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## nAChR dysfunction as a common substrate for schizophrenia and comorbid nicotine addiction: current trends and perspectives

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### Abstract

**Introduction**—The prevalence of tobacco use in the population with schizophrenia is enormously high. Moreover, nicotine dependence is found to be associated with symptom severity and poor outcome in patients with schizophrenia. The neurobiological mechanisms that explain schizophrenia-nicotine dependence comorbidity are not known. This study systematically reviews the evidence highlighting the contribution of nicotinic acetylcholine receptors (nAChRs) to nicotine abuse in schizophrenia.

**Methods**—Electronic data bases (Medline, Google Scholar, and Web of Science) were searched using the selected key words that match the aims set forth for this review. A total of 275 articles were used for the qualitative synthesis of this review.

**Results**—Substantial evidence from preclinical and clinical studies indicated that dysregulation of  $\alpha 7$  and  $\beta 2$ -subunit containing nAChRs account for the cognitive and affective symptoms of schizophrenia and nicotine use may represent a strategy to remediate these symptoms. Additionally, recent meta-analyses proposed that early tobacco use may itself increase the risk of developing schizophrenia. Genetic studies demonstrating that nAChR dysfunction that may act as a shared vulnerability factor for comorbid tobacco dependence and schizophrenia were found to support this view. The development of nAChR modulators was considered an effective therapeutic strategy to ameliorate psychiatric symptoms and to promote smoking cessation in schizophrenia patients.

**Conclusions**—The relationship between schizophrenia and smoking is complex. While the debate for the *self-medication* versus *addiction vulnerability* hypothesis continues, it is widely accepted that a dysfunction in the central nAChRs represent a common substrate for various symptoms of schizophrenia and comorbid nicotine dependence.

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## Keywords

schizophrenia; smoking; comorbidity; nAChRs; cognition; reward

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## 1. Introduction

### 1.1. Association between cigarette smoking and schizophrenia

Schizophrenia is a chronic and debilitating mental illness that affects 1% of the world population (Saha et al., 2005). People diagnosed with schizophrenia display a combination of positive (hallucinations, delusions and thought impairments), negative (diminished emotional expression, loss of motivation and psychosocial impairments) and cognitive (disorganized thought, attention and working memory deficits, and executive dysfunction) symptoms (Wong and Van Tol, 2003). The psychotic symptoms have an episodic pattern and can be controlled by antipsychotic drugs, but the negative and cognitive symptoms tend to show limited improvement and tend to persist despite treatment with these drugs (Bowie and Harvey, 2006; Hill et al., 2010; Keefe and Fenton, 2007; Tandon and Jibson, 2002). Although extensive evidence indicates alterations in several neurotransmitters systems including dopamine (DA), glutamate, and GABA (Howes and Kapur, 2009; Lewis et al., 1999; Moghaddam and Krystal, 2012), the etiology and pathophysiology of schizophrenia still remains unclear.

Patients with schizophrenia generally have a higher incidence of substance use disorders as compared to the normal individuals (Volkow, 2009). The most frequently abused substances in subjects suffering from schizophrenia include tobacco, cannabis, alcohol and cocaine (Green, 2005; Thoma and Daum, 2013; Winklbaur et al., 2006). Interestingly, nicotine - which is the main psychoactive ingredient of tobacco, is the most prevalent drug abused by patients with schizophrenia. The incidence of tobacco smoking in individuals with schizophrenia is estimated to be 80–90% versus 20–30% in the general population (de Leon and Diaz, 2005; George and Krystal, 2000). Moreover, smokers with schizophrenia consume more cigarettes and extract higher nicotine from their cigarettes as compared to normal smokers (Olincy et al., 1997; Strand and Nyback, 2005). Additionally, patients with schizophrenia experience greater reinforcing effects of smoking and more severe withdrawal symptoms during abstinence than smokers without schizophrenia (Diaz et al., 2006; Spring et al., 2003; Weinberger et al., 2007). Thus, subjects with schizophrenia are more vulnerable to develop nicotine dependence and smoking cessation in these individuals remains very challenging. Nicotine dependence is also found to be associated with symptom severity and poor outcome in patients with schizophrenia (Krishnadas et al., 2012). Furthermore, heavy smoking in these individuals makes them highly susceptible to develop various disorders such as cardiovascular diseases, lung cancer, and pulmonary conditions, resulting in premature mortality (Hennekens, 2007; Kelley et al., 2011; Shanmugam et al., 2007; Wehring et al., 2012). Therefore, a fundamental understanding of the neurobiological mechanisms that contribute to comorbid nicotine use in schizophrenia is essential to develop therapeutic strategies to improve smoking cessation, treatment outcome and life span of patients suffering from schizophrenia. Although comorbid nicotine use is also known to exist with other psychiatric conditions such as anxiety-related disorders, depression, bipolar

disorders and post-traumatic stress disorders (Kutlu et al., 2015; Lasser et al., 2000), the discussion for this review is restricted to schizophrenia only.

The causal mechanisms explaining the widespread smoking behavior among subjects with schizophrenia have remained complex. However, there have been two overarching theories proposed to explain widespread smoking behavior among subjects with schizophrenia. The first one is the *self-medication* hypothesis that posits that excessive nicotine use represents a form of self-medication strategy to alleviate the negative and cognitive symptoms of the disorder (Adler et al., 1998; Kumari and Postma, 2005; Leonard et al., 2007; Sacco et al., 2004). The remediation of schizophrenia symptoms by nicotine is proposed to involve modulation of neurotransmitter signaling that is implicated in schizophrenia pathology (Kumari and Postma, 2005). Higher comorbidity of smoking is also suggested to represent a strategy to combat the aversive effects of antipsychotic medication and this perspective complements the *self-medication* hypothesis (Barr et al., 2008; Kumari and Postma, 2005). However, there is evidence of nicotine consumption in first-episode psychotic subjects that are not exposed to any antipsychotic medication (McEvoy et al., 1999), which indicates that this view may not completely explain higher smoking rates in patients with schizophrenia. The second one is the *shared vulnerability* hypothesis that proposes that shared genetic/environmental factors and neurological deficits inherent to the pathophysiology of schizophrenia make subjects with schizophrenia more vulnerable to tobacco use (Chambers, 2009; Chambers et al., 2001). Based on this model, the shared genetic and neurobiological factors produce nicotine-sensitive cognitive deficits, sensitized reinforcing effects of nicotine, heightened craving during abstinence and increased impulsivity in the schizophrenia population increasing their susceptibility to tobacco smoking at the initiation, maintenance and relapse stages of addiction. Unlike the *self-medication* hypothesis, this model does not assume any benefits underlying the comorbidity and points only towards neurobiological mechanisms or outcomes that are detrimental. While the available evidence from human and animal studies presents merits and limitations of both models, neither one of those has been confirmed to solely explain the strong association between smoking and schizophrenia. Regardless of how comorbidity develops, a fundamental understanding of the neurobiological mechanisms that contribute to comorbid nicotine use in schizophrenia is essential to develop therapeutic strategies to improve smoking cessation, treatment outcome and life span of patients suffering from schizophrenia.

## 1.2. Objectives

In this review, we focus on neuronal nicotinic acetylcholine receptors (nAChRs) as a common modulator for functional alterations in schizophrenia and nicotine dependence and provide a framework for how these receptors account for the comorbidity between the two conditions. Additionally, emerging views that early tobacco use may itself increase the risk of developing schizophrenia are discussed in the light of nAChR dysregulation that may act as a shared vulnerability factor for comorbid tobacco dependence in schizophrenia. A particular emphasis is placed on therapeutic strategies that rectify nAChR dysfunction to ameliorate psychiatric symptoms and promote smoking cessation in schizophrenia patients in this review.

## 2. Method

### 2.1. Process

Two independent reviewers (V.P. and M.G.K.) searched Medline, Google Scholar and web of science from their inception until January 2016 according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) criteria (Liberati et al., 2009). Electronic data bases were searched using the following key words in various permutations: smoking, schizophrenia, nicotine, nAChRs, cognition, negative symptoms, positive symptoms, genetics, addiction, neurobiology, antipsychotics, nAChR ligands, addiction, dependence and relapse. The search criteria was specified in advance without publication date, publication status and language restriction.

### 2.2. Eligibility criteria

The search for this qualitative review included full text research articles, review articles, and clinical trials/case reports that matched the aims set forth for this review. Exclusion criteria included dissertations, book reviews and journal articles where the full text was not available. Titles and abstracts of articles relevant to the topic were screened and all duplicate records were eliminated. No date restrictions were applied. A total of 2359 records were identified during the search process and following exclusions based on the above criterion, the abstract of 488 articles was scrutinized. The full text of articles available through either institutional access or open/free electronic access was retrieved and evaluated once the abstracts matched the inclusion. The total number of articles selected for the qualitative synthesis of this review was 275.

## 3. Results

### 3.1. neuronal nAChRs

nAChRs are a family of ligand-gated ionotropic receptors that mediate fast synaptic transmission throughout the central nervous system by altering cation channel ( $\text{Na}^{2+}/\text{Ca}^{2+}/\text{K}^{+}$ ) fluxes. These receptors belong to one of the two classes of cholinergic receptors activated by the endogenous neurotransmitter acetylcholine (ACh). The other type of cholinergic receptors stimulated by ACh is muscarinic receptors, which are G protein-coupled receptors. Nicotine exerts its behavioral and neurochemical effects by binding specifically to neuronal nAChRs and therefore, the discussion here will focus only on these cholinergic receptors. Neuronal nAChRs are pentameric structures that are formed from a combination of five membrane-spanning units consisting of nine isoforms of  $\alpha$  subunits ( $\alpha 2$ - $\alpha 10$ ) and three isoforms of  $\beta$  subunits ( $\beta 2$ - $\beta 4$ ), and arranged either as a heteromeric or homomeric assemblies (Dani and Bertrand, 2007; Gotti et al., 2009). Both pre- and post-synaptic localization of these receptors have been reported (Lambe et al., 2003; Levy and Aoki, 2002; Lin et al., 2010; Mansvelter et al., 2002; Nashmi and Lester, 2006). Moreover, presynaptic nAChRs exist as both auto- and heteroreceptors and are known to modulate the release of multiple neurotransmitters including the monoamines, ACh, glutamate and GABA either directly or by interacting with other co-existing receptors at the terminals (Marchi and Grilli, 2010; Sher et al., 2004; Wonnacott, 1997). Within the mammalian brains,  $\alpha 7$  and  $\alpha 4\beta 2$  nAChRs are the most predominant and widely distributed receptors among the nAChR

family.  $\alpha 4\beta 2$  nAChRs possess high affinity for nicotine and have been shown to slowly desensitize and upregulate following continued nicotine exposure (Buisson and Bertrand, 2001; Fenster et al., 1999; Govind et al., 2009; Marks et al., 1983; Schwartz and Kellar, 1983; Yates et al., 1995). On the other hand,  $\alpha 7$  nAChRs are characterized by fast activation/desensitization and enhanced  $\text{Ca}^{2+}$  permeability but possess low affinity for nicotine (Castro and Albuquerque, 1995; Papke and Porter Papke, 2002; Seguela et al., 1993; Sharma and Vijayaraghavan, 2008). By virtue of higher  $\text{Ca}^{2+}$  permeability,  $\alpha 7$  nAChRs are also known to facilitate downstream signaling pathways such as ERK1/2 and CREB (Bitner et al., 2007; Bitner et al., 2010). Though  $\alpha 4\beta 2$  nAChRs have also been shown to gate  $\text{Ca}^{2+}$  (Karadsheh et al., 2004; Tapia et al., 2007).

Animal studies utilizing transgenic mice have implicated  $\alpha 4\beta 2$  and  $\alpha 7$  nAChRs receptors in various behavioral processes.  $\beta 2$  nAChR null mutant mice did not self-administer nicotine (Picciotto et al., 1998); however, re-expression of this receptor subunit in the ventral tegmental area (VTA) restored the nicotine self-administration response (Pons et al., 2008). The rewarding effects of nicotine tested using the conditioned place preference paradigm were also not observed in mice lacking the  $\beta 2$  subunits of nAChRs (Walters et al., 2006). Because  $\beta 2$  subunit-containing nAChRs mediate the reinforcing and rewarding effects of nicotine,  $\alpha 4\beta 2$  nAChRs are suggested to contribute to nicotine addiction-like behaviors (Dani and De Biasi, 2001; Changeux 2010). This nAChR subtype has also been associated with the regulation of mood and anxietylike behavior. For example, targeted deletion of  $\alpha 4$  subunits of the nAChRs specifically from dopaminergic neurons decreased sensitivity to the anxiolytic effects of nicotine (McGranahan et al., 2011). On the other hand, knock in mice that harbored a leucine to serine mutation in the  $\alpha 4$  nAChR gene displayed higher anxiety (Labraca et al., 2001). Reducing nAChR signaling through  $\alpha 4\beta 2$  nAChRs has been proposed to be a strategy to combat mood and anxiety disorders (Picciotto et al., 2015; Shytle et al., 2002). Besides exerting effects on reward and affective processes, nAChRs have been involved in regulating a number of cognitive processes. Mice with the genetic deletion of  $\alpha 7$  or  $\beta 2$  nAChR subunits displayed deficits in attention, spatial discrimination, working memory and executive functions (Fernandes et al., 2006; Granon et al., 2003; Guillem et al., 2011; Levin et al., 2009; Young et al., 2007; 2011). Nicotine-induced enhancement of sensorimotor gating was not observed in  $\alpha 7$  nAChR mutant mice (Azzopardi et al., 2013). Chronic nicotine produced impairments in reversal learning and these deficits were not observed in  $\beta 2$  nAChR heterozygous mice (Cole et al., 2015). Moreover,  $\beta 2$  nAChR knockout mice lacked nicotine withdrawal-related deficits in contextual fear conditioning (Portugal et al., 2008). Collectively, these findings indicated that endogenous ACh signaling by both  $\alpha 7$  and  $\beta 2$  nAChR receptors is important to maintain cognitive performance under baseline conditions. Moreover, these nAChRs also mediate the effects of nicotine on cognitive functions.

### 3.2. nAChR dysregulation in schizophrenia

Postmortem evaluations of the brains of patients with schizophrenia show reduced expression of the low-affinity  $\alpha 7$  nAChRs in multiple brain regions including the hippocampus, reticular nucleus of the thalamus, and cortex (Court et al., 1999; Freedman et al., 1995; Guan et al., 1999; Kunii et al., 2015; Leonard et al., 2007; Olincy and Stevens,

2007). However, the mRNA and protein levels of  $\alpha 7$  nAChR were found to be similar between smokers with schizophrenia and healthy smokers indicating an aberrant assembly or trafficking of these receptors in schizophrenia that may be corrected by smoking (Mexal et al., 2010). On the other hand, autoradiographic studies indicated an absence of the upregulation of the high-affinity  $\alpha 4\beta 2$  nAChRs in the cortex, striatum and hippocampus of smokers with schizophrenia, which is typically seen in normal smokers (Breese et al., 2000; Durany et al., 2000). Recent human neuroimaging studies employing positron emission tomography (PET) technique also show reduced  $\beta 2^*$ -nAChR availability in smokers with schizophrenia as compared to smokers without schizophrenia (Braši et al., 2012) but higher upregulation in comparison to non-smoker schizophrenia patients (Esterlis et al., 2014). These findings suggested that either desensitization or turnover of  $\alpha 4\beta 2$  nAChRs is abnormal in subjects with schizophrenia. Accumulating evidence from genetic studies points towards an association between schizophrenia and polymorphism in the  $\alpha 7$  nAChR subunit (*CHRNA7*) gene (Freedman et al., 2001; Leonard et al., 2000; Leonard et al., 1998a). Moreover, a recent study by Kunii et al. (2015) reported overexpression of the chimeric gene  $\alpha 7$  nAChRs (*CHRFAM7A*) that is considered to be a dominant negative regulator of  $\alpha 7$  nAChR function in the dorsolateral prefrontal cortex (PFC) of patients with schizophrenia. A genetic interaction between the  $\alpha 4$  and  $\beta 2$  subunits and schizophrenia has also been reported suggesting a possible link between schizophrenia and  $\alpha 4\beta 2$  nAChRs (De Luca et al., 2006; Voineskos et al., 2007). Together these studies indicate that both the high- and low-affinity nAChRs are dysregulated in schizophrenia and higher nicotine use may represent an attempt to restore nAChR function in schizophrenia. However, it must be noted that, chronic administration of antipsychotic drugs in rats affected nAChR expression in different brain regions (Terry et al., 2003; 2005). Therefore, it is possible that some of the effects on nAChR densities in smokers with schizophrenia may occur as consequence of interactions between nicotine and antipsychotic drugs. Table 1 provides a list of studies evaluating nAChR density in smoker and non-smoker schizophrenia patients.

### 3.3. Nicotinic modulation of cognitive and affective functions in schizophrenia

#### 3.3.1. nAChRs and sensory processing deficits in schizophrenia—

Neurocognitive dysfunction is a critical and enduring aspect of schizophrenia that may involve deficits in both bottom-up and top-down sensory processes (Javitt, 2009). Sensory gating is a fundamental brain mechanism to filter out irrelevant sensory information from the environment and this process occurs during the preattentive phase of information processing (Swerdlow et al., 1999). Gating functions are commonly assessed using the suppression of auditory P50 response or prepulse inhibition of the startle response. The P50 auditory-evoked potential is a positive waveform recorded in the EEG approximately 50 ms after an auditory click stimulus. The presentation of the second (test) stimulus, normally activate inhibitory brain mechanisms to minimize repetitive nonessential noise. This gating process results in diminished amplitude of the P50 component of the evoked response to the second stimulus relative to the first. Prepulse inhibition can be assessed by measuring a reduction in the eye blink response to a strong startling (acoustic) stimulus preceded shortly by a stimulus of subthreshold intensity. Like P50 wave suppression, prepulse inhibition of startle response is a measure of the capacity to suppress processing of or responding to a noise. Patients with schizophrenia display less ability to gate or suppress the response to the

second stimulus in both measures (Adler et al., 1985; Braff et al., 2001a; Braff et al., 2001b; Braff et al., 1999; Brockhaus-Dumke et al., 2008; Chen et al., 2011; Devrim-Üçok et al., 2008; Freedman et al., 2000). This loss of gating function or pre-attentive buffering capacity is suggested to contribute to sensory overload, cognitive fragmentation and thought disorder in schizophrenia (Croft et al., 2001; Venables, 1960). Eye movements represent a way by which an individual exercises active selection over complex visual environment and eye-tracking abnormalities in schizophrenia may represent deficits in visuomotor integration (O'Driscoll and Callahan, 2008) that may influence bottom-up and top-down processing in vision perception (Gilbert and Sigman, 2007; Levy et al., 2010). Individuals with schizophrenia display deficits in multiple components of the eye-tracking response including the failure of eye velocity to match target velocity, increased frequency of saccadic eye movements and reduced acceleration of pursuit initiation (Avila et al., 2006; Levy et al., 2000; Levy et al., 2010; Ross et al., 1998; Sweeney et al., 1999). It has been suggested that eye-tracking deficits in schizophrenia may reflect a loss of cortical inhibitory mechanisms (Avila et al., 2003).

Deficits in the early stage sensory information processing have been linked to the *CHRNA7* polymorphism (Freedman, 2014; Leonard et al., 1998b). Smokers with schizophrenia exhibited marked improvement in P50 sensory gating immediately after smoking a cigarette while this effect was not observed in normal smokers (Adler et al., 1998). Prepulse inhibition of the acoustic startle response improved in patients with schizophrenia when they smoked 10-min prior to testing or under smoking satiation conditions as compared to non-smoking patients (Kumari et al., 2001; Woznica et al., 2009). Likewise, eye-tracking abnormalities measured using smooth-pursuit and anti-saccade response were improved with cigarette smoking (Olincy et al., 2003; Olincy et al., 1998), nicotine nasal spray (Avila et al., 2003; Sherr et al., 2002), and nicotine patch (DePATIE et al., 2002) in patients with schizophrenia. Furthermore, the administration of partial  $\alpha 7$  nAChR agonists such as DMXB-A and tropisetron increased the inhibition of P50 auditory gating in schizophrenia (Koike et al., 2005; Olincy et al., 2006). Collectively, these findings suggest that higher nicotine use in patients with schizophrenia may represent an attempt to normalize sensory processing deficits by keeping the low-affinity nAChR activated. This view is also supported by animal studies. For example, administration of  $\alpha 7$  nAChR antagonist  $\alpha$ -bungarotoxin produced a profound reduction in auditory sensory gating similar to that observed in schizophrenia (Luntz-Leybman et al., 1992). DBA/2J mice that carry a polymorphism in the noncoding region of the *CHRNA7* gene and express reduced  $\alpha 7$  nAChRs in the hippocampus exhibited deficits in hippocampal (P20/N40; a rodent analog of human P50) sensory gating (Stevens et al., 1998) and prepulse inhibition of startle (Connolly et al., 2003). Moreover, intragastric administration of DMXB-A, a specific agonist for the  $\alpha 7$  nAChRs, normalized sensory processing deficits in mice (Simosky et al., 2001).  $\alpha 7$  nAChRs are abundant on GABAergic interneurons in the cortex (Krenz et al., 2001) and hippocampus (Heckers and Konradi, 2002), and these interneurons are disrupted in schizophrenia (Gonzalez-Burgos and Lewis, 2008; Lewis et al., 2005; Nakazawa et al., 2012). As GABA-mediated presynaptic regulation of glutamate release is critical for the gating of sensory response (Dutar and Nicoll, 1988), nicotine-mediated improvement in early information processing deficits in schizophrenia may be due to restoration of GABA

transmission in these brain regions (Wing et al., 2012). Although deficits in prepulse inhibition were not observed in  $\alpha 7$  nAChR knockout mice, these mice did show impairments in attention (Young et al., 2007). It has been suggested that neurobiological mechanisms underlying prepulse inhibition and P50 gating measures differ between schizophrenia patients and healthy control subjects (Oranje et al., 2006). Additionally, the neurochemical modulation of auditory gating measures of N40 suppression and prepulse inhibition diverge in rats (Swerdlow et al., 2006). Therefore, prepulse inhibition in rodent models may not serve as a sole indicator of sensory processing deficits in schizophrenia and  $\alpha 7$  nAChR knockout mice must be evaluated in the context of other behaviors relevant to schizophrenia (Powell et al., 2009).

**3.3.2. nAChRs and higher cognitive functions**—Deficits in sensory gating are suggested to contribute to disrupted higher-order cognitive processes including attention, working memory and cognitive control (Lijffijt et al., 2009; Smucny et al., 2013; Yadon et al., 2009), and these functions were improved with smoking in patients with schizophrenia (Lohr and Flynn, 1992; Myers et al., 2004; Sacco et al., 2005). Moreover, withdrawal from smoking worsened performance in a visuospatial working memory task in smokers with schizophrenia (George et al., 2002).  $\alpha 7$  nAChR knockout mice were impaired on measures of sustained attention as assessed using the 5-choice serial reaction time task (Young et al., 2007). Moreover, these mutants exhibited performance deficits under baseline conditions in the odor span task, delayed non-match to sample task, win-shift task and attention set-shifting task (Fernandes et al., 2006; Levin et al., 2009; Young et al., 2007; 2011) indicating that perturbations in  $\alpha 7$  nAChR signaling influence a wide range of executive processes. Administration of  $\alpha 7$  nAChR full/partial agonists or positive allosteric modulators (PAMs) exerted beneficial effects on attention, working and recognition memory, and cognitive flexibility in normal rodents and aged non-human primates (Boess et al., 2007; Bitner et al., 2007; Callahan et al., 2013; Levin et al., 1999; Nikiforuk et al., 2016; Rezvani et al., 2009; Tietje et al., 2008). On the other hand, systemic or intracranial infusions of  $\alpha 7$  nAChR antagonist produced impairments in attention and working memory in normal rats (Chan et al., 2007; Hahn et al., 2011; Levin et al., 2002).  $\alpha 7$  nAChR modulators have also been shown to improve attention and cognitive flexibility in animal models used to study cognitive symptoms of schizophrenia such as the developmental models (neonatal rat ventral hippocampus lesion, th(tk-)/th(tk-) mice), models of NMDA glutamate receptor hypofunction (MK801, phencyclidine, ketamine, kynurenic acid) and inbred mouse model (DBA/2J) with poor sensory gating (Alexander et al., 2012; Barak et al., 2009; Brooks et al., 2012; Hauser et al., 2009; Jones et al., 2014; McLean et al., 2012). Higher rate of smoking with higher nicotine extraction in schizophrenia patients has been suggested to activate the low-affinity  $\alpha 7$  nAChRs (Young and Geyer, 2013). Additionally, evidence from clinical trials of drugs acting at the  $\alpha 7$  nAChRs indicated improvement in attentional capacities in patients suffering from schizophrenia (Lieberman et al., 2013; Olincy et al., 2006). Together, these findings indicate that nicotine's procognitive effects in smokers with schizophrenia are partly mediated by  $\alpha 7$  nAChRs.

Chronic administration of  $\alpha 4\beta 2$  nAChR agonists also exerted beneficial effects on attention in both healthy adults and adults suffering from ADHD (Apostol et al., 2012; Wilens and



Decker, 2007). Although direct clinical evidence of the involvement of  $\alpha 4\beta 2$  nAChRs in the cognitive symptoms of schizophrenia is lacking, smoking-induced activation of these high-affinity nAChRs in subjects with schizophrenia is also hypothesized to exert procognitive effects (D'Souza and Markou, 2012). In this context, animal studies utilizing mice with the genetic deletion of  $\beta 2$  nAChR subunits reported deficits in attentional processing and conflict resolution (Granon et al., 2003; Guillem et al., 2011). Moreover, pharmacological stimulation of  $\alpha 4\beta 2$  nAChRs by specific ligands facilitated baseline attentional performance and performance under conditions of higher attentional load (Howe et al., 2010; McGaughy et al., 1999; Mohler et al., 2010) while antagonism of these receptors produced deficits in attention and working memory (Chan et al., 2007; Hahn et al., 2011; Levin et al., 2002). Table 2 provides a summary of animal and human studies on the effects of genetic and pharmacological manipulations of  $\alpha 7$  and  $\alpha 4\beta 2$  nAChRs on cognitive processes as it relates to schizophrenia.

DA deficiency and disrupted D1 receptors signaling in the PFC is linked to the attention, working memory and executive control deficits in schizophrenia (Goldman-Rakic et al., 2004; Brisch et al., 2014). Both  $\alpha 7$  and  $\beta 2$  subunit-containing nAChRs are known to exist on dopaminergic terminals in the PFC and modulate DA release (Cao et al., 2005; Livingstone et al., 2010; Livingstone et al., 2009). Additionally, nAChRs also regulate prefrontal glutamate release primarily from the thalamocortical terminals, which is critical for attentional processing (Konradsson-Geuken et al., 2009; Lambe et al., 2003; Parikh et al., 2010; Parikh et al., 2008; Sarter and Polone, 2011). Furthermore, aberrations in NMDA glutamate receptor-mediated signaling have been proposed to be one of the underlying mechanisms contributing to the cognitive symptoms of schizophrenia (Moghaddam and Javitt, 2012). D1 receptor activation also facilitates NMDA responsiveness via intracellular  $Ca^{2+}$  and protein kinase A, and synergistic interactions between these two receptors are critical for normal cortical pyramidal cell excitability and PFC function (Sarantis et al., 2009; Tseng and O'Donnell, 2004). As noted above, intracortical infusions of both  $\alpha 4\beta 2$  and  $\alpha 7$  nAChR antagonists impaired working memory in rats (Chan et al., 2007). Therefore, stimulation of prefrontal nAChRs either by nicotine or specific  $\alpha 4\beta 2/\alpha 7$  nAChR agonists may normalize DA-glutamate release and restore D1/NMDA receptor signaling and synergism to ameliorate some of the cognitive deficits in patients with schizophrenia (see Figure 1).

**3.3.3. nAChRs and reward function in schizophrenia**—Negative symptoms of schizophrenia such as lack of motivation to pursue goals, anhedonia and reduced emotional reactivity to affective stimuli are ascribed to deficits in reward processing (Gold et al., 2008; 2012). Although direct evidence for the role of brain reward systems in comorbidity of nicotine dependence and schizophrenia is lacking, human studies have suggested that smokers with schizophrenia find smoking more reinforcing as compared to normal smokers (Ahnallen et al., 2012; Spring et al., 2003). Moreover, smokers with schizophrenia reported more severe craving during abstinence and smoking lapse latency in these individuals correlated with baseline depression and nicotine withdrawal symptom severity (Tidey et al., 2014). These findings indicate that negative *affect* in schizophrenia patients

disproportionately increase the reward value of nicotine making them less likely to quit smoking.

The high-affinity  $\alpha 4\beta 2$  nAChRs are known to modulate reward-motivated behaviors and play a critical role in nicotine addiction (Changeux, 2010). Moreover, chronic nicotine-induced neuroadaptations underlying dependence involves desensitization and long-lasting upregulation of  $\alpha 4\beta 2$  nAChRs, which may contribute to heightened nicotine reward sensitivity and increase relapse vulnerability (Cosgrove et al., 2009; Hilario et al., 2012; Kenny and Markou, 2006; Picciotto et al., 2008). Vulnerability to nicotine dependence is related to high nicotine sensitivity (Pomerleau et al., 1993). Genetic studies have identified several chromosomal regions and specific polymorphisms that may account for individual differences in nicotine sensitivity (Li et al., 2008; Portugal and Gould, 2008). One genetic variant that has been implicated in altering nicotine sensitivity in mice is the naturally occurring T529A polymorphism in *CHRNA4*, the gene that encodes the nAChR  $\alpha 4$  subunit. This polymorphism involves a substitution of threonine to alanine at position 529 of the  $\alpha 4$  subunit that results in enhanced  $\alpha 4\beta 2$  nAChR function (Butt et al., 2003; Dobelis et al., 2002; Kim et al., 2003). Wilking and colleagues (Wilking et al., 2010) found that *CHRNA4* A529 knock-in mice exhibited greater sensitivity to the hypothermic effects of nicotine. Moreover, these animals did not develop conditioned place preference to nicotine, further illustrating that the A529 polymorphism affected the sensitivity to the rewarding properties of nicotine by altering the  $\alpha 4\beta 2$  nAChR function. Although this missense polymorphism has not been reported in humans, an association study of the *CHRNA4* gene polymorphism and heavy smoking among schizophrenia patients showed a significant association between the *CHRNA4* rs3746372 allele 1 and the number of cigarettes smoked daily (Voineskos et al., 2007). Thus, it appears that  $\alpha 4\beta 2$  nAChR function appears to be a critical regulator of nicotine reward sensitivity.

Recent human PET/SPECT imaging studies that employed a  $\beta 2$  nAChR agonist radiotracer [ $^{123}\text{I}$ ]5-IA-85380 showed not only lower  $\alpha 4\beta 2$  nAChR availability in smokers with schizophrenia as compared to normal smokers but also a negative correlation between the receptor availability and negative symptoms (D'Souza et al., 2012; Esterlis et al., 2014). Smoking cigarettes high in nicotine content reduced negative symptoms of schizophrenia more than denicotinized cigarettes (Smith et al., 2002). However, short-term smoking abstinence did not worsen the negative symptoms of schizophrenia (D'Souza et al., 2012). It is therefore possible that although nicotine intake may restore affective function in schizophrenia, the negative symptoms are not the primary force driving the urge to smoke in patients with schizophrenia.

Extensive evidence suggests that the reinforcing effects of nicotine primarily involve the activation of mesolimbic DA neurons in the ventral tegmental area (VTA) and consequent release of DA in striatal synapses via the  $\alpha 4\beta 2$  nAChRs (Dani and De Biasi, 2001; Laviolette and Van Der Kooy, 2004; Leslie et al., 2013). Therefore, a dysregulation of  $\alpha 4\beta 2$  nAChR function in schizophrenia and higher smoking rates in individuals suffering from this disorder may be related to reduced nicotine sensitivity and represent an approach to restore DA reward function by activating these nAChRs. The low-affinity  $\alpha 7$  nAChRs are known to be localized on the glutamatergic afferents in the VTA and regulate DA release in

the nucleus accumbens, and the desensitization of these receptors is suggested to motivate nicotine self-administration (Brunzell and McIntosh, 2012). The  $\alpha 7$  nAChR mutant mice exhibited impaired performance on the appetitive learning task (Keller et al., 2005); however, the motivation to obtain natural reward was not affected in these mice (Young et al., 2011). Moreover, the administration of  $\alpha 7$  agonist or genetic deletion of  $\alpha 7$  nAChR subunit did not affect nicotine reward and reinforcement (Grottick et al., 2000; Pons et al., 2008). Based on these studies, it appears that perhaps  $\alpha 7$  nAChRs are not directly involved in regulating reward function and may not contribute to altered reward sensitivity in schizophrenia patients.

#### 3.4. Early nicotine use and risk of schizophrenia: nAChR dysfunction as a shared vulnerability factor

A recent meta-analysis of prospective case-control studies on tobacco users indicated that nicotine use by itself may be associated with increased risk for psychosis and early age of onset of psychosis as compared to non-smokers (Gurillo et al., 2015). The study found that the overall prevalence of smoking in subjects with first episode of psychosis was three times higher (odds ratio 3.22) as compared to non-smokers. Moreover, this analysis reported that daily smokers developed psychiatric illness a year earlier and the risk of developing new psychotic disorders in smokers was higher (overall risk ratio 2.18) as compared to non-smokers. Another recent study that used Cox proportional hazard regression model to investigate the association between smoking and time to schizophrenia diagnosis in Swedish population found that the risk for schizophrenia was substantially higher in heavy smokers as compared to the light smokers (Kendler et al., 2015). Although these data do not establish causal links between smoking and schizophrenia, genetic studies have implicated multiple nAChR genes for a possible association between the two conditions. For example, a genetic variation in *CHRNA7* has been associated with increased vulnerability for nicotine dependence phenotype in those individuals that are diagnosed with schizophrenia (De Luca et al., 2004; Saccone et al., 2010). Another genome wide-association study of schizophrenia identified a genetic loci on chromosome 15 that contain a cluster of  $\alpha 3\alpha 5\beta 4$  nAChR subunit-containing genes *CHRNA5/A3/B4* (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014); this cluster has also been associated with nicotine dependence and early age at onset of smoking (Berrettini et al., 2008; Gage and Munafò, 2015; Hartz et al., 2012; Saccone et al., 2007; Saccone et al., 2008). Moreover, a study conducted in transgenic mice overexpressing the *CHRNA5/A3/B4* genomic cluster found increased acquisition of nicotine self-administration (Gallego et al., 2012). Therefore, it is plausible that a genetic defect in nAChRs makes individuals more susceptible to heavy smoking at an early age, which could increase the risk of developing schizophrenia, though this needs further examination. It is noteworthy that transgenic mice overexpressing the human *CHRNA5/A3/B4* genomic cluster exhibited impairments in novelty recognition memory and chronic nicotine reversed these deficits (Molas et al., 2014). Likewise, the beneficial effects of nicotine on visual attention were not observed in  $\alpha 5$  nAChR knockout mice (Bailey et al., 2010). Whether heavy nicotine use in adolescents represent a strategy to reverse cognitive deficits that might have emerged due to disrupted *CHRNA5/A3/B4* function remains to be investigated.

If smoking predicts the subsequent risk for schizophrenia, the important question that needs an answer would be what causes adolescent cigarette smoking. Impulsivity is a multifaceted construct that includes lack of inhibitory control, lack of forethought, and inability to delay gratification (see Evenden, 1999; Whiteside and Lynam, 2001 for reviews). An animal study utilizing rats trained to self-administer nicotine and perform a delayed reward task found that impulsive choice predicted a diminished ability to inhibit nicotine seeking during abstinence (Diergaarde et al., 2008). The same study also reported that impulsive action assessed using the 5-choice serial reaction time task was associated with higher rates of nicotine self-administration. Another study that compared the effects of acute nicotine in rats performing the go/no-go and delayed reinforcement tasks found that nicotine produced both behavioral disinhibition and heightened sensitivity to delayed gratification (Kolokotroni et al., 2014). Likewise, numerous human studies indicated that different components of impulsivity may contribute to increased smoking initiation and inability to quit smoking. For instance, smokers discounted the value of delayed money or the uncertainty associated with obtaining money more than the non-smokers (Audrain-McGovern et al., 2009; Bickel et al., 1999; Mitchell, 1999; Reynolds et al., 2004). In the go/no-go task, the behavioral accuracy and the amplitudes of no-go event related potentials (N2 and P300) were lower in adolescent and young adult smokers indicative of impulsive action and deficits in response inhibition in these individuals (Luijten et al., 2011; Yin et al., 2015). Assessment of impulse control function using the oculomotor task also showed higher antisaccade errors in smokers (Spinella, 2002; Powell et al., 2010). Likewise, measures of trait impulsivity evaluated through the self-reported personality test, the Barret Impulsiveness Scale, found a strong association between the total impulsivity score and measures of nicotine dependence (Chase and Hogarth, 2011; Flory and Manuck, 2009). As smokers with schizophrenia were found to be more impulsive than non-smokers with schizophrenia (Wing et al., 2011), it is conceivable that trait impulsivity in adolescents may determine smoking initiation while disinhibition impulsiveness lead to smoking maintenance that eventually increases susceptibility to develop schizophrenia-like pathology.

Stimulation of  $\alpha 4\beta 2$  nAChRs has been linked to nicotine-induced deficits in premature responding, a measure of impulsive choice, in animal studies using either a 5-choice or a 3-choice serial reaction time task (Blondel et al., 2000; Grottick and Higgins, 2000; Tsutsui-Kimura et al., 2010). Additionally, intracerebroventricular infusion of  $\alpha 4\beta 2$  nAChR antagonist suppressed impulsive behavior in normal rats that have not been given nicotine further supporting the hypothesis that activation of  $\alpha 4\beta 2$  nAChRs may provoke impulsivity in normal individuals that do not suffer from any psychiatric condition (Tsutsui-Kimura et al., 2010). Nicotine-induced impulsivity is hypothesized to involve DA release in the corticolimbic circuits triggered by the activation of  $\alpha 4\beta 2$  nAChRs (Ohmura et al., 2012). As impulsivity traits are evident during adolescence (Romer, 2010), and reduced striatal DA D2/D3 receptor function has been linked to trait impulsivity (Dalley et al., 2007), it is possible that dysregulated mesolimbic DA signaling may contribute to increased smoking initiation and restore dopaminergic signaling via  $\alpha 4\beta 2$  nAChRs. It must be noted that  $\alpha 7$  nAChRs are also known to regulate behavioral inhibition (Keller et al., 2005). Likewise, a polymorphism in CHRNA5/A3/B4 gene cluster is also linked to impulsivity (Stephens et al., 2012). Thus, an early defect in the function of these receptors may also contribute to



working memory and negative symptoms in schizophrenia patients (Freedman et al., 2008; Olincy and Freedman, 2012; Olincy et al., 2006). An early proof of concept phase II clinical trial conducted in patients with schizophrenia with EVP-6124 (encenicline), a new selective  $\alpha 7$  nAChR partial agonist, reported positive effects on mismatch negativity, P300 potentials, and on various measures of cognition such as visual attention, non-verbal working memory and decision-making (Preskorn et al., 2014). Another partial  $\alpha 7$  nAChR agonist tropisetron improved auditory sensory gating and exerted attention-enhancing effects in patients with schizophrenia (Shiina et al., 2010; Zhang et al., 2012). Moreover, the  $\alpha 7$  nAChR full agonist TC-5619 was also found to exert beneficial effects on working memory performance in smokers with schizophrenia (Lieberman et al., 2013). However, a recent phase 2 clinical trial conducted in patients with schizophrenia comprised of both tobacco and non-tobacco users showed that TC-5619 did not improve scores on the scale for the assessment of Subject Global Impression-Cognition and the negative symptoms (Walling et al., 2015). It is noteworthy that  $\alpha 7$  nAChR partial agonists such as encenicline, RG3487 and tropisetron, have also been reported to improve negative symptoms of schizophrenia (Keefe et al., 2015; Noroozian et al., 2013; Olincy and Freedman, 2012; Umbricht et al., 2014). Although the underlying neurobiological mechanism for the efficacy of these ligands for affective symptoms remain poorly understood, these ligands also possess serotonin 5HT<sub>3</sub> receptor antagonistic activity and it is possible that these beneficial effects are linked to the normalization of 5HT<sub>3</sub> signaling in schizophrenia. However, the presence of  $\alpha 7$  nAChRs in brain regions known to be involved in regulating emotion, motivation and goal-directed behavior could also plausibly relate the affective symptoms of schizophrenia to  $\alpha 7$  nAChR dysfunction. Future research is warranted to establish a link between  $\alpha 7$  nAChRs and the negative symptoms of schizophrenia and whether targeting these receptors would effectively treat these symptoms.

An alternative therapeutic approach to control cognitive symptoms of schizophrenia is to develop PAMs of  $\alpha 7$  nAChRs. PAMs bind to an allosteric site distinct from the binding site of the endogenous ligand and do not directly activate the receptor but potentiate the effects of the endogenous ligand. In this case, a key advantage of this approach would be that  $\alpha 7$  nAChR modulation will occur only in the presence of the endogenous ligand ACh; therefore, the temporal and spatial integrity of neurotransmission is preserved (Bertrand et al., 2008). Moreover,  $\alpha 7$  PAMs enhance the activity elicited by agonists (ACh or nicotine) either by increasing the gating process (type I PAMs) or by reducing the receptor desensitization (type II PAMs) (Gill-Thind et al., 2015). Thus, the use  $\alpha 7$  PAMs may not only amplify the behavioral/cognitive effects produced by  $\alpha 7$  nAChR activation but also prevent the tolerance to these effects that may occur due to the desensitization of these receptors (Uteshev, 2014). In this regard, galantamine, a cholinesterase inhibitor that is also a  $\alpha 7$  nAChR-PAM has shown neurocognitive improvement in subjects with schizophrenia (Buchanan et al., 2008; Schubert et al., 2006). A number of type I and type II PAMs have shown beneficial effects on sensory gating, working memory and executive functions in animal models (reviewed in (Beinat et al., 2015; Terry Jr et al., 2015). However, a recent phase I clinical trial with JNJ-39393406, an  $\alpha 7$  nAChR PAM, did not reveal any beneficial effects on P50 sensory gating and other electrophysiological markers of early information processing in regularly smoking patients with schizophrenia (Winterer et al., 2013). Future

clinical studies with PAMs will determine whether these modulators offer any potential advantages over the orthosteric  $\alpha 7$  nAChR ligands.

As discussed above, there is a plethora of evidence from preclinical studies indicating the efficacy of  $\alpha 4\beta 2$  nAChR agonists in exerting procognitive effects. Clinical studies conducted with  $\alpha 4\beta 2$  nAChR-selective agonists such as AZD3480, ABT-418 and ABT-089 showed improvements in attentional performance in adults with ADHD (Potter et al., 2014; Wilens et al., 1999; Wilens et al., 2006). Varenicline, which is an  $\alpha 4\beta 2$  nAChR partial agonist and a full agonist for  $\alpha 7$  nAChRs (Mihalak et al., 2006), has shown significant improvements in cognitive performance of smokers with schizophrenia on the Wisconsin Card Sorting Task and the Digital Symbol Substitution Test (Shim et al., 2012) as well as visuospatial working memory performance measured by the Spatial Delayed Response Task (Wing et al., 2013). Moreover, this drug was effective for smoking cessation in smokers with schizophrenia (Pachas et al., 2012; Williams et al., 2012). Varenicline is proposed to control affective symptoms of schizophrenia and reduce craving for smoking by stimulating DA release via  $\alpha 4\beta 2$  nAChRs (Coe et al., 2005). Additionally, its procognitive effects may be related to its ability to stimulate  $\alpha 7$  nAChRs (Mackowick et al., 2014). A recent study found that maintenance therapy with varenicline prolonged tobacco abstinence rates in patients with schizophrenia (Evins et al., 2014). Moreover, schizophrenia patients with lower baseline symptoms of affective flattening were more likely to achieve smoking abstinence and demonstrated larger increases in reward sensitivity during varenicline treatment (Dutra et al., 2012). Table 3 depicts the results of clinical trials of nAChR agonists and PAMs in patients with schizophrenia.

Based on the existing evidence, it appears that both  $\alpha 7$  and  $\alpha 4\beta 2$  nAChR ligands may hold promise as potential therapeutic targets in alleviating the negative and cognitive symptoms of schizophrenia. Additionally, targeting  $\alpha 4\beta 2$  nAChRs may also be beneficial in reducing smoking relapse in schizophrenia patients. At this point it is not known whether partial nAChR agonists would be better in clinical efficacy than full agonists as the procognitive efficacy of full  $\alpha 7$  nAChR agonist (TC-5619) has yielded mixed results in schizophrenia patients. Likewise, it remains unclear whether mixed  $\alpha 4\beta 2/\alpha 7$  agonists would be superior to agonists targeting specific nAChR subtype. Rapid nAChRs desensitization is another issue with orthosteric agonists that may limit some of the clinical effects of these drugs and current evidence is limited demonstrating that PAMs would be more effective than the former. Ongoing investigation with newer nAChR ligands and results from pending clinical trials will possibly address these issues.

#### 4. Conclusions

The research on the relationship between schizophrenia and smoking is complex and has remained inconclusive. While the debate for the *self-medication* versus *addiction vulnerability* hypothesis continues, it is widely accepted that dysfunction in central nAChRs represent a common substrate for various symptoms of schizophrenia and comorbid nicotine dependence. A growing number of studies have found evidence that there may be an interaction between the genetic and environmental factors that underlie deficient nAChR signaling (Wing et al., 2012). Nicotine is known to exert both positive and negative effects

on patients with schizophrenia. Moreover, the highly addictive properties and the development of tolerance following prolonged treatment limit its use as a drug candidate. There is now convincing evidence that the development of nAChR subtype-specific agonists represents a viable therapeutic option to treat schizophrenia symptoms and minimize nicotine use in subjects with schizophrenia. Another goal of utilizing this strategy would be to improve smoking cessation to circumvent smoking-related health hazards in smokers with schizophrenia. The negative and cognitive symptoms precede the onset of psychosis (Addington et al., 2003; Simon et al., 2007; Yung and McGorry, 1996) and there is a temporal link between the initiation of smoking and the prodromal phase of schizophrenia (Riala et al., 2005). Moreover, the current antipsychotic drugs are not very successful in alleviating these symptoms. Therefore, specific nAChR ligands appear to be reasonable candidates for minimizing the use of nicotine during the earlier course of the schizophrenia pathology and eventually improving the treatment outcome.

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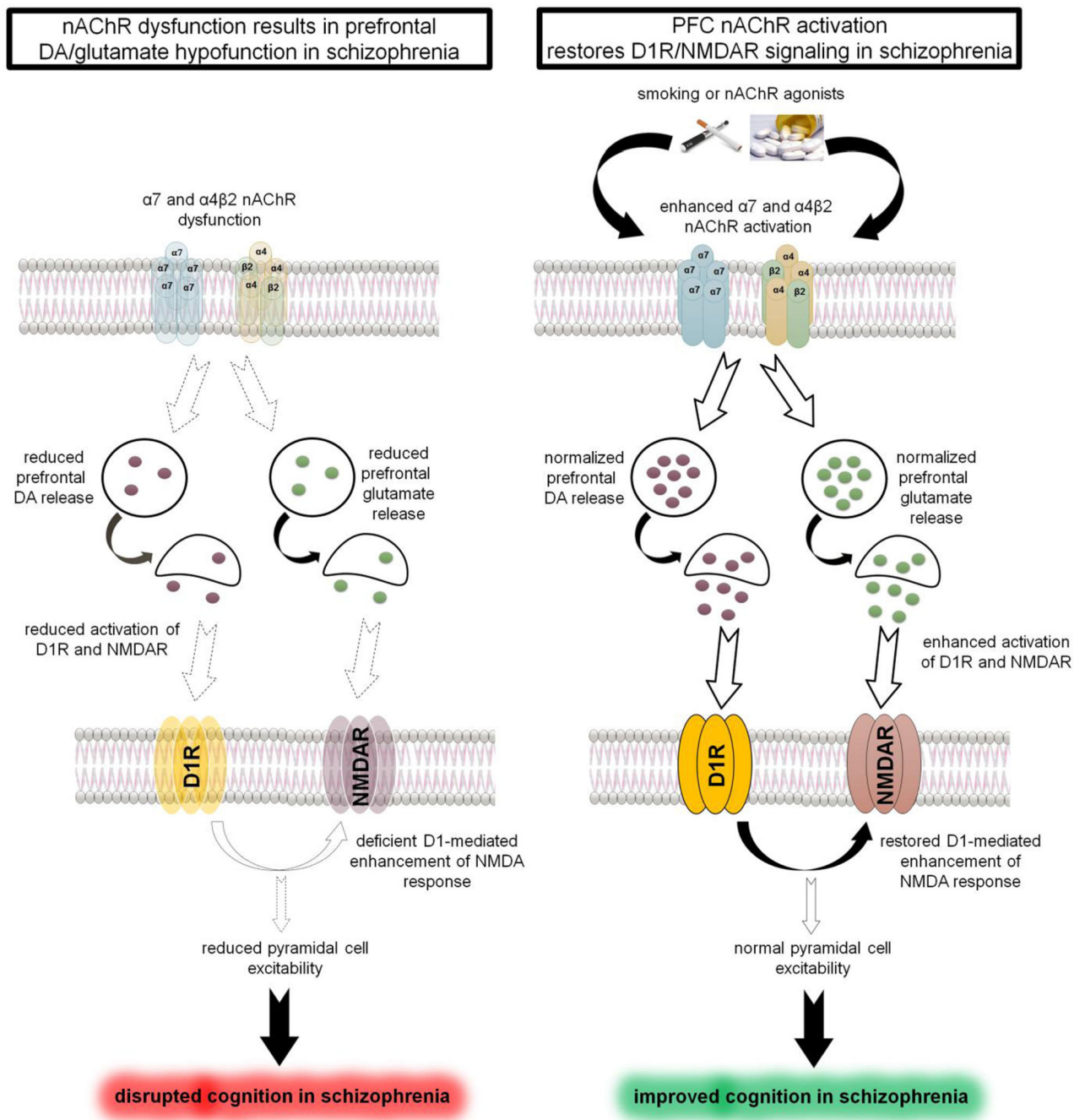
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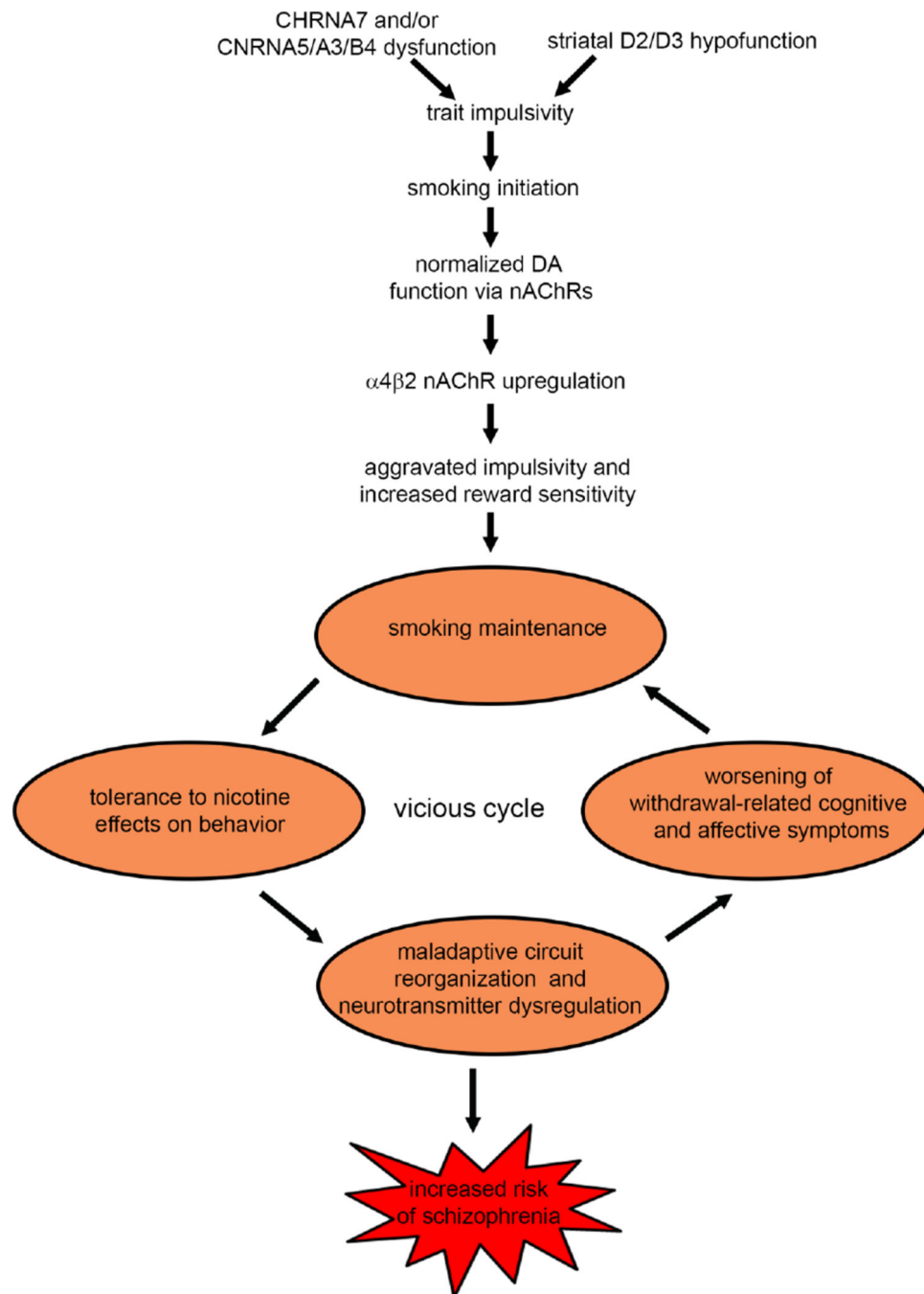
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**Figure 1.**

Cartoon depicting the role of prefrontal nAChRs in cognitive deficits of schizophrenia. Left Panel: nAChR dysfunction in schizophrenia produces deficient DA and glutamate release in the PFC resulting in diminished D1 and NMDA receptor signaling. Reduced synergy between D1 and NMDA receptor disrupts PFC excitability and cognitive functions. Right Panel: Smoking (nicotine) or activation  $\alpha 4\beta 2$  and/or  $\alpha 7$  nAChRs increases DA/glutamate release in the PFC and restore synergistic interactions between the DA and glutamate signaling to normalize PFC function and improve cognition in schizophrenia.





**Figure 2.**

A hypothetical model illustrating the central role of nAChRs and trait impulsivity in increasing the risk of schizophrenia in adolescent nicotine users. Susceptibility mechanisms such as a defective nAChR system (e.g. CHRNA7, CHRNA5/A3/B4 polymorphism) or D2/D3 receptor hypofunction may make adolescents more impulsive and engage in smoking initiation. Nicotine use by itself may aggravate impulsivity by upregulating the high-affinity  $\alpha 4\beta 2$  nAChRs leading to smoking maintenance. Sustained nicotine use initiates a vicious cycle in schizophrenia-susceptible adolescents that involves tolerance to the behavioral

effects of nicotine, maladaptive circuit and neurochemical changes, enhanced sensitivity to withdrawal-related worsening of the cognitive and affective symptoms and higher relapse rates. Thus, nicotine use maintained in adolescent smokers may eventually put them at higher risk of developing schizophrenia.

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**Table 1**  
Postmortem studies evaluating nAChR densities in smoker and non-smoker schizophrenia patients.

nAChRs	Imaging Technique	Comparison	Brain Regions	Effects	Study	
$\alpha 7$ nAChRs	$\alpha$ -bungarotoxin (αBGT) autoradiography	SZ vs. normal	hippocampus, thalamus and cortex	reduced $\alpha 7$ nAChRs density	Court et al., 1999; Freedman et al., 1995; Guan et al., 1999	
	Fluorescent in-situ hybridization	SZ vs. normal	dorsolateral PFC	overexpression of the chimeric gene for $\alpha 7$ nAChRs (CHRFAM7A)	Kunii et al., 2015	
$\alpha 4\beta 2$ nAChRs	[ <sup>3</sup> H]-epibatidine binding; [ <sup>3</sup> H]cytisine binding	SZ smokers vs. normal smokers	cortex, striatum and hippocampus	reduced $\alpha 4\beta 2$ nAChRs density	Breese et al., 2000; Durany et al., 2000	
	PET (2-[ <sup>18</sup> F]FA)	SZ smokers vs. normal smokers	thalamus	reduced $\beta 2$ -nAChR availability	Braši et al., 2012	
	PET ([ <sup>123</sup> I]5-IA)	SZ smokers vs. normal smokers during early abstinence	SZ smokers vs. SZ non-smokers	frontal cortex, parietal cortex, and striatum	higher $\beta 2$ -nAChR upregulation	Esterlis et al., 2014
			SZ smokers vs. normal smokers during early abstinence	frontal cortex, parietal cortex, and thalamus	lower $\beta 2$ -nAChR availability	D'Souza et al., 2012

Abbreviations: nAChR: nicotinic acetylcholine receptor; PFC, prefrontal cortex; SZ, schizophrenia.

**Table 2** Animals studies evaluating the contributions of  $\alpha 7$  and  $\alpha 4\beta 2$  nAChRs in the cognitive processes affected in schizophrenia.

	nAChRs	Manipulation	Species	Model	Effects	Study
<i>Genetic studies</i>	$\alpha 7$ nAChRs	$\alpha 7$ subunit deletion	mice	normal animals	impaired attention, short-term memory, working memory, decision making, cognitive flexibility	Fernandes et al., 2006; Levin et al., 2009; Young et al., 2007; 2011
	$\alpha 4\beta 2$ nAChRs	$\beta 2$ subunit deletion	mice	normal animals	deficits in attentional processing and conflict resolution	Granon et al., 2003; Guillem et al., 2011
<i>Antagonists</i>	$\alpha 7$ nAChRs	$\alpha$ -bungarotoxin, methyllycaconitine	rats	normal animals	reduced auditory sensory gating and impaired working memory	Luntz-Leybman et al., 1992; Chan et al., 2007; Hahn et al., 2011; Levin et al., 2002
	$\alpha 4\beta 2$ nAChRs	dihydro- $\beta$ -erythroidine	rats	normal animals	impaired working memory	Chan et al., 2007; Levin et al., 2002
<i>Full agonists</i>	$\alpha 7$ nAChRs	A-582941, TC-5619, PNU-282987	mice, rats	SZ model (transgenic <i>th1(k-)/th1(k-)</i> mice/ DBA/2 mice/ MK801)	reversed sensory gating and attentional set-shifting deficit in SZ model	Bitner et al., 2007; Hauser et al., 2009; Jones et al., 2014
		ABBF, A-582941, AR-R17779	mice, rats, non-human primates	normal animals	enhanced sensory gating, working memory, and recognition memory in normal animals	Bitner et al., 2007; Boess et al., 2007; Levin et al., 1999; Tietje et al., 2008
<i>Positive allosteric modulators (PAMs)</i>	$\alpha 7$ nAChRs	S38232, ABT-418, ABT-594	rats	normal animals	enhanced attention	Howe et al., 2010; McGaughy et al., 1999; Mohler et al., 2010
		PNU-120596, CCMI, galantamine	rats, non-human primates	SZ model in rats (KYN/PCP/ ketamine), aged rats and rhesus monkeys	normalized attentional set-shifting and recognition memory in SZ models, improved spatial and working memory in aged animals	Alexander et al., 2012; Callahan et al., 2013; McLean et al., 2012; Nikiforuk et al., 2016
<i>Partial agonists</i>	$\alpha 7$ nAChRs	R3487/MEM3454	rats	normal animals	enhanced attention	Rezvani et al., 2009

nAChRs	Manipulation	Species	Model	Effects	Study
	DMXB-A (GTS21), SSRI80711	mice, rats	SZ model (NVH/ MK- 801/ DBA/2 mice)	normalized attentional set- shifting, latent inhibition, and sensory processing	Barak et al., 2009; Brooks et al., 2012; Jones et al., 2014; Simosky et al., 2001

Abbreviations: KYN, kynurenic acid; NVH, neonatal ventral hippocampus; PCP, phencyclidine; SZ, schizophrenia;  $th(k-)/th(k-)$ , dominant negative mutant of the fibroblast growth factor receptor-1 in tyrosine hydroxylase (TH)-expressing neurons.

**Table 3**

Clinical studies assessing the effects of nAChR ligands on cognitive and negative symptoms, and tobacco cessation in schizophrenia patients.

Ligand	Specificity	Stage	Effects	Study
<b><i>GTS-21 (DMXB-A)</i></b>	$\alpha 7$ nAChR partial-agonist	Phase II clinical trial	improved P50 sensory gating function, attention, working memory and negative symptoms	Freedman et al., 2008; Olincy et al., 2006; Olincy and Freedman, 2012
<b><i>EVP-6124 (encenicline)</i></b>	$\alpha 7$ nAChR partial-agonist	Phase II clinical trial	exerted beneficial effects on mismatch negativity, P300 potentials, visual attention, non-verbal working memory decision-making and negative symptoms	Keefe et al., 2015; Preskorn et al., 2014;
<b><i>Tropisetron</i></b>	$\alpha 7$ nAChR partial-agonist	Phase II clinical trial	improved auditory sensory gating, attention and negative symptoms	Noroozian et al., 2013; Shiina et al., 2010; Zhang et al., 2012
<b><i>RG3487</i></b>	$\alpha 7$ nAChR partial-agonist	Phase II clinical trial	improved negative symptom assessment scores	Umbricht et al., 2014
<b><i>TC-5619</i></b>	$\alpha 7$ nAChR full agonist	Exploratory Trial	enhanced working memory performance	Lieberman et al., 2013
		Phase II clinical trial	no effects on negative symptoms or Subject Global Impression-Cognition	Walling et al., 2015
<b><i>Galantamine</i></b>	$\alpha 7$ nAChR PAM	Phase III clinical trial	improved attention and memory	Buchanan et al., 2008; Schubert et al., 2006
<b><i>JNJ-39393406</i></b>	$\alpha 7$ nAChR PAM	Phase I clinical trial	no beneficial effects on P50 sensory gating and other electrophysiological markers of early information processing	Winterer et al., 2013
<b><i>varenicline</i></b>	$\alpha 4\beta 2$ nAChR partial-agonist	Phase III clinical trial	improved cognitive flexibility, visuoperceptual processing, and visuospatial working memory performance	Shim et al., 2012; Wing et al., 2013
		Phase III clinical trial	prolonged tobacco abstinence rates, increased in reward sensitivity, reduced negative symptoms	Dutra et al., 2012; Evins et al., 2014; Pachas et al., 2012; Williams et al., 2012

Abbreviations: PAM, positive allosteric modulator.