and learning compared to daily use of tobacco during childhood and early adolescence (Brook et al., 2004). The study only included self-report measures of cognitive functioning, and therefore future studies including more objective task-based measures will be informative.

4.2. Limbic system: reward sensitivity and craving

Heightened reward sensitivity and reduced sensitivity to the aversive effects of tobacco and nicotine have been postulated to put adolescents at increased risk of escalating their cigarette use compared to adults (Lydon-Staley and Geier, 2018; Wilmouth and Spear, 2004). In line with this notion, 12 out of 13 studies investigating CPP point towards increased rewarding effects of nicotine in adolescents compared to adults (Adriani et al., 2006; Ahsan et al., 2014; Belluzzi et al., 2004; Dannenhoffer and Spear, 2016; Kota et al., 2008; Kota et al., 2009; Kota et al., 2011; Shram et al., 2006; Torrella et al., 2004; Torres et al., 2008; Torres et al., 2009; Vastola et al., 2002), which aligns with previous reviews (Leslie, 2020; Yuan et al., 2015). The mesolimbic dopamine brain system plays a key role in modulating the rewarding effects of nicotine (Self, 2004). Mirroring the behavioural findings, greater sensitivity in the limbic reward circuitry was found in adolescents exposed to nicotine compared to when exposure took place in adulthood. Adolescent exposure elevated D1 levels in the NAc to a larger extent than adult exposure (Smith et al., 2015). DRD1 antagonists have been found to reduce the development of CPP for nicotine (Acquas et al., 1989), which suggests the nicotine induced enhanced DRD1 mRNA expression present in adolescent rodents may be related to the elevated reinforcement value of nicotine found in this age group (Ostadali et al., 2004). Additionally, the region-dependent changes in 5-HT levels in the BLA (Dao et al., 2011), increased SERT binding in the BLA, PFC and DS (Dao et al., 2011), greater plasticity of pyramidal neurons in the pre-limbic cortex and medium spiny neurons in the NAc (Bergstrom et al., 2008; McDonald et al., 2007), greater c-fos and deltaFosB expression in the thalamus and NAc and increases in nAChRs in the midbrain, striatum and mPFC (Counotte et al., 2012; Doura et al., 2008; Kota et al., 2008, 2009; Levin et al., 2007; Trauth et al., 1999), have previously been found to mediate the reward processing of nicotine (Bouarab et al., 2019; Hnasko et al., 2007; Kota et al., 2009; Kleijn et al., 2011). These mechanisms could underlie the increased behavioural response to the rewarding effects of nicotine present in adolescents.

In humans, craving and elevated substance cue-induced activity in mesocorticolimbic brain areas are taken as an index of the incentive motivational and reward value of substance use. Human neuroimaging studies showed increased activity in the NAc and functional connectivity between frontostriatal and frontolimbic regions in adolescent smokers compared to adult smokers and non-smokers when presented with smoking-related stimuli (Do and Galván, 2015, 2016). Additionally, activation of the NAc was found to mediate the association between cigarette cue-induced craving and the subsequent desire to smoke post-scanning specifically within the adolescent smoking group. Further, increased craving in adolescent smokers was associated with functional coupling between cortical and striatal regions. Animal studies mirrored these findings. For example, changes in DA and serotonin functioning within mesolimbic brain regions, known to play a role in craving, were altered to a larger extent in adolescent exposed rodents (Dao et al., 2011). Although findings at the neural level suggest that adolescents are more sensitive to the effects of nicotine on craving-related brain activity and functioning, this is not reflected in

findings at the behavioural level in both rats and humans. While craving was generally higher in human smokers compared to non-smokers, it did not differ between adolescent and adult smokers (Do and Galván, 2015, 2016). In addition, in the one study to investigate craving in rats, withdrawal-induced craving was higher in adults (Funk et al., 2016). Longitudinal studies exploring how craving on a neural and subjective level varies across time in adolescent smokers will be informative to establish whether the increased neural activity in adolescence results in increased craving on a behavioural level in adulthood.

4.3. Impulsivity and impulse control

Similar to reward, there were limited studies investigating aspects of impulsivity and impulse control in relation to tobacco and nicotine. In the one animal study to investigate impulsivity, nicotine exposure resulted in increased impulsive action in both adolescents and adult rats (Burton and Fletcher, 2012). Similarly, in a human sample of smokers, associations between impulse control, and any smoking in the previous 30 days, or daily smoking, were significant across adolescence and young adulthood, although the association was strongest during the late-20 s to early 30 s (Lydon-Staley and Geier, 2018). This suggests that smoking and levels of impulse control are related, independent of age of onset. Both the dopamine and serotonin neuromodulatory systems are implicated in impulsivity (Dalley and Roiser, 2012). Nicotine was found to increase DA levels in the NAc regardless of age (Dao et al., 2011), whilst region-dependent changes in 5-HT levels were only found after adolescent-exposure (Dao et al., 2011). Most findings point towards increased impulsivity across both adolescence and adulthood, and this could be due to elevations in DA levels (Sonntag et al., 2014). Delay discounting tasks are generally considered to provide an index of impulsive behaviour (Amlung et al., 2017). Delay discounting was found to be elevated in young-adult smokers compared to both adolescent smokers and young adult non-smokers. However, the study in question consisted of a cross-sectional design including adolescents which reported using seven cigarettes per day, whilst the adult group reported an average of 21 cigarettes per day and no adjustment for covariates were performed. Although measuring a different construct of impulsivity, Burton and Fletcher (2012) found no differences in impulsive action between age groups in rats when the dose and length of exposure to nicotine were controlled. This suggests that the differences in delay discounting between age groups may not have been driven by age of exposure effects (Burton and Fletcher, 2012).

4.4. Translational considerations, limitations, and future directions

Across the limited human studies, the constructs of cognition investigated varied considerably, and only two studies investigated the brain-based mechanisms underlying the behavioural changes within the same participants (Do and Galván, 2015, 2016). Further replication studies are necessary to establish whether the findings hold true. Moreover, the included participants tended to have low to moderate use of cigarettes, and levels of dependence were only formally measured in two studies (Do and Galván, 2015, 2016). Studies including a sample of participants with moderate to high dependence will be informative to establish whether age-dependent effects are present and how they relate to frequency of use and level of dependence. Of the two studies that measured levels of dependence (Do and Galván, 2015, 2016), the number of cigarettes per day and dependence severity differed across the adolescent and adult smokers, although only the number of cigarettes per day significantly differed across groups. This highlights a key limitation of human studies, whereby there is difficulty matching

adolescent and adult groups on amount of use and level of dependence. Levels and length of tobacco use cannot be controlled, and whether environmental factors are at play cannot be elucidated. Animal models offer the potential to overcome these limitations as environmental factors, genetic factors and exposure characteristics can be explicitly controlled (Spanagel, 2017), aiding findings from human studies to understand whether age specific differences exist.

Although informative across the animal studies, like the human studies, there was great variability in terms of the aspects of cognition that were investigated, and brain-related processes involved. In addition, when studies investigated the same cognitive construct or brain process, the mode of administration, length and dose of nicotine exposure varied considerably, along with the method used to elicit a behavioural response and the duration of time before testing commenced. These factors, among others, made it challenging to draw strong conclusions, particularly when integrating behavioural and brain-related outcomes across studies and species.

Nevertheless, adolescent exposure to nicotine does appear to increase fear learning and the risk of suffering from anxiety-related phenotypes, with findings from animal studies consistent on both a behavioural and neural level. There are no human studies that investigated the age-dependent effects of nicotine on fear learning, extinction, avoidance behaviours, or anxiety-related behaviour. Future human research comparing adolescent and adult smokers may shed light on fear learning and anxiety-related behaviours in relation to tobacco and nicotine use in humans.

For animal studies to have enhanced translational value, animal models should mimic human behaviour wherever possible. In the pre-clinical studies to date, nicotine was typically administered in a forced manner, mainly by injection or subcutaneous osmotic minipumps, and only a minority of the studies included free access to voluntarily self-administered nicotine. This highlights a critical limitation as self-administration mirrors human behaviour to a larger extent than forced exposure. However, it should be noted that the time frame of adolescence in rodents is very short, i.e. from postnatal day 25–42 (Spear, 2000), which challenges the use of self-administration protocols as they require longer training periods and access to nicotine than forced exposure protocols. A further limitation is the use of male rats in most studies reviewed. Future studies should also incorporate female samples, particularly because there are known sex differences in the association between exposure to tobacco/nicotine and emotion regulation, impulsivity, CPP and craving (Burton and Fletcher, 2012; Delfino et al., 2001; Perez Diaz et al., 2021). In fact, the limited studies which did include both sexes of rats or mice, revealed age-dependent differences that varied across sexes (Kaser et al., 2013; Trauth et al., 1999). Additionally, comparisons between mice and rats are made somewhat more complex due to the species differences in nicotine metabolism. Mice metabolise nicotine at a faster rate than rats (Matta et al., 2007). Due to this, when comparisons are made between the doses used across different studies with different species of rodents, caution should be taken. When extracting and comparing doses across studies it is critical to evaluate whether doses were reported in free base weight or salt weight as there are large differences between the two forms (Matta et al., 2007). There is also evidence to suggest that rodents respond differently to nicotine based on genetic background. Strain dependent effects have been found to modulate the effect of nicotine on both fear conditioning and anxiety-related behaviour (Portugal et al., 2012; Wilking et al., 2012), suggesting, in addition to the effects of age, genetic variability within species may be also a contributing factor.

Some of the rodent studies point to unique sensitivity periods within adolescence, which are important to further investigate in both rodents

and humans. That is, age-related differences in several studies were found during a specific stage of adolescence i.e., Pre- (PND23–35), Mid- (PND36–48) and Post- (PND49–61), with mid-adolescents displaying heightened vulnerability to the effects of nicotine on anxiety-related behaviour compared to both adult-exposed and pre- and post-adolescent exposed rats (Adriani et al., 2004). Therefore, to capture aspects of risk and resilience to the effects of nicotine on cognition and the brain during development, future studies should include rodents at different stages of adolescence. When comparing the period of adolescence across humans and rodents it becomes somewhat more complex. In humans, adolescence is generally considered to range from 12 to 18 years, although from a neurodevelopmental perspective, the brain is still maturing until the age of 25 (Dumontheil, 2016). Based on rodent cognitive developmental milestones, PNDs 28–42 are considered to mark adolescence (Spear, 2000), although more recent literature suggests early adolescence starts from as early as PND 21 (McCormick and Mathews, 2010). Several studies investigated the effects of nicotine on adolescent rodents from PND 25, hence the current review includes studies with an adolescent group exposed to nicotine during this period (PND 25–42). Due to the ambiguity in defining the span of adolescence in rodents and humans alike, caution should be taken when integrating findings across species.

4.5. Concluding remarks

In conclusion, the findings point to increased vulnerability in adolescence to repeated and long-term effects of nicotine and/or tobacco exposure on several aspects of cognition and the brain mechanisms underlying these processes. The limited human studies and more extensive but heterogeneous animal studies, provide preliminary evidence of the unique effects of tobacco and/or nicotine on processes encompassing learning and memory in adolescence. In particular, adolescents show heightened fear learning and anxiety-related behaviour, both of which may be mediated by the upregulation of $\alpha 4\beta 2^*$ and $\alpha 7$ nAChRs in the amygdala or hippocampus. Similarly, adolescents were found to be more sensitive to the rewarding effects of nicotine and showed increased craving related neural activity and functioning. Moreover, several brain mechanisms that are known to mediate the reward processing of nicotine, such as the expression of DRD1 mRNA and serotonin functioning in the BLA were altered in adolescents only. The limited studies investigating impulsivity, provide preliminary evidence of comparable effects of nicotine and/or tobacco across both age groups. Although promising, this review also shed light on the lack of studies and variability of the methodology performed within these limited studies when investigating cognitive and brain-based outcomes. Cognitive and brain-based outcomes were predominantly investigated independently of one another, which highlights a research gap that still needs to be addressed. Most findings to date were based on animal studies; human research investigating these constructs will be informative to understand whether the findings translate to human behaviour. Studies investigating aspects of resilience to the effects of nicotine or tobacco on neurocognition were largely missing, highlighting an important direction for future research. Overall, this review provided evidence that adolescents are uniquely vulnerable to the effects of nicotine on cognition and the brain and highlighted key future directions that may hold promise. In the future, this knowledge may contribute to the development of preventative interventions against and policies on smoking targeting adolescents.

Conflict of interest statement

The authors have no conflicts to declare.

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Appendix A

See Appendix Tables A1–A5 here.

Table A1

Search syntax from Medline database, last accessed on December 10, 2021.

MedlineOvid MEDLINE ALL, which includes Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily, 1946 to December 10, 2021 #1 Tobacco/cigar smoking/ OR cigarette smoking/ OR electronic nicotine delivery systems/ OR nicotine/ OR smoking/ OR tobacco/ OR tobacco smoking/ OR "tobacco use"/ OR "tobacco use disorder"/ OR (cigaret* OR nicotin* OR smoker* OR smoking OR tobacco).ti,ab,kf.#2 Cognition/attention/ OR cognition/ OR cognitive dysfunction/ OR decision making/ OR executive function/ OR impulsive behavior/ OR inhibition, psychological/ OR memory, long-term/ OR memory, short-term/ OR memory/ OR neural inhibition/ OR neuropsychological tests/ OR neuropsychology/ OR prepulse inhibition/ OR proactive inhibition/ OR reactive inhibition/ OR social cognition/ OR spatial learning/ OR spatial memory/ OR ((attention ADJ3 (difficulties OR measure* OR span OR sustained OR test* OR task* OR reduced)) OR aversion OR behavior* inhibition* OR brain* OR cognit* OR conditioning OR craving OR executive function* OR inhibition task* OR inhibitory control* OR inhibitory process* OR intellectual* function* OR learning OR locomotor OR memory OR neural inhibition* OR neuro* OR prepulse inhibition* OR proactive inhibition* OR processing speed* OR reactive inhibition* OR response inhibition* OR retroactive inhibition*).ti,ab,kf.#3 Age/age factors/ OR (age-related OR age difference* OR age depend* OR (adolesc* ADJ3 adult*)).ti,ab,kf. 1 AND 2 AND 3

Table A2

Search syntax from PsycINFO database, last accessed on December 10, 2021.

PsycINFOovid, APA PsycInfo, 1806 to November Week 5 2021 #1 Tobacco/electronic cigarettes/ OR nicotine/ OR passive smoking/ OR tobacco smoking/ OR "tobacco use disorder"/ OR (cigaret* OR nicotin* OR smoker* OR smoking OR tobacco).ti,ab, id.#2 Cognition/behavioral inhibition/ OR cognitive ability/ OR cognitive assessment/ OR cognitive impairment/ OR cognitive processes/ OR decision making/ OR executive functioning measures/ OR long term memory/ OR "memory and learning measures"/ OR memory/ OR neural inhibition/ OR exp neuropsychological assessment/ OR neurocognition/ OR neuropsychology/ OR neuropsychology/ OR prepulse inhibition/ OR proactive inhibition/ OR response inhibition/ OR retroactive inhibition/ OR short term memory/ OR social cognition/ OR spatial memory/ OR ((attention ADJ3 (difficulties OR measure* OR reduced OR span OR sustained OR task* OR test*)) OR aversion OR behavior* inhibition* OR brain* OR cognit* OR conditioning OR craving OR executive function* OR inhibition task* OR inhibitory control* OR inhibitory process* OR intellectual* function* OR learning OR locomotor OR memory OR neural inhibition* OR neuro* OR prepulse inhibition* OR proactive inhibition* OR processing speed* OR reactive inhibition* OR response inhibition* OR retroactive inhibition*).ti,ab,id,tm.#3 Age/age differences/ OR generational differences/ OR (age-related OR age difference* OR age depend* OR (adolesc* ADJ3 adult*)).ti,ab, id. 1 AND 2 AND 3

Table A3

Search syntax from Embase, last accessed on December 10, 2021.

EmbaseOvid, Embase Classic+Embase 1947–2021 December 10 #1 Tobacco/adolescent smoking/ OR cigarette smoking/ OR electronic cigarette/ OR nicotine/ OR passive smoking/ OR smoking/ OR tobacco dependence/ OR "tobacco use"/ OR (cigaret* OR nicotin* OR smoker* OR smoking OR tobacco).ti,ab,kw.#2 Cognition/decision making/ OR executive function/ OR "inhibition (psychology)"/ OR "learning and memory test"/ OR long term memory/ OR memory/ OR nerve cell inhibition/ OR neuropsychological test/ OR neuropsychology/ OR short term memory/ OR social cognition/ OR spatial memory/ OR working memory/ OR ((attention ADJ3 (difficulties OR measure* OR span OR sustained OR test* OR task* OR reduced)) OR aversion OR behavior* inhibition* OR brain* OR cognit* OR conditioning OR craving OR executive function* OR inhibition task* OR inhibitory control* OR inhibitory process* OR intellectual* function* OR learning OR locomotor OR memory OR neural inhibition* OR neuro* OR prepulse inhibition* OR proactive inhibition* OR processing speed* OR reactive inhibition* OR response inhibition* OR retroactive inhibition*).ti,ab,kw. #3 Age (age-related OR age difference* OR age depend* OR (adolesc* ADJ3 adult*)).ti,ab, kw. 1 AND 2 AND 3Limit to Embase

Table A4

Search syntax from Web of Science, last accessed on December 10, 2021.

Web of Science Core Collection Web of Science Core Collection Editions: Science Citation Index Expanded (SCI-EXPANDED), 1975 – 2021, Social Sciences Citation Index (SSCI), 1975 – 2021, Arts & Humanities Citation Index (A&HCI), 1975 –present, Emerging Sources Citation Index (ESCI), 2015 – 2021) #1 **Tobacco**TS= ("cigaret*" OR "nicotin*" OR "smoker*" OR "smoking" OR "tobacco") #2 **Cognition**TS= (("attention" NEAR/2 ("difficulties" OR "measure*" OR "span" OR "sustained" OR "test*" OR "task*" OR "reduced")) OR "aversion" OR "behavior* inhibition*" OR "brain*" OR "cognit*" OR "conditioning" OR "craving" OR "executive function*" OR "inhibition task*" OR "inhibitory control*" OR "inhibitory process*" OR "intellectual* function*" OR "learning" OR "locomotor" OR "memory" OR "neural inhibition*" OR "neuro*" OR "prepulse inhibition*" OR "proactive inhibition*" OR "processing speed*" OR "reactive inhibition*" OR "response inhibition*" OR "retroactive inhibition*") #3 **Age**TS= ("age-related" OR "age difference*" OR "age depend*" OR ("adolesc*" NEAR/2 "adult*")) #1 **AND** #2 **AND** #3

Table A5

Search syntax from Scopus, last accessed on December 10, 2021.

ScopusElsevier, 1788–2021 #1 **Tobacco**TITLE-ABS-KEY(cigaret* OR nicotin* OR smoker* OR {smoking} OR {tobacco}) #2 **Cognition**TITLE-ABS-KEY((attention W/ 2 (difficulties OR measure* OR span OR sustained OR test* OR task* OR reduced)) OR aversion OR "behavior* inhibition*" OR brain* OR cognit* OR conditioning OR craving OR "executive function*" OR "inhibition task*" OR "inhibitory control*" OR "inhibitory process*" OR "intellectual* function*" OR learning OR locomotor OR memory OR "neural inhibition*" OR neuro* OR "prepulse inhibition*" OR "proactive inhibition*" OR "processing speed*" OR "reactive inhibition*" OR "response inhibition*" OR "retroactive inhibition*") #3 **Age**TITLE-ABS-KEY(age-related OR "age difference*" OR "age depend*" OR (adolesc* W/2 adult*)) **INDEX (medline)** #1 **AND** #2 **AND** #3 #5 **AND** **NOT** #4

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