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Neurobiological Considerations for Tobacco Use Disorder

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Abstract

Purpose of review: Neurobiological studies of tobacco/nicotine use examining genetic, molecular, functional, and behavioral correlates have improved our understanding of nicotine/tobacco dependence and have informed treatment. Recent work extending previously established findings and reporting novel methodologies and discoveries in preclinical and human studies are reviewed.

Recent findings: Recent work in preclinical models has focused on the differential roles of nicotinic receptor subtypes and nicotine's effects on neural systems beyond cortico-striatal dopaminergic pathways, and utilizing advanced methodologies such as pharmacogenetics, optogenetics and rodent fMRI to identify targets for treatment. Likewise, human neuroimaging studies have identified molecular and functional dynamic shifts associated with tobacco/nicotine use that further inform treatment.

Summary: Nicotine/tobacco use is associated with widespread neural adaptations that are persistent and function to maintain addiction. The continued identification of genetic, molecular, neural, and behavioral endophenotypes related to nicotine/tobacco use, dependence, and addiction will facilitate the development and delivery of personalized treatment.

Keywords

neurobiology; neuroscience; tobacco; nicotine; addiction; smoking

Introduction

Tobacco use kills more than seven million people worldwide each year [1]. While the prevalence of tobacco use has steadily declined, smoking and other tobacco product use continues to be one of the most preventable causes of death and disease worldwide. Nicotine

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Compliance with Ethics Guidelines

Conflict of Interest

Megha Chawla and Kathleen Garrison declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

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is the main addictive component of tobacco products and sustains tobacco product dependence. Studies have shown nicotine to be as addictive as heroin, cocaine and methamphetamine [2]. Despite many smokers wanting to quit, smoking cessation rates remain low; for example, over the last 15 years in the U.S., the prevalence of annual quit attempts increased to ~52% of smokers, yet only ~6% quit successfully [3]; quit rates are also low for other combustible and non-combustible tobacco products [1]. A better understanding of the neurobiology of tobacco/nicotine use should facilitate the development of more efficacious treatments (and prevention). This need is heightened by the recent surge in the popularity of alternative nicotine delivery systems such as electronic cigarettes (e-cigarettes), which have both the potential for harm reduction and abuse liability. This review highlights new evidence in neurobiology of nicotine's effects on the brain; the transition to habitual use, nicotine dependence, and addiction; withdrawal and relapse; and how these findings inform treatments for tobacco use.

Nicotinic Acetylcholine Receptors

Nicotine acts as an agonist at nicotinic acetylcholine receptors (nAChRs), widely distributed cholinergic receptors in the central and peripheral nervous systems and other bodily tissues [4]. nAChRs are ligand-gated ion channels comprised of heteromeric or homomeric combinations of eight alpha subunits ($\alpha 2$ - $\alpha 7$, $\alpha 9$ and $\alpha 10$) and three beta subunits ($\beta 2$ - $\beta 4$) [4], each combination having different pharmacological and kinetic properties and cellular and subcellular localization [5]. The most prevalent neural subtypes are $\alpha 7$ and $\alpha 4\beta 2$, with the high-affinity $\alpha 4\beta 2$ considered to be the main receptor mediating the response to nicotine from tobacco [4]. nAChRs have glutamatergic or GABAergic (gamma-Aminobutyric acid) interactions with virtually all other neurotransmitter systems, thereby precipitating nicotine's global effects on the brain.

Nicotine initiates the addictive process by acting on cortical and limbic brain regions mediating reward, in particular the mesocorticolimbic dopamine (DA) system [6]. The mesocorticolimbic pathway is a significant dopaminergic pathway which connects the midbrain ventral tegmental area (VTA) to the prefrontal cortex (PFC) and limbic and striatal regions including the nucleus accumbens (NAcc). Acting primarily through $\alpha 4\beta 2$ receptors, nicotine stimulates glutamate release and increases phasic firing of midbrain DA neurons, resulting in elevated DA in the NAcc, considered to be primarily responsible for rewarding and pleasurable effects of nicotine. DA is also elevated in the PFC and hippocampus, considered to be responsible for the cognitive-enhancing effects of nicotine on attention and memory [7] along with direct effects of acetylcholine (e.g. in the hippocampus [8]) on learning and memory effects of nicotine.

Nicotine's effects on the brain are characterized by interactions with the mesocorticolimbic pathway, with cascading effects on other neural systems [9]. Accordingly, functional magnetic resonance imaging (fMRI) in nicotine-naïve rats was used to show increased blood oxygen-level dependent (BOLD) signal after high-dose nicotine administration in the NAcc shell and prelimbic area [10]. Likewise, human positron emission tomography (PET) studies show that smoking decreased DA binding, indicating increased DA release, in the ventral striatum and the DA-rich ventral pallidum, smoking puff rate increased magnitude of DA

release in the striatum, and striatal DA release correlated with reduced self-reported craving and withdrawal [6].

Even low doses of nicotine cause partial desensitization of most heteromeric nAChRs in the brain, though the rate of desensitization varies between subtypes [4]. nAChR subtypes on GABAergic neurons desensitize faster than those mediating glutamatergic excitatory inputs to DA neurons, resulting in enhanced DA release in the NAcc [11]. Studies in rats have found glutamate hypersensitivity and increased extracellular glutamate in the dorsal striatum, VTA and NAcc following repeated nicotine administration [12, 13]. This hypersensitization is accompanied by a homeostatic response of subtype-specific nAChR upregulation and subsequent increased DA neurons in the NAcc, resulting in DA hypersensitivity following nicotine exposure [14]. One study found increased DA-D1 receptor mRNA expression, a dopaminergic receptor subtype, in the PFC of rats after nicotine exposure, capturing epigenetic changes in DA receptor genes induced by nicotine [15]. These mechanisms enhance the reinforcing properties of nicotine mediated by the mesocorticolimbic dopaminergic pathway, contributing to the maintenance of nicotine-seeking behavior.

Advancements in genetic knock-out and knock-in animal models, transgenic techniques and in-vivo functional imaging have greatly aided our characterization of receptor subtype interactions with nicotine and their role in nicotine dependence [16, 17]. Variants in the CHRNA5-A3-B4 gene cluster, coding for the $\alpha 5$, $\alpha 4$ and $\beta 4$ nAChRs subunits, have consistently been implicated as moderators of nicotine's effects on the brain [reviewed in: 18]. For example, polymorphisms in CHRNA5 have been shown to increase vulnerability to tobacco smoking [18]. CHRNA5 knock-out mice show increased nicotine intake compared to wild-type, and rescued "normal" nicotine intake with re-expression of $\alpha 5^*$ nAChRs in the medial habenula [19]. In translational work in humans, a CHRNA5 risk allele was associated with lower aversive effects of high dose nicotine, increased smoking intensity (puff volume), and better treatment response to nicotine replacement therapy (NRT) [20–22]. Studies like these have broadened our understanding of the roles of nAChR subtypes.

Furthermore, although nicotine effects via interactions with dopaminergic nAChRs are well-established, recent advances demonstrate the complexity of nicotine's interactions with other neuromodulatory and neurotransmitter systems [23]. For example, PET imaging in male smokers revealed decreased μ -opioid receptor (MOR) binding, indicating decreased MOR availability, in the basal ganglia and thalamus, compared with nonsmokers [24]. MOR availability was correlated with lower craving and nicotine dependence severity, and smokers with a risk-allele of the MOR (OPRM1) gene had significantly lower MOR availability in the NAcc and right amygdala [24]. These studies explicate the widespread effects of nicotine on neural function and concomitant behavioral manifestations and facilitate the identification of pharmacological targets for tobacco dependence.

Neuroscience of Tobacco/Nicotine Use Disorder

The complexity of drug addiction at the whole-brain level was recently exemplified in a systematic review of neuroimaging studies of drugs of abuse including nicotine [25]. The review identified consistent impairments in brain function across a range of tasks including

cue-exposure, decision making, inhibitory control, and social-emotional tasks, in six functional brain ‘networks’ including regions involved in reward and habit; the canonical salience network (SN), implicated in (re)orienting attention to salient stimuli; executive control network (ECN), implicated in selection of behavioral responses; and default mode network (DMN), implicated in self-referential processing; and regions involved in memory. Findings supported predictions that brain regions and networks involved are more strongly engaged by drug-related processing and blunted by non-drug-related processing. Data further supported that brain regions implicated in habit (dorsal caudate and putamen) are associated with drug use initiation and relapse, consistent with their role in the transition from voluntary use to compulsive drug-taking behavior [25].

Tobacco/nicotine use initially involves this transition from voluntary use to habitual drug-taking that is engaged in despite harmful consequences [26]. This behavior has been modeled in animals; for example, in a study in rats, intravenous nicotine self-administration was devalued by pairing with lithium for rats with brief training, whereas rats with extended training were insensitive to devaluation, demonstrating a shift from goal-directed to habitual behavior [27]. That study also demonstrated a neurobiological hallmark of this transition, a shift in neural drug response from the ventral to dorsal striatum [9], here by measuring c-fos expression, an indirect marker of neuronal activity. Alongside behavioral changes, where any training was associated with increased c-fos expression in the NAcc, NAcc shell and VTA, only extended training was associated with increased c-fos expression in the dorsal striatum [27]. The outcome devaluation paradigm has been modeled in humans [28] and tested in smokers, for whom goal-directed tobacco-seeking can be devalued by smoking satiety [29] or NRT [30], but cue-elicited tobacco-seeking is insensitive to devaluation.

After repeated pairing with drug reward, reinforcement learning leads to drug-related cues alone inducing reward expectation and motivating drug-seeking behavior [31]. Some recent developments in the study of drug cue-reactivity have tested conditioned place preference, a preference for place previously paired with reward that endures in the absence of reward. Nicotine induces conditioned place preference in preclinical studies and even in zebrafish [32], and recent studies have focused on neurobiological and genetic factors that mediate this learning. For example, using a knockout mouse model, one study found that cannabinoid 2 (CB₂) receptors are required for nicotine-induced conditioned place preference [33]. CB₂ agonists have been found to inhibit the rewarding effects of alcohol and cocaine but facilitate rewarding effects of nicotine [34, 33]. Recent work in humans has examined how resting state brain network dynamics relate to cue-reactivity, with growing evidence for a role of the SN, considered to (re)direct attention to salient internal and external stimuli to guide behavior [35]. One study found that greater resting state functional connectivity in smokers between the anterior insula and dorsal anterior cingulate cortex, hubs of the SN, predicted increased cue-reactivity to smoking cues in a separate task [36]. Additionally, activation in the anterior insula in response to smoking cues was correlated with increased cue-reactivity throughout the SN, suggesting that the role of the insula in smoking cue-reactivity (and relapse) may not be functionally independent, but instead may represent engagement of the entire SN [36]. Other work indicates that drug cue-reactivity, or incentive sensitization, may lead to habitual drug-taking by pathological coupling with drug-affected motivational processes, such as the avoidance of negative affective states during

withdrawal, supported by the recruitment of stress-related brain regions such as the amygdala [31]. Nicotine dependent individuals exhibit cognitive and affective impairments that are alleviated by nicotine in both humans and animals [37]. The complexity of these interactions can be modeled using relatively new approaches in ecological momentary assessment and time-varying effect models [e.g., 38].

Alongside increased salience of drug-related cues, tobacco dependence is characterized by reduced responsiveness to nondrug rewards. In a randomized trial, smokers showed reduced monetary reward sensitivity on a probabilistic reversal learning task, indicated by decreased BOLD signal in *a priori* regions of interest, the dorsal striatum and dorsal anterior cingulate cortex, as compared to nonsmokers [39]. This lower reward sensitivity was not alleviated by nicotine or varenidine (a $\alpha 4\beta 2$ receptor agonist), and was correlated with higher nicotine dependence severity [39]. In another series of studies, smokers showed reduced responsiveness to appetitive rewards compared with nonsmokers, indicated by blunted striatal activation [40] and connectivity [41] in response to favorite-food cues. Blunted neural responses to naturally rewarding stimuli have also been related to craving, smoking abstinence, and treatment outcomes in smokers [42–44].

Another mechanism underlying the shift from voluntary drug use to compulsive drug-taking habits is impaired PFC inhibitory control mechanisms [9], including impairments in regulation of limbic reward regions and executive function, including emotion regulation, inhibitory control, salience attribution, and self-awareness [45]. For example, in a study by Bi and colleagues, decreased resting state functional connectivity in young-adult smokers between the anterior insula and anterior cingulate cortex (ACC) was correlated with poor performance on a Stroop task, a measure of cognitive control, and to greater nicotine dependence severity, suggesting a role for the SN in cognitive impairments in smokers [46]. In that study [46] and another [47], subjective craving was correlated with decreased resting state functional connectivity between the right anterior insula and ventromedial PFC, implicated in emotion regulation, suggesting a functional circuit for craving during withdrawal. In a recent multi-modal meta-analysis, decreased gray matter integrity identified between smokers and nonsmokers in structural MRI studies was found to overlap with brain regions showing acute functional effects of nicotine in smokers in pharmacological fMRI studies, in the insula, ventromedial PFC and thalamus, supporting the importance of these brain regions to smoking [48]. Further, using meta-analytic connectivity modeling and behavioral decoding, that study identified additional structural-functional relationships that may be relevant to smoking, such those related to pain perception [48]. Indeed, nicotine has multiple other cognitive effects, including on sensory processing, social-emotional processing, attention, and working memory [25], including cognitive-enhancing effects on attention and memory even in nonsmokers [49]. A potential mechanism was suggested by a meta-analysis of pharmacological neuroimaging studies, which consistently indicate that nAChR administration leads to decreased activity in the DMN and increased activity in the ECN, suggesting a shift from internal to external-directed attention that may underlie the cognitive-enhancing effects of nAChR agonists including nicotine and varenicline [50]. Nevertheless, despite these short-term cognitive-enhancing effects, chronic smoking has been associated with decreased cognitive performance in middle age [49], and increased risk of dementia (Alzheimer's disease, vascular dementia, and dementia) and cognitive decline

(e.g., Mini-Mental State Examination and other measures of cognitive performance) in late adulthood [51; meta-analysis]. There is some indication of reduced risk of cognitive decline with smoking cessation, in that former smokers were at lower risk than current smokers for Alzheimer's disease and yearly cognitive decline, but no different from current smokers for risk of vascular dementia and any dementia [51].

Finally, an important consideration in substance abuse research is that only some individuals who use drugs transition to addiction. Recent efforts have been made to characterize endophenotypes related to drug addiction (and to mental disorders more broadly) across genetic, molecular, cellular, and circuit-level measures [52] to better characterize individual differences. A recent summary of preclinical animals studies suggests that some predictive behavioral endophenotypes (i.e. of genetic origin), such as anxiety, novelty seeking, and impulsivity, may have specific effects on drug-taking behavior, such as differential effects on the loss of control over drug intake, and on drug choice/preference [53]. A dimensional approach should improve our understanding of the protective and risk factors for tobacco/nicotine addiction, and of the factors that either precipitate or are a consequence of nicotine/tobacco use.

Neurobiology and behavior of abstinence

Nicotine withdrawal—Short-term abstinence from tobacco/nicotine disrupts homeostatic neuroadaptations that have been caused by chronic nicotine use and require nicotine for maintenance [14], leading to intense somatic, cognitive and affective withdrawal symptoms including irritability/anger/frustration, anxiety, depressed mood, difficulty concentrating, increased appetite, insomnia, and restlessness, that peak in the first 4–24 hours and last for several weeks [54]. nAChR agonist administration ameliorates withdrawal symptoms and restores neurochemical homeostasis [55]. Avoidance of withdrawal symptoms is a key motivator for repeated nicotine use via negative reinforcement and therefore contributes to the maintenance of nicotine addiction despite negative long-term consequences. Early abstinence is a period of heightened vulnerability to relapse and therefore a critical period for intervention.

Nicotine withdrawal symptoms coincide with decreased levels of extracellular DA in the NAcc, reflecting changes in DA release and uptake that normalize within 48 hours of abstinence [55]. One study found reduced regional cerebral blood flow using fMRI arterial spin labeling in mesocorticolimbic structures as soon as four hours after smoking abstinence, and this correlated with self-reported craving [56]. Bupropion, a nAChR inhibitor and DA re-uptake blocker that has been shown to increase smoking quit rates [57], may help to alleviate withdrawal by normalizing DA levels [14]. Preclinical studies have similarly demonstrated that $\beta 2^*$ heteromeric nAChRs in the midbrain, striatum and PFC all returned to control levels by withdrawal day 14 [58]. As nicotine is washed out and $\alpha 4\beta 2$ receptors are functionally restored, the stimulation of GABAergic neurons by endogenous acetylcholine is strengthened, resulting in overactive cholinergic signaling in the mesocorticolimbic circuit that may underlie negative withdrawal symptoms and is therefore a target for early intervention [7].

The medial habenula and one of its main targets, the interpeduncular nucleus also appear to be critical for nicotine withdrawal symptoms, presumably because this pathway richly expresses $\beta 4$ and $\alpha 5$ nAChRs [reviewed in: 59]. One study used optogenetics to visualize activation of GABAergic neurons in the interpeduncular nucleus during withdrawal, and to demonstrate that optical activation of these neurons induced withdrawal regardless of nicotine exposure; withdrawal symptoms could be relieved by reducing the excitability of these neurons via an N-Methyl-D-aspartate receptor antagonist, or by blocking neurotransmission in the medial habenula [60]. Additional neuromodulatory systems including opioid and endocannabinoid systems, neuropeptides, and serotonergic, glutamatergic and GABAergic neurotransmitters systems have been implicated in mediating nicotine withdrawal [23].

The insula has also been implicated in withdrawal, with a particular role in craving, in line with its broader role in conscious urges. Smokers with insula damage from stroke tended to have quit smoking easily, without relapse, and without experiencing urges to smoke [61]. In line with insula activity being a marker for involvement of the SN, it has been further demonstrated that nicotine abstinence is associated with a shift in the balance of resources between the DMN, SN, and ECN, mediated by the insula [62]. One study showed that during abstinence, the insula integrates neurochemical homeostatic disequilibrium and directs attentional resources internally, increasing connectivity between the SN and the DMN at the cost of SN-ECN interactions [63]. The increased salience of internal, self-reflective processing may relate to the affective dysphoria of abstinence, and the decreased salience of external cues and executive control may relate to cognitive deficits. A following study identified increased SN-DMN and decreased SN-ECN interactions in the resting state during short-term abstinence from smoking as compared to smoking satiety, within subjects [64]. Furthermore, weaker resting state SN-ECN connectivity correlated with increased craving, poorer performance on a behavioral working memory task, and decreased suppression of DMN activity on a separate working memory task [64]. Another fMRI study found decreased BOLD signal in *a priori* regions of interest in the dorsolateral PFC, a hub of the ECN, and increased BOLD signal in the posterior cingulate cortex, a hub of the DMN, during a working memory task in 24 hours abstinence versus smoking satiety, and these changes predicted relapse to smoking in a 7-day quit attempt beyond clinical variables [65], consistent with a shift in resources from the ECN to the DMN, although insula/SN activity or connectivity between these regions was not examined.

Prolonged Abstinence—While some neural and behavioral characteristics of abstinence from nicotine/tobacco use appear to recover to nonsmoking levels over time, others do not, at least in the time frame studied. For example, DA synthesis capacity as measured by PET was found to be lower in current male smokers versus nonsmokers, but this effect normalized at three months abstinence [66]. Another study compared past smokers with current smokers and nonsmokers on a monetary incentive delay task, which measures responses to monetary gains and losses as an index of reward sensitivity. During an monetary incentive delay task in fMRI, both current and past smokers showed increased BOLD signal in the lateral orbitofrontal cortex and anterior insula during gain/loss anticipation, and past smokers showed increased BOLD response in striatal regions during

loss anticipation [67], suggesting persistence of reward processing alterations in past smokers.

Many comparative studies of past smokers suggest factors that may facilitate prolonged abstinence. For example, when studying reward outcomes on the monetary incentive delay task, one fMRI study identified reduced BOLD signal in both current and past smokers in the left amygdala during monetary gain and in the ACC during monetary gain/loss, and past smokers showed increased BOLD signal in the right amygdala during monetary loss; the latter suggesting alterations in negative valence processing in past smokers that may facilitate abstinence [68]. Another study compared past smokers to current smokers and nonsmokers in two fMRI experiments on an attention bias task, measuring cue-reactivity, and a go/no-go task, measuring error monitoring and response inhibition [69]. For the attention bias task, despite equivalent behavioral performance, past smokers showed increased BOLD signal in prefrontal cortical areas involved in cognitive control compared with current smokers, suggesting persistence of incentive salience toward smoking cues in past smokers (i.e. behavior), but increased cognitive control (i.e. prefrontal cortical activity). On the go/no-go task, past smokers had slower reaction times than both groups and again showed increased prefrontal cortical activity, here during error monitoring. Together these findings suggest that increased cognitive control may promote nicotine abstinence in former smokers [69]. A related study tested a Stroop task, a measure of cognitive flexibility, and found that past smokers had less Stroop interferences compared with current smokers, with increased BOLD signal in the ACC and superior frontal gyrus during trials requiring effortful control, again suggesting a role for prefrontal cognitive control in successful abstinence [70].

The studies above additionally highlight the role of impulsivity in tobacco/nicotine addiction and unsuccessful cessation. Relatedly, studies using delay discounting, a measure of impulsivity in which outcomes decrease in value based on delayed time to receipt, have found steeper discounting of delayed rewards in smokers, with the degree of discounting correlated with nicotine dependence severity [71]. One study found greater functional connectivity during a delay discounting task in smokers between the frontoparietal network, involved in cognitive control, and the anterior insula (i.e. SN), that additionally predicted steeper delay discounting, providing a potential neural basis for immediate reward preference in addictions [72]. A meta-analysis found that reduced delay discounting in smokers predicted reduced future smoking and better quit rates [73]. Past smokers have been found to discount less steeply than current smokers [74], and this finding has recently been extended to e-cigarette use [75]. Delay discounting seems to follow an inverted-U trajectory following cessation, with increased discounting in early abstinence that is attenuated with prolonged abstinence. These nonlinear changes, along with temporally-correlated trajectories of impulsivity and negative affect, may serve as important predictors of relapse.

Together these studies suggest some candidate mechanisms that may precipitate or facilitate prolonged abstinence in smokers, such as increased neural sensitivity to negative outcomes and increased prefrontal cognitive control. Longitudinal studies are needed to clarify whether these changes promote or follow abstinence from smoking. Few longitudinal studies have examined the effects of prolonged abstinence from smoking, as presumably only a

small percentage of participants remain abstinent for long periods of time. A better understanding of the neurobiological and behavioral changes associated with abstinence within-subjects will provide a more complete delineation of the prospective vulnerabilities of current smokers and help to identify protective factors for cessation.

Co-use of tobacco/nicotine with other drugs of abuse

Apart from being an addictive substance on its own, nicotine may prime the nervous system for addiction to other substances of abuse such as cocaine and alcohol, as evident in epidemiological data on the co-use of nicotine with other drugs, including the majority of individuals with alcohol, cocaine, and methamphetamine use disorders [76, 77]. Recent evidence has described the possible underlying genetic and molecular mechanisms precipitating co-use and dependence, largely based on common effects on the midbrain dopaminergic reward pathway [78]. For example, transgenic mouse models have demonstrated the role of $\alpha 6$ nAChR subunits, highly expressed in VTA DA neurons, and implicated in nicotine addiction, also mediate the rewarding effects of alcohol [79]. Nicotine pretreatment has also been found to enhance the locomotor response to cocaine and accelerate the development of conditioned place preference to cocaine by enhancing long-term potentiation and expression of FosB, a protein whose accumulation is crucial for the development of addiction, in the striatum [80]. The reverse effects were not observed with nicotine pretreatment. Other work has established that vulnerability to developing addiction to multiple drugs of abuse (nicotine, cannabis, cocaine, alcohol) in humans can be attributed to a single nucleotide polymorphism [81]. The consideration of nicotine use with other comorbid substance use disorders is critical, given the high rates of co-use, substantial negative health outcomes, and the impact on treatment seeking and treatment outcomes [77].

Neurobiological considerations for the treatment of tobacco dependence

Novel approaches for the treatment of tobacco dependence are needed given the low success rates for smoking abstinence particularly in the longer-term. Pharmacological treatments for nicotine dependence, including NRT, nicotinic partial agonists (e.g., varenicline), and antidepressants (e.g., bupropion), have been found in a meta-analysis of randomized controlled trials to be comparably more effective for smoking cessation than placebo, however, effects diminish at one year [82]. Supplementing pharmacological treatments with behavioral support was found by another meta-analysis to increase long-term abstinence (> 6 months) by an additional 10–25% compared with pharmacological treatments alone, and 70–100% compared with usual care [83]. Nevertheless, smoking cessation rates at the population level remain low. Advancements in our understanding of the neurobiology of tobacco/nicotine use are informing treatment, including pharmacogenetic and other pharmacological interventions, and neural and behavioral interventions.

Treatments can be improved by delivering precision medicine, i.e. tailoring to the individual's unique genetic, environmental and psychobehavioral characteristics. Within precision medicine, pharmacogenetics is being used to test genetic influences on individual responsiveness to smoking cessation drugs, to identify biomarkers for treatment response. Current evidence suggests that high-risk genotypes of CHRNA5 predict cessation failure, and that interactions between CHRNA5 genotypes, nicotine metabolism rate, and

pharmacotherapy, affect cessation outcomes, although additional data is needed, including prospective studies assigning smokers to treatment group based on genetic markers [84, 85]. Relatedly, sex and gender differences in nicotine use and addiction can be utilized to inform more effective treatments. For example, sex and menstrual phase differences in the response to nicotine and vulnerability to nicotine addiction have been identified and indicate that progesterone is a protective factor in females and may therefore be a potential treatment for nicotine addiction [86, 87].

Additional and alternative approaches for smoking cessation treatment are being developed and tested and their efficacy compared in meta-analyses [57]. For example, cannabinoid type 1 (CB₁) receptor antagonists may aid smoking cessation by rebalancing the endocannabinoid system, involved in the regulation of energy balance (or “exostasis”- accumulating energy reserves for future needs: [88]). CB₁ antagonists have been associated with increased smoking quit rates and may additionally moderate weight gain, a major concern for quitters; however, none are currently available on the market for smoking cessation due to the type and incidence of adverse events [89, 57]. In another promising approach for the treatment of tobacco and other substance use disorders, the psychedelic psilocybin is being tested as an adjunct to treatment [90]. One study using psilocybin in combination with cognitive behavioral therapy found 9 out of 12 participants to be smoking abstinent at 16-months follow-up [91]. Psilocybin was found to decrease functional connectivity between hubs of the DMN (medial PFC and posterior cingulate cortex) in an fMRI study [92], suggesting a potential mechanism for action on smoking cessation that is consistent with the large-scale network dynamics associated with smoking abstinence outlined above.

New approaches in neurofeedback and neural stimulation are also being developed and tested, using targets identified by studies such as those outlined in this review. One promising approach is the use of real-time fMRI neurofeedback to train individual smokers to self-regulate brain activation patterns related to smoking, such as subjective craving and smoking cue-reactivity. A recent study trained smokers to regulate activity in an individualized craving-related region of interest in the PFC or ACC and found reduced cue-reactivity and craving compared to no feedback controls [93]. Clinical applications of real-time fMRI are under development [94], including incorporating feedback from large-scale brain networks; however, few studies have been able to link success in brain self-regulation to clinically meaningful outcomes [95]. Another interesting approach for treatment is noninvasive electromagnetic stimulation of the brain via repetitive transcranial magnetic stimulation (rTMS; reviewed in: 96). A recent prospective clinical trial found that ‘deep’ high frequency rTMS targeted to the lateral PFC and insula reduced cigarette consumption and nicotine dependence in heavy smokers who had failed previous treatments, with some preliminary evidence of added benefit from exposure to smoking cues prior rTMS [97]. Another feasibility and limited efficacy trial found that high frequency rTMS to the left dorsolateral PFC combined with a self-help intervention increased abstinence rates and decreased relative risk of relapse in moderate to heavy smokers, among other promising outcomes [98].

Advances in our neurobiological understanding of nicotine/tobacco use are also informing behavioral treatments for nicotine/tobacco use cessation. For example, increasing evidence

for the neurobiological effects of mindfulness meditation support mindfulness training as a treatment for smoking cessation. Mindfulness has been shown to enhance attention, with associated changes in ACC activity; improve emotion regulation and reduce stress, as evident in fronto-limbic networks; and affect self-referential processing and improve present-moment awareness, indicated by alterations in DMN processing [99]. A recent clinical trial supplemented NRT with either mindfulness training, cognitive behavioral therapy or usual care, and found that mindfulness training led to higher recovery rates following a lapse and higher recovery of abstinence post-treatment as compared with cognitive behavioral therapy and usual care [100]. Again, more work is needed to better link mindfulness training, neural changes, and clinical measures to inform treatments [99].

Finally, the recent uptake of electronic nicotine delivery systems such as e-cigarettes and their potential for harm reduction compared with conventional cigarette smoking should also be considered [101], although the effects of e-cigarettes also indicate their abuse liability. For example, a recent PET study demonstrated that nicotine delivery via e-cigarettes led to comparable $\alpha 2^*$ nAChR occupancy as conventional cigarettes [102]. Given substantial evidence that nicotine can negatively impact adolescent brain development [2], including cellular, structural, and functional alterations in serotonergic and dopaminergic pathways [reviewed in: 103], a major drawback of e-cigarettes is their rapid uptake among young people. A recent study found that rats treated with nicotine as adolescents, but not those treated as adults, increased ethanol self-administration and showed alterations in VTA GABAergic neurons one month later, supporting that adolescence is a vulnerable period for nicotine exposure, including that it may increase risk for later alcohol use, and implicating VTA GABAergic neurons as mediating this vulnerability [104]. Overall, the impact of e-cigarettes on smoking cessation is an area of heated debate [105, 106].

Conclusions

There have been a number of recent advances in our understanding of nicotine's neurobiological effects, highlighted in this review, including not only novel methodology and discoveries, but also informative analytical approaches such as multi-modal meta-analyses and systematic reviews, and developments that have been summarized by other recent reviews and perspectives. In addition, it is promising that preclinical models of addiction have been developed to have shared construct validity with human addiction, allowing us to address core clinical features and identify additional neurobiological mechanisms [reviewed in: 107]. Additionally, the adoption of methods for scientific transparency and data sharing should further improve the replicability and efficiency of research in addictions [108], for example enabling more powerful cross-modal meta-analyses. Further work in the areas highlighted should continue to improve our understanding of the neurobiology of nicotine/tobacco use and importantly inform treatments.

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