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A review of neurobiological vulnerability factors and treatment implications for comorbid tobacco dependence in schizophrenia

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There is converging evidence that certain subpopulations of smokers, such as smokers with a serious mental illness like schizophrenia (SCZ), are more likely to become addicted to tobacco and are less likely to quit smoking. This review focuses on the unique risk factors that may increase vulnerability to the initiation and maintenance of nicotine addiction in persons with schizophrenia and other psychotic disorders and also reviews the latest approaches to treating nicotine addiction and schizophrenia based on our neurobiological understanding of central nicotinic receptor systems and related neurotransmitters. In addition, suggestions for future lines of research to better understand reasons for the comorbidity of nicotine addiction in schizophrenia are discussed.

Keywords: cigarette smoking; nicotine; schizophrenia; cognition; self-medication; addiction vulnerability

Introduction

Estimates of cigarette smoking prevalence in persons with schizophrenia (SCZ) and schizoaffective disorder range from 45 to 88%, compared to < 20% in the general population.[1] Individuals with SCZ also experience more difficulty quitting smoking, with reported cessation rates of 10.0–27.2% in people with psychotic disorders compared to 42.5% in smokers with no history of mental health or addiction problems.[2] As a result, persons with SCZ suffer considerable morbidity and mortality due to tobacco-related illnesses.[3] In fact, it is estimated that approximately half of the 25 years (*circa* 12–13 years) of shortened life span associated with SCZ and other serious mental illnesses is attributable to tobacco smoking.[4] Thus, there is an urgent need to develop improved smoking cessation therapies for this hard-to-treat population; understanding the relationship between tobacco smoking and SCZ will undoubtedly benefit treatment development in this area.

While environmental and psychosocial factors certainly play a role in this comorbidity (reviewed in Refs. 3 and 5), recent findings indicate that the rates of smoking in SCZ cannot be solely attributed to these factors.[6] Two overarching theories have been proposed to explain the high rates of comorbid tobacco addiction in SCZ. The self-medication hypothesis proposes that persons with SCZ smoke in an attempt to self-medicate psychiatric symptomatology (e.g., positive and negative symptoms, anxiety, and depression) and side effects associated with antipsychotic medications (e.g., neuroleptic-induced Parkinsonism).[7] The addiction vulnerability hypothesis proposes that common genetic factors and abnormalities in brain reward pathways inherent to the pathophysiology of SCZ make patients with SCZ more vulnerable to tobacco use.[6,8] This review will focus primarily on the neurobiological links between tobacco addiction and SCZ. Several vulnerability markers for tobacco addiction in SCZ—spanning neurotransmitter signaling, sensory information processing, cognition, and behavior—will be reviewed, and in each stage we will discuss the contribution of genetics to these vulnerabilities. We attempt to assimilate these data to produce an overall model of tobacco addiction vulnerability in SCZ that could

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be used to guide the development of more effective treatments for tobacco addiction in SCZ. Finally, we provide suggestions for future directions of research.

Neuropharmacological effects of tobacco at nicotinic acetylcholine receptors

Nicotine, the main psychoactive ingredient in tobacco smoke, exerts its effects by binding to nicotinic acetylcholine receptors (nAChRs), which are members of the neurotransmitter-gated ion channel superfamily.[9] There are two families of central nAChRs: high-affinity (β_2 subunit–containing nAChRs, which exist as a heteropentameric combination of α and β subunits) and low-affinity (α_7 subunit–containing nAChR homopentameric complexes) receptors. Chronic exposure to nicotine results in desensitization[10] and inactivation of nAChRs and a paradoxical upregulation of receptors,[11] the degree to which this occurs is dependent on the subunit composition of the nAChR subtype.[12]

Nicotinic acetylcholine receptors are widely expressed throughout the brain, are situated on numerous neuronal cell types, and can be found on different neuronal locations (the cell soma, dendrites, preterminal axon regions, axon terminals, and myelinated axons).[12] Nicotine and the endogenous agonist of nAChRs, acetylcholine, are therefore able to modulate the release of a range of neurotransmitter systems, including dopamine (DA), norepinephrine (NE), serotonin (5-HT), glutamate (GLU), γ-aminobutyric acid (GABA), and endogenous opioid peptides. Nicotine exerts its reinforcing and procognitive effects, important determinants of tobacco addiction in SCZ, by modulating DA release in the mesocorticolimbic system and hippocampus through an intricate interplay with GLU- and GABA-ergic mechanisms. Below, we review the localization and synaptic function of nAChRs thought to play key roles in the comorbidity between tobacco addiction and SCZ. We focus on $\alpha4\beta2$- and $\alpha7$-nAChRs as these have been the most widely studied in relation to tobacco addiction and SCZ; however, other nAChR subtypes, such as those containing $\alpha3$, $\alpha5$, $\alpha6$, and $\beta4$ subunits, may also be involved.

nAChRs in the mesolimbic DA system

The mesolimbic DA system primarily consists of DAergic projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAcc). A common feature of addictive drugs, including nicotine, is that they reinforce drug-taking behavior by increasing DA in the NAcc.[13] Nicotine directly modulates the DAergic tone of the limbic system by binding to nAChRs situated on the cell bodies[14] and terminals[15] of midbrain DAergic projections from the VTA, and does so indirectly by modulating excitatory (GLUergic) and inhibitory (GABAergic) inputs onto DAergic neurons (see Fig. 1).[16,17]

In the VTA, $\alpha4\beta2$-nAChRs are expressed on soma of DAergic neurons, which project to the NAcc.[18] Thus, their stimulation results in an increased DA release in the NAcc.[19] $\alpha4\beta2$-nAChRs are also expressed on GABAergic interneurons, which exert inhibitory control over DA transmission.[18,20] In addition, GABA- and DAergic transmission in the VTA is under excitatory control from GLUergic projections.[21] $\alpha7$-nAChRs are expressed presynaptically on these excitatory projections and, when activated, GLU release is enhanced, leading to stimulation of postsynaptic GLU receptors on GABAergic and DAergic VTA neurons.[18,22] It is thought that the relatively low nicotine concentrations obtained from tobacco smoking result in rapid desensitization of high-affinity nAChRs located on inhibitory GABAergic neurons, whereas low-affinity nAChRs located on excitatory GLUergic neurons are subject to minimal desensitization, leading to the persistent DA release observed following nicotine exposure.[16] Nicotine administration can also shift DA transmission from tonic into burst firing mode by acting on $\alpha7$ nAChRs presynaptically located on GLUergic projections, resulting in increased subcortical DA release.[23]

nAChRs in the mesocortical DA system

The mesocortical DA system consists of DA projections from the VTA to the frontal lobes. Nicotine increases DA release in cortical areas directly by binding high-affinity nAChRs on VTA DAergic projections to the cortex and indirectly by stimulating low-affinity nAChRs on incoming excitatory GLUergic projections to the prefrontal cortex (PFC) (see Fig. 1);[19,24,25] these effects are thought to underlie the cognitive enhancing properties of cigarette smoking.[26,27]

In the VTA, $\alpha4\beta2$-nAChRs are expressed on soma of DAergic neurons that project to the cortex, the stimulation of which results in increased

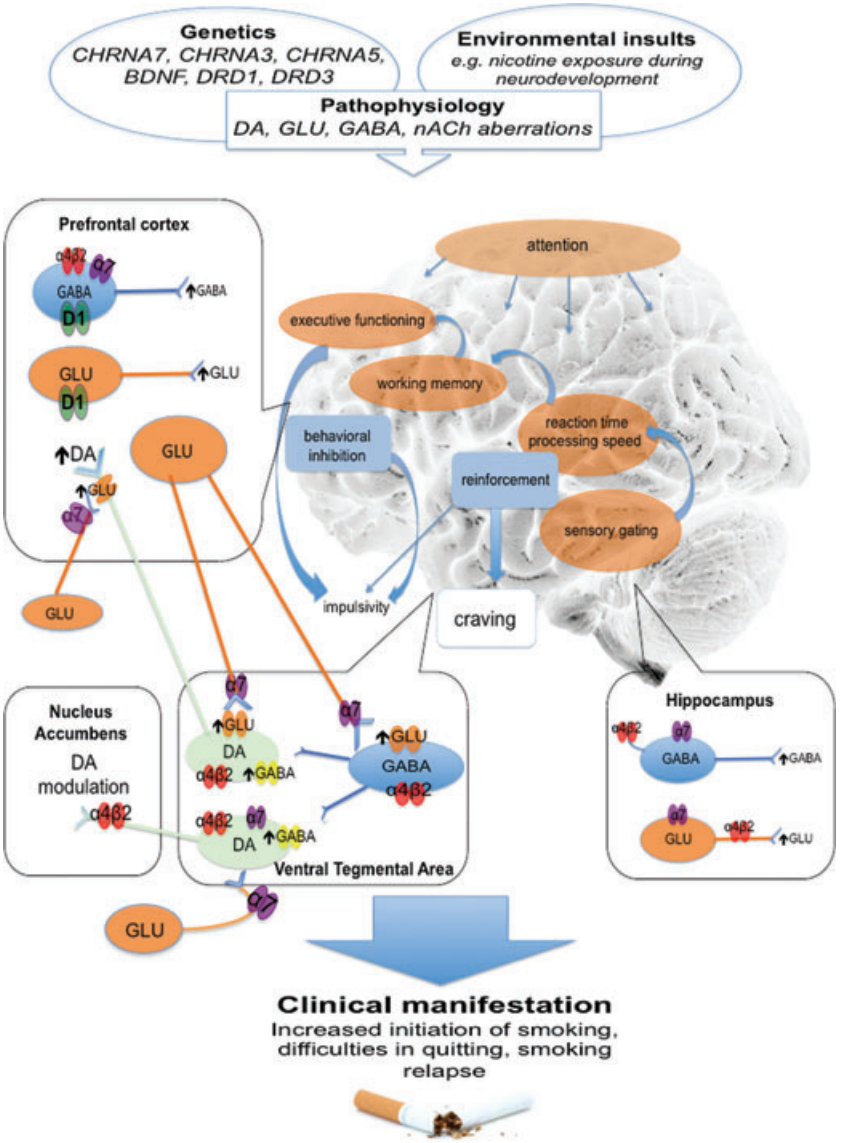

Figure 1. Vulnerability markers for tobacco addiction in SCZ and potential treatment targets. This model presents the neurobiological factors contributing to vulnerability to tobacco addiction in SCZ and potential nAChR-related treatment targets. Genetic and environmental factors associated with SCZ result in aberrant dopamine (DA), glutamate (GLU), γ-aminobutyric acid (GABA), and nicotinic acetylcholine receptor (nAChR) signaling in brain regions of particular importance to comorbid tobacco addiction. This pathophysiological brain function results in intermediate phenotypes for tobacco addiction vulnerability, ranging from subcortically mediated deficits in sensory gating and reaction time/processing speed to higher order, cortical-dependent, deficiencies in working memory and executive functioning. Attention is positioned as an overarching function as it modulates information processing on several different levels. Executive functioning and behavioral inhibition depend on prefrontal cortex functioning and contribute to the ability to tolerate negative experiences (e.g., drug withdrawal) and inhibiting impulsive (e.g., relapse) behavior. Increased reinforcement by nicotine may pose another vulnerability marker for addiction in SCZ, which in this model we hypothesize may lead to increased levels of craving or impulsivity. The clinical manifestations of this multilevel vulnerability to tobacco addiction in persons with SCZ are an increased likelihood of smoking initiation, difficulties quitting, and smoking relapse. The callouts illustrate the neurotransmitter systems (DA, GABA, and GLU) in mesolimbic, mesocortical, and hippocampal brain areas that may result in tobacco addiction vulnerability in SCZ and highlight the potential nAChR treatment targets and the desired neurochemical outcome in these regions.

DA release in cortical areas.[19] In the PFC, α7- and α4β2-nAChRs are expressed on the soma of inhibitory GABAergic interneurons, while α7-nAChRs are situated on presynaptic terminals of excitatory GLUergic projections.[28,29] Stimulation of these α7-nAChRs in the PFC induces local DA release, an effect mediated via activation of ionotropic GLU receptors on neighboring DA terminals.[29] It is not clear by what specific cellular mechanism nicotine improves PFC-dependent cognition. However, in the face of concurrent pyramidal cell burst firing as induced by cognitive activities, such as working memory, effects of nicotine on long-term potentiation (LTP) are enhanced.[30] Moreover, DA release in the PFC is thought to enhance cognition by increased stimulation of modulatory DAD1 receptors (DAD1Rs) situated on GABAergic interneurons as well as on GLUergic pyramidal cell dendrites.[31]

nAChRs in the hippocampus

The distribution of nAChRs in the hippocampus is highly diverse and varies between the different strata. Predominant expression occurs on pyramidal GLUergic and GABAergic neurons and GABAergic interneurons (Fig. 1). α4β2-nAChRs are present on somatodendritic spines of GABAergic pyramidals and GLUergic axons, while α7-nAChRs are present on the somata of GLUergic and GABAergic pyramidals and GABAergic interneurons (reviewed in Ref. 12). The functional outcome of these nAChRs varies depending on location. However, taken together, enhancement of both GLUergic[32] and GABAergic transmission,[33] specifically through modulating α7-nAChR–mediated mechanisms, seems to be of primary importance for cognition in SCZ.[33]

The pathophysiology of SCZ and its relevance to cigarette smoking

Tobacco addiction and SCZ involve common neural circuits (e.g., corticostriatal circuits) and neurotransmitter systems (e.g., DA, GLU, and GABA), thus providing an heuristic link between cigarette smoking and the underlying pathophysiology of SCZ. The specific mechanisms by which SCZ pathophysiology may lead to tobacco addiction vulnerability are discussed below.

Mesocorticolimbic DA systems

SCZ was historically thought of as a disease of excessive DA in subcortical brain regions; more recently, this hypothesis has been qualified to reflect the observation that while subcortical areas appear to be in hyperDAergic state at striatal DA D2 receptors (DA2R),[34] cortical areas are in a hypoDAergic state resulting in hypostimulation of PFC DAD1Rs.[31] Striatal hyperDAergia is thought to result in the positive symptoms associated with SCZ (i.e., delusions and hallucinations), and DAD2Rs constitute the primary target for antipsychotic action.[35] Reduced DAD1R function in the PFC is thought to result in the cognitive deficits associated with SCZ.[36]

Nicotine induces both subcortical and cortical DA release, and therefore it likely interacts with the pathophysiological DA transmission displayed in SCZ (see Fig. 1). It is thought that nicotine-induced increases in PFC DA levels counteract DA imbalances in SCZ by increasing the stimulation of DAD1Rs and thus resulting in beneficial effects on cognitive performance.[6] It is less obvious how nicotine interacts with the subcortical DAergic pathology observed in SCZ. It is possible that nicotine increases subcortical DA release, similarly to the way it does in nonpsychiatric smokers,[37] but this release is not enough to exacerbate psychotic symptoms, particularly in the face of the substantial DAD2R blockade achieved by antipsychotic medication. However, the neurobiological consequences of the substantial (30–80%) blockade of DAD2Rs produced by antipsychotics, along with varying degrees of affinity for other DA receptors, on tobacco-induced DA release are unclear and warrant further investigation.

Glutamate and GABA systems

It is becoming increasingly apparent that other neurotransmitters, such as GABA and GLU, play a key role in the pathophysiology of SCZ. The GLU hypothesis for SCZ suggests that underactivity at the *N*-methyl-D-aspartate receptor contributes to the cognitive deficits in SCZ (as reviewed in Ref. 38). Imaging studies suggest that patients with SCZ have abnormal GLU activity in the hippocampus[39] and PFC.[40] Furthermore, subcortical DA activity is highly regulated by excitatory GLUergic projections onto DAergic neurons in the VTA projecting to the PFC and NAcc, as well as onto GABAergic neurons in the VTA (Fig. 1).[41] Consequently, compromised PFC glutamate function in SCZ[42] is hypothesized to result in DAergic aberrations in SCZ.[43,44]

As GLU excitatory drive is modulated by presynaptically situated α_7 nAChRs[16] such, nicotine may

activate nAChRs located on excitatory GLUergic projections onto DAergic VTA neurons and inhibitory GABAergic interneurons in the VTA. This would result in an increased GABAergic tone to DAergic neurons and thereby modulate mesolimbic DA efflux. In addition, activation of postsynaptic α4β2-nAChRs on GABAergic VTA neurons may further potentiate this effect. Such an enhancement of GLU–GABA interactions may constitute another mechanism by which nicotine counteracts the pathophysiology of SCZ.

Dorsolateral PFC (DLPFC) dysfunction has been proposed to be one of the most central contributions to higher order cognitive deficits in SCZ.[45] Alterations in GABAergic cortical inhibition is suggested to be one of the key abnormalities in SCZ that contributes to DLPFC-dependent cognitive impairments.[46,47] Case-control postmortem studies indicate reduced production of GABA in the PFC[48] and hippocampus[49] in SCZ. Interestingly, α7-nAChRs are abundant on GABAergic interneurons in the hippocampus, PFC, and thalamus,[33] and thus nicotine could hypothetically counteract these GABAergic deficits (see Fig. 1). Moreover, recently published data show that α4β2-nAChRs in the mouse PFC regulate epigenetic changes of GABAergic interneurons, suggesting that α4β2-nAChRs may also constitute a suitable target to treat GABAergic deficits in SCZ (see Fig. 1).[50]

nAChR systems

Several postmortem studies show that low-affinity nAChRs are reduced in the PFC, thalamus, and hippocampus of patients with SCZ.[33,51,52] Moreover, the upregulation of high-affinity nAChRs, which is typically found in the brains of healthy smokers in areas such as the hippocampus, cortex, and caudate nucleus, was not found in smokers with SCZ;[53] this finding has recently been replicated in a SPECT study.[54] On the contrary, a study by Mexal *et al.*[55] found that CHRNA7 (the α7 nAChR subunit gene) mRNA and protein levels in smokers with SCZ were normalized to the levels of healthy smokers, suggesting that smoking may in fact counteract some of the pathophysiological aberrations of SCZ. The authors propose that the sufficient protein but low surface expression of the α7-nAChR, seen in the autoradiographic and SPECT studies, reflects aberrant assembly or trafficking of the receptor.

Genetic studies have also highlighted the apparent link between nAChR function, SCZ, and smoking. The CHRNA7 gene is considered a heritability site for SCZ.[56] The 15q14 locus near the coding region of the CHRNA7 gene has been consistently linked to SCZ[56–58] and deficits in sensory gating found in the disorder (see section "P50 suppression"). The CHRNA4 gene in combination with the CHRNB2 gene[59] and a single nucleotide polymorphism (SNP) in the CHRNA5 gene[60] have also been associated with SCZ, again suggesting genetic overlap between tobacco addiction and SCZ. Another study found a polymorphism of the CHRNA3 gene to be associated with negative symptom severity, number of psychotic episodes, and dose of antipsychotic treatment in SCZ.[61] Additionally, studies have found linkage between smoking in SCZ and both loci on genes encoding the α2, β2, and α7 nAChR subunits[62] and a dinucleotide repeat in intron 2 of the CHRNA7.[63]

In summary, postmortem and genetic findings indicate that both high- and low-affinity nAChRs are dysregulated in SCZ. This aberrant nAChR neurochemistry likely contributes to increased vulnerability to tobacco addiction found in SCZ; however, the precise mechanism through which this occurs is not yet known. Leonard *et al.* proposed that alterations in nAChRs in SCZ lead to changes in overall neurotransmitter release and altered gene expression (via intracellular calcium signaling).[64]

Taking the above findings together, the pathophysiology of SCZ, specifically abnormalities in GABA, GLU, and DA neurotransmitter systems, may be due to aberrant nAChR signalling, which likely contributes to tobacco addiction vulnerability in SCZ. As such, stimulation of nAChRs by nicotine may increase GLU and GABA activity and modulate DA signaling in the mesocorticolimbic pathways, thereby counteracting the neurochemical aberrations associated with SCZ.

Procognitive effects of nicotine and cigarette smoking in SCZ

A core feature of SCZ is the cognitive impairment deficits that is found in a wide range of cognitive domains and is an important predictive factor for functional outcome in SCZ.[65] Deficits in preattentive sensory information processing (i.e., the inability to filter out or gate sensory information) are hypothesized to contribute to the higher order cognitive deficits, such as attention, working memory (WM), verbal learning and memory, decision making, and

executive functioning.[66–68] These deficits are poorly alleviated by available antipsychotic treatments, and despite plentiful efforts to identify cognitive enhancing compounds for patients with SCZ, relatively few successful strategies have emerged.

As reviewed herein, dysregulation of nAChRs in the hippocampus and PFC seems to contribute to the deficient preattentive sensory gating and subsequent higher order cognitive deficits observed in SCZ. Thus, it is not surprising that studies of both neurophysiological and neuropsychological measures of cognitive function in SCZ have consistently identified improvements following nicotine challenge and impairments following nicotine abstinence.

Sensory information processing

P50 suppression. P50 suppression measures cortical electroencephalography (EEG) response, which occurs 50 ms after an auditory stimulus. When a second tone is presented 500 ms after the first tone, the EEG response to the second tone is suppressed.[69] Patients with SCZ fail to suppress the response to the second tone and thus display gating deficits.[70] A total of 40–50% of first-degree relatives of patients with SCZ also display P50 abnormalities, suggesting that the inability to gate incoming sensory information is partially heritable.[71] Several studies have shown that acute nicotine challenge may improve P50 suppression, but this appears to be dependent on diagnosis, genotype, and baseline gating levels. As such, cigarette smoking transiently improves P50 suppression in abstinent smokers with chronic SCZ[72] and first episode psychosis.[73] In addition, nicotine gum transiently improves P50 suppression in nonsmoking, gating-impaired relatives of people with SCZ.[74] Although smoking typically reduces P50 suppression in healthy smokers,[72,73] Knott *et al.* found nicotine gum improved P50 suppression in healthy controls that were low-baseline gaters.[75–77]

P50 deficits have been linked to a locus on chromosome 15 (q14) near the coding region for the α7-nAChR[56] as well as to polymorphisms in the promoter region of the CHRNA7 gene.[78] Moreover, P50 suppression is dependent upon GABAergic interneurons in the hippocampus, which are populated by α7-nAChRs.[79] Consequently, it has been hypothesized that the reduced expression of α7-nAChRs in SCZ may contribute to P50-gating abnormalities[33,79] and that the improvement of P50 suppression by nicotine is mediated by hippocampal α7-nAChRs located on GABAergic neurons (Fig. 1).[33]

Prepulse inhibition. Prepulse inhibition (PPI) measures the blinking reflex to a startling tone, using electromyographic (EMG) recordings of the eye muscle. In healthy individuals, the blinking reflex following a loud startling stimulus is attenuated by a weak proceeding prepulse (i.e., "prepulse inhibition"); this gating mechanism is deficient in patients with SCZ.[80] PPI deficiencies have been found to make up a stable endophenotypic marker as it is genetically transmitted and present in first-degree relatives of patients with SCZ.[81,82] Interestingly, one study found PPI performance in SCZ and control populations was associated with a polymorphism of the CHRNA3 gene.[61] Nicotine (via nasal spray or subcutaneous injection) has been shown to improve PPI in both healthy smokers and in smokers as well as nonsmokers with SCZ.[83,84] However, another study found that PPI in smokers with SCZ—but not control smokers—was impaired by overnight smoking abstinence.[85] Moreover, abstinence-induced PPI deficits were reversed by the resumption of smoking, an effect that was blocked by the nAChR antagonist mecamylamine,[85] thus demonstrating that the effects of smoking on PPI are dependent upon stimulation of high-affinity nAChRs. In addition, cross-sectional findings suggest PPI is reduced in nonsmokers with SCZ compared to control nonsmokers, whereas (satiated) smokers with SCZ have comparable levels of PPI to control smokers.[86] Finally, smoking status may modulate the association between sensory gating and higher order cognitive functions in SCZ, as such PPI was correlated with executive function in SCZ smokers but not in controls or SCZ nonsmokers.[87] Overall, nicotine seems to modulate PPI differentially in persons with, compared to without, SCZ.

PPI activates various brain regions, such as the hippocampus, thalamus, striatum, and the parietal and frontal cortex; the same regions are activated in patients with SCZ, but to a lesser extent.[88] Nicotine-induced improvements in PPI correlated with increased hippocampal activity in both patients with SCZ and in control subjects,[84] further highlighting the connection between nicotine, the hippocampus, and sensory gating. Taken together, these results

indicate that the dysfunctional nAChR mechanisms may contribute to the PPI deficits found in SCZ.

Smooth pursuit eye movement. Smooth pursuit eye movement (SPEM) tasks measure visual sensory processing by recording saccades (fast eye movements in the direction of a stimulus) and antisaccades (eye movements away from a stimulus) and thus assess inhibitory mechanisms within the visual domain. Patients with SCZ display less SPEM and more intruding saccades than their healthy counterparts,[89] and similarly to other gating deficits, these abnormalities appear to be heritable.[90] Certain aspects of SPEM (e.g., abnormalities in leading saccades) can be improved by nicotine in persons with SCZ, but not in controls,[91–94] suggesting specificity of nicotine's effects to SCZ. Functional magnetic resonance imaging (fMRI) studies have shown that nicotine reduces hippocampal activity during a SPEM task in both SCZ and control groups[95] and may also alleviate the overactivity found in patients with SCZ in the fusiform gyrus and posterior hippocampus during performance of SPEM tasks in patients with SCZ.[96]

Mismatch negativity. Mismatch negativity (MMN) is a measure of auditory sensory memory, assessed by measuring event-related potentials (ERP). Patients with SCZ demonstrate reduced ERP amplitudes in MMN tasks compared with controls.[97] In smokers with SCZ, acute nicotine gum treatment was found to improve specific aspects of sensory memory (i.e., abnormalities in the duration amplitude),[98] thus inferring that nicotine can alleviate higher order deficits in sensory information processing besides inhibitory gating impairments.

Neuropsychological performance

Evidence for the "procognitive" effects of nicotine and cigarette smoking on neuropsychological performance comes from both laboratory paradigms and smoking cessation treatment trials. Nicotine administration (via the patch or gum) to both satiated and abstinent cigarette-smoking patients with SCZ has been shown to improve a range of cognitive functions including reaction time, attention, and verbal and spatial working memory (WM).[99–104] Furthermore, both short- (overnight)[26] and long-term (10 weeks)[27] abstinence from cigarette smoking has been shown to impair spatial WM in persons with SCZ; this effect was remediated by the resumption of smoking.[26] The procognitive effects of tobacco smoking reported by Sacco *et al.* (2005) were blocked by administration of the nAChR antagonist mecamylamine[26] and were correlated with circulating levels of nicotine,[105] thereby demonstrating that these effects were mediated by nicotine and not one of the other constituents of tobacco smoke or by nonspecific effects related to the act of smoking. Cross-sectional data from our laboratory also support the notion of cognitive-enhancing effects of cigarette smoking in SCZ; as such, nonsmokers with SCZ were found to have poorer neuropsychological performance than smokers with SCZ, particularly in the domains of sustained attention, WM, and processing speed.[27,106] Finally, it has been reported that smokers with SCZ who have the most severe PFC-related neuropsychological impairments (e.g., WM and executive function deficits) are the least likely to achieve trial endpoint smoking cessation.[107,108] Cognitive deficits may therefore constitute important targets for smoking cessation therapies aimed at patients with SCZ.

Where a nonpsychiatric control group was included in the studies described in the paragraph above, the procognitive effects of nicotine and cigarette smoking were less robust or even absent in the control group.[26,27,101,104,107] Brain imaging studies are beginning to reveal the neural mechanism underlying these differences. In tasks involving WM and selective attention, the improved performance produced by nicotine administration to SCZ patients is related to enhanced activation of, and functional connectivity between, brain regions that mediate task performance.[101] However, other studies suggest that although nicotine enhances visual sustained attention and associated brain activity in SCZ, it does not normalize it.[109]

In summary, nicotine administration and cigarette smoking have been found effective in remediating various neurophysiological and neuropsychological deficits associated with SCZ. Deficits of sensory information processing are stable endophenotypic markers of SCZ that seem to be particularly sensitive to alterations of the nicotinic system and manipulations thereof. The remediation of neuropsychological performance by nicotine has been most consistently observed in cognitive domains associated with DA release in cortical and

subcortical brain regions, such as sustained attention, reaction time, and WM.[26,27,99,101–104] In contrast, the effects of nicotine and cigarette smoking on the cognitive performance of nonpsychiatric control smokers are more heterogeneous and likely relate to deprivation-reversal effects.[110] Taken together, these findings suggest that in SCZ there is a link between the cholinergic system and cognition that is fundamentally different from that in healthy control smokers. Accordingly, neurocognitive deficits form an important vulnerability marker for smoking in SCZ and targeting these deficits (via nAChR and related neurotransmitter systems) may improve smoking cessation outcomes in patients with SCZ.

Cigarette smoking behavior in schizophrenia

Not only are individuals with SCZ more likely to smoke, but there appear to be distinct differences in their smoking behavior compared to smokers without a psychiatric illness. Smokers with SCZ smoke on average more cigarettes per day and are more nicotine dependent.[2] Genetic studies have begun to identify markers associated with the risk of smoking and heaviness of smoking. With regard to nicotinic receptor signaling, Hong *et al.* found that a SNP in the CHRNA5 gene was significantly associated with smoking severity in smokers with and without SCZ.[60] Genes relating to brain-derived neurotrophic growth factor (BDNF) and DAergic signaling have also been associated with the risk of smoking and the quantity of tobacco smoked in persons with SCZ,[111] while recent evidence indicates that an SNP in the NR4A3 orphan nuclear receptor, which is expressed throughout DAergic signaling pathways, is associated with heaviness of smoking.[112,113] However, further studies are needed to determine whether these genetic markers contribute to the increased smoking prevalence found in SCZ compared to the general population.

Even when matched on the number of cigarettes smoked per day and indices of nicotine dependence, smokers with SCZ have higher plasma and urine levels of nicotine and cotinine (the proximal metabolite of nicotine).[114–116] It is thought that these differences are the results of the manner in which cigarettes are smoked by persons with SCZ rather than differences in the metabolism of nicotine.[117] Smoking topography studies indicate that persons with SCZ smoke more intensely: they take significantly more puffs, have shorter inter puff intervals, and have larger total cigarette puff volumes compared to matched healthy control smokers.[118] Such measures are thought to represent an *in vivo* measure of the reinforcing effects of smoking, supporting the idea that nicotine is more reinforcing in people with SCZ. In addition, in a cigarette demand task, smokers with SCZ exhibited significantly higher intensity of demand and greater consumption and expenditure (which correlated with smoking topography measures), indicating higher incentive value of cigarettes among patients with SCZ.[119]

Craving is a well-recognized and important aspect of dependence, but it is unclear whether smokers with SCZ crave tobacco more than control smokers, as some studies report high levels in smokers with SCZ,[120] while others do not.[115] There is, however, evidence to suggest that there are differences in the type of craving experienced; for example, smokers with SCZ are more likely report a reduction in negative affect as their greatest smoking expectancy.[121] With regards to cue-induced craving, there appears to be little difference between SCZ and control smokers.[122–124] Nevertheless, a recent study of responses to personalized smoking cues (10 minutes after having smoked a cigarette) reported that scores on the Minnesota Nicotine Withdrawal Scale, specifically the negative mood item, were increased in the SCZ but not in the control group.[122] Finally, mecamylamine, an nAChR antagonist, reduced cue reactivity in smokers with SCZ, but not in control smokers;[123] the authors proposed that this difference may be due to the lower levels of *central* nAChRs in patients with SCZ.

The increased reinforcing effects of, and craving for, tobacco found in persons with SCZ suggest that these factors are likely to be important targets for tobacco treatments aimed at smokers with SCZ, particularly given that topographic measures of smoking behavior[125] and self-reported craving[126] have been associated with smoking abstinence and relapse rates in nonpsychiatric smokers.

A neurobiological vulnerability model for comorbid tobacco addiction in SCZ

Patients with SCZ display various neurobiological abnormalities that may result in an addiction-vulnerable behavioral state that in turn produces the increased susceptibility to the initiation and maintenance of tobacco addiction and failure to quit

smoking found in SCZ. This model (outlined in Fig. 1) highlights the critical pathologies that contribute to this comorbidity, ranging from genetics and neurochemical aberrations, to information processing and cognitive deficits, to behavioral phenotypes. In addition, we highlight potential nAChR-related treatment targets for smokers with SCZ, discuss the treatment implications of the proposed model, and provide an example of how this model could be used to guide future medication development for this population.

A model to explain the vulnerability of people with SCZ to tobacco addiction

We propose that genetic and environmental factors (which are beyond the scope of this review) lead to deficient nAChR signaling and aberrant DAergic transmission in the mesocorticolimbic systems (increased DA in subcortical areas and reduced DA in cortical areas) in SCZ, in concert with GABA ergic and GLUergic imbalances. Such a brain pathophysiology results in cognitive deficits ranging from preattentive sensory information processing to reaction time, attention, and WM. These intermediate neurocognitive phenotypes are hypothesized to result in a nicotine addiction–sensitive state, as such deficits are, at least transiently, alleviated by cigarette smoking in SCZ. The contribution of abnormalities in the mesolimbic DAergic reward system to comorbid tobacco addiction in SCZ is less clear. In this model, we propose that such abnormalities, through as yet unknown mechanisms, may underlie the increased tobacco craving and sensitivity to the reinforcing effects of tobacco that have been reported in SCZ. Given the apparent heightened significance of tobacco reinforcement and craving in smokers with SCZ and their association with relapse rates in non–mentally ill smokers (which are assumed to extend to smokers with SCZ), these are hereby suggested to be important intermediate markers of tobacco addiction in SCZ and therefore should be assessed in smoking cessation trials conducted in this population.

Finally, deficits in response inhibition and increased levels of impulsivity are known to contribute to increased smoking initiation and inability to quit in nonpsychiatric populations. A recent study from our laboratory found delay discounting (a form of impulsivity) to be higher in current and former smokers with SCZ compared to never smokers with SCZ, suggesting that in SCZ this is a trait associated with having ever smoked.[127] Given that the high impulsivity associated with smoking does not decrease to the level of a never smoker upon quitting, as is the case in nonpsychiatric smokers,[128] increased delay discounting may posit a potential risk factor for continued smoking in SCZ. Therefore, although mainly speculative at present, deficits in impulsivity have been positioned as a possible catalyst of smoking behavior in SCZ in this model.

Hypothetical neurobiological treatment targets highlighted in the proposed model

A primary focus of this review has been the nAChR system as it contributes to comorbid tobacco addiction in SCZ, and thus we propose several nAChR-related approaches of attenuating the neurochemical, cognitive, and behavioral vulnerabilities underlying this comorbidity and thus potentially treating tobacco addiction in SCZ. These strategies include modulating DA-, GLU-, and GABA-ergic transmission in the striatum, PFC, and hippocampus via nAChRs. Needless to say, there are many other alternative approaches to modulate these neurotransmitter systems; however, it is not within the scope of this article to review these approaches.

DA release in the NAcc, resulting from stimulation of nAChRs on DA, GABA, and GLU neurons, is critical to the reinforcing effects of nicotine. Two nAChR-related approaches could be taken to modulate the subcortical release of DA: stimulation of nAChRs by agonists to mimic the action of tobacco smoke or blockade of nAChRs by antagonists to attenuate the effects of tobacco smoke. Both approaches have been tested in nonpsychiatric smokers, with the former being more effective. Studies in SCZ have found nicotine replacement to be somewhat effective in treating tobacco dependence. It is unlikely that nAChR antagonism will be a desirable approach in smokers with SCZ, as this will likely result in unwanted detrimental effects on cognitive function. It may seem counterintuitive to increase striatal DA in persons suffering from a disorder characterized by subcortical hyperDAergia; however, given that cigarette smoking and nicotine administration have limited effects on psychotic symptoms, increasing DA release, at least to the level achieved by nicotine, will unlikely result in exacerbation of psychiatric symptomatology. Nevertheless, recent research, currently limited

to nonpsychiatric populations, indicates that partial agonism may in fact be the most effective nAChR-related approach to treat tobacco dependence and may also be a suitable approach for smokers with SCZ.

In the PFC, it is desirable to increase DA release, along with increasing GLU and GABAergic tone, in an effort to remediate the cognitive deficits associated with SCZ, and thereby eliminating the need for tobacco smoking to achieve the same effect. As discussed above, such modulation is complicated by the need to maintain an optimal balance with the DAD2R blockade achieved by antipsychotic treatment. Ideally, treatment should be optimized to enhance DA tone to a level that does not override the desirable effects of antipsychotic, or to specifically target DA release onto DAD1Rs located in the PFC. To counteract sensory gating deficits and possibly memory impairments associated with SCZ, increased GABA and GLU signaling in the hippocampus is suggested.

Treatment implications of the proposed model

Treatment strategies for tobacco dependence in SCZ currently rely on the three standard first-line pharmacotherapies approved by the Food and Drug Administration for use in adult smokers: nicotine replacement therapies (NRTs), the antidepressant bupropion (Zyban®), and the nAChR partial agonist varenicline (Chantix® in the United States and Champix® in the United Kingdom and Canada). NRT is safe in smokers with SCZ, but lower than expected long-term abstinence rates have been reported.[129,130] Bupropion is also well tolerated by patients with SCZ and appears to be somewhat more effective than NRT.[131] Varenicline is believed to be the most effective smoking cessation pharmacotherapy currently available,[132] and it appears to be effective in smokers with SCZ, but these data were obtained in small or uncontrolled trials.[133–135] While the currently available pharmacotherapies are of benefit to smokers with SCZ, relapse rates remain high, and it is apparent that this population, with its high vulnerability to tobacco addiction, would benefit from more targeted treatment strategies. In this review, we have presented a neurobiological vulnerability model for tobacco addiction in SCZ that highlights potential targets (genetic, neurochemical, cognitive, and behavioral) for novel and, importantly, more effective tobacco treatments for smokers with SCZ; the practical application of some of these options are discussed below.

Given that cognitive functioning can predict smoking cessation success in SCZ[107,108] and that abstinence can result in further cognitive decline,[26,27] it can be hypothesized that improving cognitive deficits in SCZ (by pharmacological and behavioral techniques) may improve quit rates. In addition, this information has led researchers to begin to view the nAChR system not only as an important target for smoking cessation in SCZ but also for the remediation of cognitive deficits associated with SCZ itself (regardless of cigarette-smoking status). Of particular significance is the inclusion of nAChRs in the list of the most promising targets for the treatment of cognitive deficits in SCZ by the National Institute of Mental Health consensus panel on the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS).[136] As a result, plentiful research efforts have been directed to investigating ways in which nAChR neurotransmission may be modulated to enhance cognitive functioning. Compounds targeting the low-affinity α7-nAChR subtype have been particularly well investigated. The Freedman laboratory has conducted a series of studies examining the effects of the α7-nAChR partial agonist DMXB-A on cognitive function in SCZ. The phase I trial revealed promising effects on memory, attention, and P50 inhibition deficits in patients with SCZ.[137] Although these effects were not replicated in a larger phase II study, improvements in negative symptoms were observed.[138] Tropisetron, another α7-nAChR partial agonist, has been shown to improve the auditory gating deficits in SCZ.[139] It is important to note that these studies were conducted in nonsmokers, and it will therefore be of great interest to evaluate these compounds in smoking patients. Moreover, given that both high-[26,85] and low-affinity[78] nAChRs appear to play a role in the procognitive effects of nicotine, medications targeting both receptor subtypes simultaneously may be particularly effective. Varenicline, a α4β2-nAChR partial agonist and α7-nAChR full agonist,[140] can improve cognitive function[141] and increase WM-related brain activity during abstinence in non–mentally ill smokers.[142] Some beneficial cognitive effects of varenicline have also been reported in smokers with SCZ, but these studies were limited by open-label[134] and nonrandomized designs.[143]

Cognitive deficits associated with SCZ are thought to be the result of reduced DA transmission in the PFC; therefore, enhancing DA transmission in this region is also regarded as a promising cognitive-enhancing strategy.[136] A small preliminary study of atomoxetine, a DA and NA reuptake inhibitor that acts primarily in the PFC, found a trend toward improved spatial WM and verbal fluency and a reduction in cigarette smoking in SCZ.[144] Further large-scale studies are needed to provide a definitive answer on the future of drugs targeting PFC DA dysfunction. GABAergic and GLUergic neurotransmission also plays an important role in nicotine addiction and the pathophysiology of SCZ. Interestingly, compounds targeting these systems have shown some promise as potential smoking cessation therapies in healthy populations. For example, Baclofen (a $GABA_B$ agonist)[145] and *N*-acetylcysteine (a cysteine prodrug that acts as an Na^+/Ca^{2+} exchange pump inhibitor to normalize synaptic glutamate levels) have demonstrated promising antismoking effects in initial clinical trials.[146] It is therefore of great importance to determine the effects of these and other pharmacologic compounds targeting GLU- and GABAergic signaling in smokers with SCZ. Additionally, an intriguing observation is that the clinically superior antipsychotic drug, clozapine, may reduce smoking rates in patients with SCZ,[147,148] an affect that has been ascribed primarily to its $GABA_B$ receptor affinity.[149] Further large-scale long-term studies are needed to clarify the efficacy and safety profile of administering clozapine to aid smoking cessation in SCZ. Lastly, the potential of behavioral strategies to improve cognitive function should not be overlooked. Studies using cognitive remediation therapies (CRTs) are reporting promising effects in SCZ,[150] and it will be interesting to elucidate the effect of CRTs on smoking cessation in persons with SCZ.

An example of how the model can guide novel treatment development for smokers with SCZ

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive brain stimulation technique that is currently under investigation for a range of psychiatric and addictive disorders. When targeted to the DLPFC (an area not only involved in higher order cognitive functions but also in drug craving and decision making), rTMS reduces cigarette craving (and consumption) in nonmentally ill smokers[151,152] and improves cognitive deficits in SCZ (Daskalakis *et al.*, personal communication). Given the promising effects of rTMS effects on two intermediate markers of tobacco addiction in SCZ proposed in our model (ie., craving and cognitive problems), we recently examined its safety and efficacy in a preliminary study of treatment-seeking smokers with SCZ. Craving induced by short-term abstinence was attenuated in patients treated with active compared to sham rTMS (Wing *et al.*, preliminary findings), suggesting this treatment should be evaluated further. This study demonstrates how vulnerability factors proposed in the model may be targeted to improve the efficacy of smoking cessation targets aimed at patients with SCZ.

Future directions

In this review, we have attempted to assimilate the current literature describing the neurobiological links between smoking and SCZ. While the field has clearly provided many recent advances in knowledge, there are still areas that remain underresearched either due to anticipated methodological issues, technological restrictions, or lack of awareness. Based on the current state of the research field, suggested future research directions are provided below.

Improving neuroplasticity: a pathway to reducing smoking behavior in SCZ?

In the face of plentiful efforts to enhance cognition, it is feasible that the lack of successful development of cognitive-enhancing agents (which we hypothesize will decrease tobacco addiction in SCZ) may be due to an overly optimistic belief in pharmacologically induced cognitive improvement being viable without concurrent cognitive training (i.e., simultaneous *neuroplasticity* rearrangements such as LTP). Given the neurochemical imbalances apparent in SCZ, it is not suprising that patients with SCZ display decreased LTP-like activity-dependent facilitation in the motor cortex, accompanied by decreased motor learning.[153] As discussed above, nicotine could improve cognition by enhancing GLU- and DAergic transmission in the PFC, and thereby modulate synaptic plasticity and LTP.[29] In addition, strengthening plasticity of neuronal networks governing beneficial behaviors (e.g., response

inhibition) may prove to be a useful strategy for tackling drug addiction. It remains to be tested if nicotine can enhance synaptic plasticity in SCZ; however, if this is the case, it provides further rationale for using nicotine-like drugs (alone or in combination with other pharmacological agents or CRT) to improve cognitive deficits and decrease nicotine addiction in SCZ.

Nicotine reinforcement and impulsivity: what role do they play in comorbid tobacco addiction in SCZ?

While much attention has been paid to the procognitive effects of nicotine in SCZ, somewhat surprisingly there has been relatively little study of the reinforcing effects of nicotine in SCZ. Some studies suggest that smokers with SCZ may find cigarette smoking more reinforcing and perhaps crave tobacco more than their nonpsychiatric counterparts. Further studies are needed to confirm these effects and clarify their role in the initiation, maintenance, and relapse to tobacco addiction and therefore their suitability as intermediate markers of dependence and ability to quit, as proposed in our model.

Another potentially important vulnerability factor for tobacco addiction in SCZ is *impulsivity*. Impulsivity is a common trait among cigarette smokers,[128] predicts relapse to smoking in nonpsychiatric populations,[154,155] and is also a common feature of SCZ,[156] yet investigation into its role in comorbid tobacco addition in SCZ is in its infancy.[119,127] Further within subject and longitudinal studies are needed to determine the effects of abstinence from smoking on impulsivity in SCZ and its role in mediating smoking initiation and ability to quit. It is possible that therapies aimed at reducing impulsivity may help smokers quit and, more important, maintain abstinence.

Cigarette smoking status: an endophenotypic marker for SCZ?

The majority of research in this field has focused on the effects of nicotine in smokers with SCZ, but two very important but often overlooked groups of patients with SCZ are those who have been able to quit smoking (former smokers) and those who never took up cigarette smoking (never smokers). We took such approach in two of our recent studies and interestingly found substantial differences in the never smoker group in that they had the poorest performance on neuropsychological tests assessing attention and processing speed[106] but were significantly less impulsive.[127] These subtypes of patients could potentially provide us with important insights into the factors that provide some form of "protection" from tobacco dependence, either at the initiation (never smokers) or relapse stage (former smokers).

Can brain imaging help us understand the links between SCZ and tobacco addiction?

With ever-advancing technology, one area that promises to provide great insights into the neurobiological mechanisms underlying comorbid tobacco dependence in SCZ is *brain imaging*. fMRI studies will be able to inform us if regions associated with nicotine reward (e.g., the NAcc), aversion (e.g., the habenula), craving (e.g., the anterior cingulate), and cognitive function (e.g., the PFC) are over- or underactive in smokers with SCZ, while positron emission tomography (PET) studies could elucidate the distribution and expression of nicotinic, DA, GABA, and GLU receptor subtypes in SCZ, with respect to smoking initiation, maintenance, and cessation, and shed light on the neurotransmitter systems affected by smoking in people with and without SCZ (e.g., does smoking lead to increased striatal and/or cortical DA release in persons with SCZ?).

What are the genetic contributions to tobacco addiction vulnerability in SCZ?

The field of genetics is allowing new insights to be gained into the heritability of addictive disorders. With regard to cigarette smoking behavior, genes coding for nAChRs and cytochrome P450 enzymes involved in the metabolism of nicotine have been most consistently linked to nicotine dependence and smoking cessation outcomes.[157] To date, there have been few such studies in SCZ, possibly due to the high numbers of subjects required for genetic studies and the difficulties with subject recruitment in SCZ populations. However, it will be important to determine the genetic contributions toward smoking in SCZ (e.g., craving and withdrawal symptoms and risk of relapse). One area in which genetics has already provided significant insights is the role of α7-nAChRs in information-processing deficits (i.e., P50 suppression) in SCZ. Future genetic studies should explore the role of alternative nAChR subtypes and their contribution to nicotine's effects on other cognitive domains (e.g., PPI, attention, and WM). A particularly exciting area of addiction treatment research at the moment

is the implementation of pharmacogenetics to guide treatment choices;[158,159] it will be of interest to see if such methods could also be applied successfully to mentally ill smokers.

Conclusions

SCZ is associated with a range of neurobiological vulnerability factors that likely act in concert to result in the clinical manifestations of tobacco addiction observed in SCZ (i.e., increased susceptibility to tobacco smoking at the initiation, maintenance, and relapse stages of addiction). We have proposed a model to illustrate the genetic and neurochemical mechanisms (particularly DA, GABA, GLU, and nAChR dysfunction in the PFC, striatum, and hippocampus) that lead to nicotine-sensitive cognitive deficits, increased sensitivity to the reinforcing effects of tobacco smoke and craving, and possibly the increased impulsivity found in SCZ. The emerging genetic, neurochemical, and behavioral studies that link tobacco dependence and the pathophysiology of SCZ promise to increase our understanding of this complex comorbidity and facilitate the development of much needed novel treatment approaches for tobacco comorbidity in these patients, as well as better treatments directed at the pathobiology of SCZ.

Conflicts of interest

The authors declare no conflicts of interest.

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