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# **Title:** The effects of acute nicotine administration on cognitive and early sensory processes in schizophrenia: a systematic review

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## 1. INTRODUCTION

### 1.1. Cognitive and early sensory dimensions of schizophrenia

Schizophrenia is a chronic medical condition that affects 1% of the population worldwide (McGrath et al., 2008). Individuals with schizophrenia experience hallucinations, delusions, behavioral/thought disorganization, affective disturbances, and withdrawal from social activity (van Os and Kapur, 2009). In addition to clinical symptoms, impaired cognitive functioning has been reported as a core feature of the disease. Several cognitive processes are affected during both the acute and remission phases of schizophrenia, namely processing speed, attention, memory, executive functioning, and social skills (Greenland-White et al., 2017; Lewandowski et al., 2011; Valaparla et al., 2017). These deficits interact closely with clinical symptoms and can predict important aspects of the functional impairments associated with the disorder (Green, 1996; Green et al., 2014; Kern et al., 2011).

More recent evidence suggests that early sensory deficits may also play an important role in the pathophysiology of schizophrenia (rev. in (Butler et al., 2008; Javitt and Sweet, 2015)). Behavioral paradigms such as the tone-matching task (rev. in (Donde et al., 2019a; Donde et al., 2017)) and event-related potential measures (rev. in (Avissar et al., 2018; Javitt, 2009; Javitt and Sweet, 2015)) have demonstrated impairments in the early auditory processing of basic features in patients with the disorder. Another important sensory impairment in schizophrenia consists of alterations in early visual tracking, which refers to retinal motion information processing and the integration of visual sensory information into motor commands. These alterations include the impairment of smooth ocular pursuit in schizophrenia, which was originally described by Holzman and colleagues (Holzman, 1972), oculomotor deficits during eye-tracking tasks (Levy et al., 2010), and impairments in the identification of simple visual features (Butler et al., 2008). Critically, the effect sizes of early sensory deficits are commensurate with those of cognitive measures (Avissar et al., 2018; Levy et al., 2010), and contribute highly to impairments in real-life functioning (Donde et al., 2019b; Javitt and Freedman, 2015). Moreover, a rich body of evidence indicates that the outcome of schizophrenia is primarily driven by these deficits in cognition and early sensory processes (Green, 1996; Green et al., 2014; Javitt and Freedman, 2015; Kern et al., 2011). Therefore, it is relevant to further investigate the biological mechanisms of these critical

cognitive impairments, and whether specific pharmacological interventions can reduce these alterations.

## 1.2. Nicotine and schizophrenia

Nicotine use is frequent among schizophrenia patients, with prevalence rates of tobacco (nicotine) use disorder in this population approximating 60-90% (Cooper et al., 2012; de Leon et al., 1995; McClave et al., 2010; Williams and Ziedonis, 2004). This exceeds the prevalence rates in the general population, which is more or less 20% (Morisano et al., 2009)). Moreover, schizophrenia subjects exhibit very low successful quit rates (i.e., 10-27% vs. 42% in the general population (Lasser et al., 2000)). Heavy smoking, i.e. smoking more than 30 cigarettes per day, also appears to be much more frequent among schizophrenia smokers than non-schizophrenia smokers (de Leon and Diaz, 2005). Furthermore, individuals with schizophrenia preferentially smoke high-tar cigarettes (McCreadie and Kelly, 2000), present more rapid smoking patterns (Tidey et al., 2005; Williams et al., 2013; Williams and Ziedonis, 2004), and extract more nicotine from smoking cigarettes than non-schizophrenia smokers (Olinck et al., 1997; Strand and Nyback, 2005; Williams et al., 2010). Although higher rates of nicotine use are observed in the majority of neuropsychiatric disorders in comparison to the general population, this difference is particularly striking in schizophrenia (de Leon et al., 2002; Li et al., 2017; Uçok et al., 2004).

Critically, nicotine use is also associated with more severe overall features in patients with schizophrenia. Schizophrenia smokers show more intense clinical symptoms (Aguilar et al., 2005; Hickling et al., 2017; Iasevoli et al., 2013; Krishnadas et al., 2012; Yee et al., 2015), poorer quality of life (Dixon et al., 2007; Medici et al., 2016), and worse long-term outcomes (Aguilar et al., 2005; Patkar et al., 2002) relative to schizophrenia nonsmokers. Nicotine use makes them highly vulnerable to non-psychiatric medical consequences, such as cancer, and cardiovascular and pulmonary diseases (Carney et al., 2016; Shanmugam et al., 2007; Wehring et al., 2012). Schizophrenia is associated with a mean decrease in life expectancy of 14.5 years (Hjorthøj et al., 2017), and more than half of this potential life lost is at least partly related to nicotine use (Wildgust et al., 2010). In addition, according to large-sample studies, nicotine use appears to be a strong independent predictor of psychotic-like experiences in young individuals (Bhavsar et al., 2018; Gage et al., 2014; van Gastel et al., 2013). This suggests that the increased need for nicotine may be closely associated with pathophysiological determinants of schizophrenia. Supporting this hypothesis, a recent meta-

analysis suggests that tobacco consumption is associated with an earlier age of schizophrenia onset (Gurillo et al., 2015). Considering the above epidemiological evidence, nicotine could be globally considered as an aggravating factor for schizophrenia symptoms and alterations in cognitive processes. However, neurobiological findings temper this one-way statement.

### 1.3. Neurobiological hypotheses linking nicotine use and schizophrenia

Nicotine use and schizophrenia are entangled in a complex cause-and-effect relationship. Two main addiction models have been proposed to explain chronic and severe nicotine use in schizophrenia.

First, the *self-medication* model posits that nicotine is used to alleviate manifestations of the illness, especially negative symptoms, through the substance's ability to raise the dopamine levels in brain circuits that are dopamine-depleted in schizophrenia. Patients may also use nicotine to help reduce the unpleasant side effects of antipsychotics on nigrostriatal pathways, including abnormal motor activity (Kumari and Postma, 2005). Critically, a large body of evidence indicates that striatal dopamine activity, which is altered in schizophrenia, plays an important role in cognitive processes that are influenced by prefrontal cortex functions (rev. in (Condray and Yao, 2011)). In parallel, the alteration of specific cognitive and early sensory functions in schizophrenia, such as prepulse inhibition, sensory gating and eye-tracking movements, can be normalized with smoking (rev. in (Leonard et al., 2007)). Moreover, aberrant genes expression linked to excitatory postsynaptic NMDA (N-methyl-D-aspartate) receptors in schizophrenia appears to be normalized in smokers but not in nonsmokers, suggesting that patients may indeed be attempting a type of self-medication through nicotine use (Mexal et al., 2005). Also in support of the self-medication model, from a clinical perspective, schizophrenia smokers show a significantly greater craving for relief than for reward compared to non-schizophrenia smokers (Dondé et al., 2020). However, the self-medication model does not explain why schizophrenia smokers have more severe clinical profiles, and greater impairments in cognitive functioning, compared to schizophrenia nonsmokers (Krishnadas et al., 2012; Wang et al., 2010).

Second, the *shared vulnerability* model proposes that shared genetic/environmental risk factors and neurobiological dysfunctions inherent to the pathophysiology of schizophrenia make these subjects more vulnerable to nicotine consumption, but does not induce a “volitional” act of nicotine use for self-help (Chambers, 2009; Chambers et al., 2001). This common pathophysiological mechanism is thought to involve neurobiological

abnormalities within the mesolimbic dopamine system (Chambers et al., 2001). This central system mediates the rewarding effects of drugs, specifically via dopamine neurons in the ventral tegmental area and their target neurons in the ventral striatum and the prefrontal cortex (Koob and Volkow, 2010). Crucially, this implication of the mesolimbic dopamine system is one of the most robust findings in schizophrenia (rev. in (Brunelin et al., 2013)). It is also argued that changes in NDMA receptor-dependant mechanisms may constitute risk factors underlying both schizophrenia and the development of nicotine addiction in this patient population (Mexal et al., 2005). In parallel, the shared vulnerability model explains the sensitized reinforcing effects of nicotine, increased impulsivity traits, and heightened craving patterns in schizophrenia individuals that, in turn, increase their susceptibility to consume nicotine (Parikh et al., 2016).

Although some debate remains on which addiction model is the most accurate, it is widely accepted that a dysfunction in the central nicotinic acetylcholine receptors (nAChRs) represents a common substrate for both the clinical manifestations and comorbid nicotine addiction in individuals with schizophrenia (Parikh et al., 2016).

#### 1.4. The importance of investigating the experimental effects of acute nicotine administration on cognitive and early sensory processes

The closely intertwined relationships between schizophrenia and the propensity for nicotine raise questions about the effects of this pharmacological agent on cognitive and early sensory functioning. It is well established that smoking tobacco can normalize alterations in these domains in individuals with schizophrenia (rev. in (Featherstone and Siegel, 2015; Leonard et al., 2007; Wing et al., 2012)). However, while scientific evidence highlights nicotine as the main agent addictive agent in cigarettes (Stolerman and Jarvis, 1995), information about the specific effects of nicotine on cognitive/early sensory processes remain sparse or controversial across studies about schizophrenia. There are several reasons why the explicit role of nicotine on core pathophysiological processes should be clarified. First, besides nicotine extraction, smoking a cigarette involves a constellation of sensory (e.g., tobacco taste, tracheobronchial sensations) and behavioral (e.g., handling, puffing) factors that may contribute to smoking addiction independently from nicotine intake (Rose, 2006). Recent evidence indicates that these factors have a subtle but significant effect on cognitive functioning, even in the absence of nicotine delivery (Addicott et al., 2014; McClernon et al., 2016). Second, cigarette smoke contains numerous non-nicotine chemicals, which can have

central activating effects independent of nicotine (Arnold et al., 2014; Danielson et al., 2014; Ryu et al., 2018), and may enhance or reduce the reinforcing properties of nicotine (Hall et al., 2014). For instance, anabasine and anatabine have been shown to significantly improve attentional and memory functions in rats (Levin et al., 2014). Although preclinical, these results suggest that non-nicotine intake through tobacco smoking could conceivably bias the inputability of nicotine on cognitive and early sensory aspects in schizophrenia. Third, nicotinic agents that target the nAChRs were recently developed to promote smoking cessation and ameliorate psychiatric symptoms in patients with schizophrenia (Featherstone and Siegel, 2015; Tregellas and Wylie, 2019), making the investigation of the specific effects of nicotine on pathophysiological determinants of the disorder all the more timely. For these reasons, , we conducted a systematic review of experimental studies that explored the impact of acute nicotine intake on cognitive and early sensory processes in schizophrenia. We chose to focus on nicotine administration carried out in experimental frameworks because this design is best suited to disentangle the relationship between nicotine and the core cognitive/early sensory processes altered by consumption, and to rule out potential non-nicotine confounds. This implies the examination of short-term effects only.

### 1.5. Aim of the present review

The major objective of this systematic review was to examine the effects of acute nicotine administration on cognitive and early sensory outcomes in patients with schizophrenia. The included studies involve pre-to-post nicotine or between-condition comparisons (e.g., nicotine vs. placebo intake). When available, comparisons of these effects between schizophrenia patients and controls without schizophrenia, and between smoking and non-smoking schizophrenia patients were reported. Relevant neurobiological correlates were also included in this review, when available. While several reviews have examined baseline cognitive performance in smoking vs. non-smoking patients (D'Souza and Markou, 2012; Featherstone and Siegel, 2015; Wang et al., 2019), no systematic review has focused on the immediate effects of acute nicotine administration on cognitive and early sensory outcomes in schizophrenia. We believe this systematic review will help improve the management of smoking and its negative consequences in this population.

## 2. METHOD

## 2.1. Inclusion criteria

Recommendations from the PRISMA guidelines for systematic reviews were followed (Moher et al., 2015).

The criteria for inclusion were:

- (i) English and French language studies published in peer-reviewed journals.
- (ii) Individuals with an established clinical diagnosis of schizophrenia or schizoaffective disorder (criteria of the DSM-III to 5 (APA, 1983, 1989, 1996, 2003) or the ICD-9 to 10 (WHO, 1996, 2011)) who are smokers (tobacco use disorder or substance dependence for tobacco criteria of the DSM-III to 5 (APA, 1983, 1989, 1996, 2003) or the ICD-9 to 10 (WHO, 1996, 2011)) or nonsmokers. No consumption threshold was required.
- (iii) Experimental administration of nicotine. No specific dose of nicotine was required.
- (iv) Quantitative assessment of cognitive, and/ or early sensory functions before and after acute nicotine administration, and/or between conditions (e.g., nicotine vs. placebo administration).
- (v) If control smokers without schizophrenia were involved in a study fulfilling the above criteria, tobacco use disorder or substance dependence for tobacco criteria of the DSM-III to 5 (APA, 1983, 1989, 1996, 2003) or the ICD-9 to 10 (WHO, 1996, 2011) were required.

The criteria for exclusion were:

- (i) Article types not suitable for inclusion in a systematic review (conference posters, reviews, unpublished studies, opinions and comments).
- (ii) Simultaneous administration of nicotine and non-nicotine components.
- (iii) No pre-to-post comparison of cognitive, and/ or early sensory outcomes.

## 2.2. Literature search strategy

We searched the Medline, Embase, ScienceDirect and Clinical Trials databases using the following Medical Subject Heading (MeSH) terms with no publication date restrictions until December 2019: *(nicotine) AND (cognition OR cognitive OR attention OR vigilance OR memory OR “executive function” OR “social cognition” OR sensory OR visual OR auditory) AND (schizophrenia OR psychosis OR psychotic)*. The references from all eligible papers were screened to identify possible references that did not come up during the initial search.



Two reviewers (CD, FH) independently screened the title and/or abstract of each study identified by the search and applied the inclusion criteria. Following this first screen, we applied the same procedure to the full text of eligible studies. The literature search strategy is detailed in the flow-chart diagram (Figure 1).

### 2.3. Data extraction

Two reviewers (CD, FH) independently extracted the following data, when it was provided: (i) population and clinical data (sample size, gender ratio, intellectual quotient, education level, smoking status, nicotine use —duration and intensity—, schizophrenia features, antipsychotic medication), (ii) nicotine administration protocol (time points, condition of nicotine administration, dosage, route of administration), (iii) cognitive and/ or early sensory assessment tools and quantitative measures. When present, relevant data regarding neuroimaging correlates of cognitive/early sensory measures were extracted. To measure the overall quality of the included references, a global rating score (maximum score = 26) was calculated for each study using the Standard Quality Assessment (QualSyst tool (Kmet, 2004)).

## 3. RESULTS

### 3.1. Literature search

As shown in Fig.1, the initial search returned 2,586 references after removing duplicates. A preliminary screening of the titles and/or abstracts allowed the exclusion of 2,539 references. Among the 47 studies that were reviewed in detail, 18 were excluded because they either did not conduct any cognitive or sensory assessment (n=7), did not administer nicotine (n=8), or did not include a schizophrenia group (n=3). Finally, 29 studies were selected for systematic review, including 560 patients with schizophrenia and 346 non-schizophrenia controls. These studies investigated the effects of an experimental administration of nicotine on cognitive processes (18 studies (AhnAllen et al., 2015; AhnAllen et al., 2008; Barr et al., 2008; Boggs et al., 2013; Ghiasi et al., 2013; Hahn et al., 2013b; Harris et al., 2004; Hong et al., 2011a; Jacobsen et al., 2004; Jubelt et al., 2008; Kochunov et al., 2013; Levin et al., 1996; Myers et al., 2004; Quisenberts et al., 2014; Smith

et al., 2002; Smith et al., 2006; Smucny et al., 2016a; Smucny et al., 2016b)), early sensory processes (10 studies (Avila et al., 2003; Dulude et al., 2010; Fisher et al., 2012; Inami and Kirino, 2019; Inami et al., 2007; Larrison-Faucher et al., 2004; Mobascher et al., 2012; Petrovsky et al., 2013; Sherr et al., 2002; Tregellas et al., 2005)) or both (one study (Depatie et al., 2002)). Details about sociodemographic and clinical characteristics are shown in Supplementary Material S1. All protocols involved an acute administration of a single dose of nicotine. In other words, no studies investigating the effect of chronic nicotine administration in schizophrenia were retrieved, likely for ethical reasons. Only three studies compared the effects of nicotine vs. tobacco administration (Ghiasi et al., 2013; Hahn et al., 2013b; Smith et al., 2002). Overall, the quality assessment was satisfactory (mean: 22.27 +/- 2.22). Details of the assessment are given in Supplementary Material S2.

### 3.2. Impacts of nicotine on cognitive processes in schizophrenia

In each cognitive study identified through the literature search (N=19), validated tests were used to assess cognitive processes. These processes included processing speed, attention/vigilance, working memory, verbal fluency, verbal and visual memory, executive functioning, and social cognition (Kern et al., 2008; Nuechterlein et al., 2008). Studies investigating the impact of acute nicotine administration on cognition are detailed in Table 1 and results from placebo-controlled studies are highlighted in Table 2.

Ten studies used randomized placebo-controlled crossover procedures to compare the cognitive effects of acute nicotine administration between schizophrenia participants and non-schizophrenia controls, with trials involving either smokers (AhnAllen et al., 2015; Depatie et al., 2002; Hahn et al., 2013b; Hong et al., 2011a; Jacobsen et al., 2004; Kochunov et al., 2013) or nonsmokers (Barr et al., 2008; Jubelt et al., 2008; Smucny et al., 2016a; Smucny et al., 2016b). Blinded and crossover modalities were used in all of these trials. In parallel, seven randomized placebo-controlled crossover blinded trials investigated the effects of acute nicotine administration in schizophrenia subjects only, either in schizophrenia smokers alone (Boggs et al., 2013; Ghiasi et al., 2013; Levin et al., 1996; Smith et al., 2002) or between the schizophrenia smoker and schizophrenia nonsmoker subgroups (Harris et al., 2004; Quisenberts et al., 2014; Smith et al., 2006). Finally, two trials involving both schizophrenia and non-schizophrenia controls did not include a placebo condition (AhnAllen et al., 2008; Myers et al., 2004).

Four placebo-controlled studies observed statistically significant improvements of

cognitive performance after acute nicotine administration in schizophrenia patients. These improvements were greater in schizophrenia smokers vs. control smokers (AhnAllen et al., 2015; Barr et al., 2008; Depatie et al., 2002; Jacobsen et al., 2004) and in schizophrenia nonsmokers vs. control nonsmokers (Barr et al., 2008). The enhanced processes were attention, verbal working memory and executive function (inhibitory control). Also, a significant superiority of nicotine vs. placebo administration was repeatedly observed for attention and processing speed in schizophrenia smokers and control smokers equally, i.e. with no interaction effects with schizophrenia status (AhnAllen et al., 2015; Hong et al., 2011a; Jubelt et al., 2008). In two uncontrolled studies, baseline measures were conducted after periods of withdrawal. Interestingly, these studies reported that nicotine depletion has greater adverse effects on cognitive performance in schizophrenia smokers, with nicotine replenishment ameliorating the deficits to the levels of control smokers (AhnAllen et al., 2008; Myers et al., 2004).

Five placebo-controlled studies involved groups of schizophrenia smokers but no comparison groups of non- schizophrenia controls. In these studies, post-nicotine performances were repeatedly increased for attention, verbal memory, and visual processes (visual memory and visual working memory) (Ghiasi et al., 2013; Levin et al., 1996; Smith et al., 2002; Smith et al., 2006), while no improvements were shown for processing speed, verbal memory, verbal fluency, and executive functions (inhibitory control). Finally, three studies that compared schizophrenia smokers and schizophrenia nonsmokers demonstrated superior post-nicotine improvement in smokers vs. nonsmokers for both attention and visual memory processes (Harris et al., 2004; Myers et al., 2004; Quisenbary et al., 2014).

In parallel, five studies investigated the neurobiological correlates of acute nicotine impact on cognition using Magnetic resonance imaging (Hong et al., 2011a; Jacobsen et al., 2004; Kochunov et al., 2013; Smucny et al., 2016a; Smucny et al., 2016b). Most findings revealed an enhancement of the area activity and network strength associated with cognitive functions after nicotine administration in both smoking and non-smoking patients, especially regarding attention-related fronto-parietal brain regions.

### 3.3. Impact of nicotine on early sensory processes in schizophrenia

Some studies that investigated the effects of nicotine on early sensory processes used oddball paradigms to quantify event-related potential, in which infrequent target items (“deviants” that elicit event-related MMN (Mismatch Negativity) and P300) are typically mixed with non-target items (“standards” that elicit N1) within repetitive patterns of sensory

stimuli. In parallel, some studies focused on early visual processes using eye-tracking paradigms. Visual pursuit tasks require participants to track a dot that moves across a screen at a constant velocity, followed by fixation periods. In saccade tasks, subjects are asked to fixate on a central point and instructed to look towards (pro-saccade) or away from (anti-saccade) a target that appears near a fixed point. Studies investigating the impact of nicotine on early sensory processes are detailed in Table 3.

Five event-related potential studies were included (Dulude et al., 2010; Fisher et al., 2012; Inami and Kirino, 2019; Inami et al., 2007; Mobascher et al., 2012). All of them used a crossover placebo-controlled design. Among these studies, four measured auditory MMN (Dulude et al., 2010; Fisher et al., 2012; Inami and Kirino, 2019; Inami et al., 2007), either in groups of patients with schizophrenia alone (Dulude et al., 2010; Fisher et al., 2012) or along with groups of control smokers and nonsmokers (Inami and Kirino, 2019; Inami et al., 2007). Among the two studies that involved only schizophrenia samples, smokers showed a significant improvement in auditory MMN amplitude (Dulude et al., 2010), whereas nonsmokers showed improved auditory MMN latency (Fisher et al., 2012) after nicotine administration. By contrast, in two other MMN studies that compared groups of patients with schizophrenia to controls—including both nonsmokers and smokers—significant improvements of auditory MMN latency were only observed in controls (Inami and Kirino, 2019; Inami et al., 2007). In addition, one study measured visual P300 in groups of schizophrenia smokers compared to control smokers (Mobascher et al., 2012), and one measured auditory N1 in a sample of schizophrenia smokers alone (Dulude et al., 2010). No changes in visual P300 and auditory N1 were observed after nicotine administration across samples (Dulude et al., 2010; Mobascher et al., 2012).

Six eye-tracking experiments were retrieved, of which five used crossover placebo-controlled (Depatie et al., 2002; Larrison-Faucher et al., 2004; Petrovsky et al., 2013) or uncontrolled (Avila et al., 2003; Sherr et al., 2002) designs. One study (Depatie et al., 2002) out of two (Depatie et al., 2002; Sherr et al., 2002) measured visual pursuit performance and demonstrated significant amelioration of smooth pursuit accuracy in both schizophrenia smokers and control smokers under nicotine vs. placebo conditions. Regarding saccade performances, nicotine-induced improvements in pro- and anti-saccades were equally observed in schizophrenia and control participants—smokers and nonsmokers—across studies (Avila et al., 2003; Depatie et al., 2002; Petrovsky et al., 2013; Sherr et al., 2002). Finally, a single study that investigated smooth pursuit in schizophrenia smokers compared to

schizophrenia nonsmokers observed similar improvements that were associated with functional changes within brain structures involved in visual pursuit (Tregellas et al., 2005).

## 4. DISCUSSION

The aim of this study was to gather knowledge about the specific effects of acute experimental nicotine administration on cognitive and early sensory processes in schizophrenia. Overall, 29 studies were reviewed, including 560 patients with schizophrenia and 346 non-schizophrenia controls.

### 4.1. Nicotine can enhance cognitive functioning

The main findings of our systematic review highlight that acute nicotine administration essentially improves a wide range of cognitive functions in patients with schizophrenia. This is particularly true for 1) attention, 2) working memory, and 3) executive functions, with attention being the most responsive process. Cognitive enhancements after acute nicotine administration were also reported in control smokers and control nonsmokers, which has been linked to an improved learning effect in repeated neuropsychological testing (Calamia et al., 2012). However, in most of the reviewed studies, the effect sizes were significantly more important in schizophrenia samples. In addition, some studies observed concomitant disappearances of abnormal brain activity and connectivity patterns related to cognitive performance in schizophrenia patients after nicotine administration (Jacobsen et al., 2004; Kochunov et al., 2013; Smucny et al., 2016b).

Knockout mice studies have provided extensive demonstrations of the critical involvement of the nicotine receptor nAChR and its related cholinergic neurotransmission in cognitive processes including attention, working memory, and executive functions (rev. in (Parikh et al., 2016)). Accordingly, improved cognitive functioning after nicotine administration in schizophrenia supports the assumption that patients smoke as a mean to alleviate cognitive impairments due to the effects of medication and/or illness (i.e., *self-medication* model), and suggests that nicotine activity on nAChRs might be a key mechanism from which patients derive such pro-cognitive effects. This concept is supported by findings of larger post-nicotine improvements in schizophrenia smokers vs. nonsmokers (Harris et al.,

2004; Myers et al., 2004; Quisenbaerts et al., 2014). In addition, the alleviation of cognitive alterations through nicotine consumption might explain the specific pattern of craving experienced by schizophrenia smokers, with a higher sensitivity for relief than for reward-seeking (Dondé et al., 2020).

In line with the above, two studies demonstrated that nicotine administration better improved attention and processing speed than *ad libitum* cigarette smoking in both schizophrenia smokers and control smokers. This suggests a differential effect of tobacco and nicotine alone on these cognitive processes (AhnAllen et al., 2015; Hahn et al., 2013b). A potential explanation is that cigarette-derived nicotine is characterized by rapidly metabolized nicotine (Williams et al., 2010), whereas protracted release from a patch is more likely to ensure a more sustained nicotine concentration throughout the entire period of cognitive testing (Fant et al., 2000). Given the preclinical evidence that the absorption of non-nicotine components through smoking may have specific central effects (Arnold et al., 2014; Danielson et al., 2014; Hall et al., 2014; Levin et al., 2014; Ryu et al., 2018), further studies are warranted to investigate the effects of pure nicotine vs. non-nicotine components of tobacco on cognitive and early sensory outcomes in schizophrenia. It is worth noting that medication might represent a potential confound, since antipsychotics can hamper cognitive abilities in patients according to daily dosage (Rehse et al., 2016). Nevertheless, medication status was controlled by crossover designs in most studies, and no interactions between medication dose and cognitive modifications under nicotine were reported.

#### 4.2. Nicotine can modulate early detection of change in auditory and visual stimuli

In addition to improving cognition in schizophrenia, nicotine intake can modulate early detection of change in the early sensory environment at both the auditory and visual levels. Within the auditory domain, nicotine was shown to improve the event-related potential MMN to deviant sounds, with larger effects in schizophrenia than non-schizophrenia controls. Furthermore, MMN was specifically renormalized in schizophrenia smokers and not in nonsmokers, suggesting that early auditory deficits are partially reversible, and could potentially be restored by chronic nicotine administration in schizophrenia (Inami and Kirino, 2019). The MMN has main generators in the frontal and temporal (auditory) cortices, and is altered at both sources in schizophrenia (Kim et al., 2017; Seol et al., 2017). MMN is closely related to NMDA receptor activity and Glutamate/GABA balance, both of which are crucial for the sensory processes that occur prior to further cognitive treatment. In parallel, nicotine activation of nAChRs facilitates the activation of NMDA receptors, with glutamate release in

sensory cortices in schizophrenia (Ochoa and Lasalde-Dominicci, 2007). These neuronal mechanisms may underlie the ability of nicotine to improve sensory processes indexed by MMN.

Regarding the visual domain, nicotine was shown to improve pro- and anti-saccade performance in schizophrenia samples. An important finding is that smoking status does not influence the effect of nicotine on saccade performance (Avila et al., 2003; Petrovsky et al., 2013; Sherr et al., 2002; Tregellas et al., 2005), which indicates a genuine effect of nicotine instead of a simple relief-from-withdrawal phenomenon in patients. This result is supported by the demonstration of a significant reduction in antisaccade error rates by the nAChR agonist varenicline in schizophrenia regardless of smoking status (Hong et al., 2011b). In parallel, mesocortical and nigrostriatal dopamine pathways are known to play an important role in eye movement processes (Gibson et al., 1987; Straube et al., 1998). Given that nicotine is thought to enhance dopaminergic function (Herman et al., 2014), which is abnormal in schizophrenia (Howes et al., 2015), it may be that the effect of nicotine on early visual processes is mediated via an improvement of abnormal dopaminergic transmission in these subjects. Finally, it has been suggested that nicotine may lead to early visual improvements, both through enhanced activity in brain areas involved in attending to moving visual stimuli as well as through the inhibition of regions involved in intrusion of non-relevant eye movements (Tregellas et al., 2005).

#### 4.3. Limitations and caveats

Notably, the pro-cognitive effects of nicotine found in several of the studies were unable to be replicated. Some of this inconsistency may be related to discrepancies in cognitive assessments. For instance, a significant impact of nicotine was mostly observed when sustained attention was measured with the Continuous Performance Test, whereas non-significant effects were observed with tasks presenting stronger working memory loads than the Continuous Performance Test, such as the Rapid Visual Information Processing Task (Wesnes and Warburton, 1983). It is thus possible that more demanding tasks may hamper the alleviating effects of nicotine on cognitive deficits in schizophrenia. Furthermore, since improvements in cognitive performance were mostly observed within the attention domain, it would be interesting to explore if brain networks that are specifically related to attention are more sensitive to nicotine compared to other networks related to other cognitive processes. Differences in the severity of nicotine use across samples, as well as dose and route (patch, spray, intravenous...) of administration of nicotine may also explain the discrepancies in

results across studies. Nevertheless, the pro-cognitive effects of nicotine remained significant after matching or controlling with the Fagerström Test for Nicotine Dependence scores (Depatie et al., 2002; Jacobsen et al., 2004). Although one study reported greater cognitive improvements with high-nicotine cigarettes vs. very-low-nicotine cigarettes (Smith et al., 2002), cognitive improvements were observed across several dosages delivered through non-cigarette devices, suggesting dose-independent effects. Regarding route of administration, the vast majority of reviewed studies used a transdermal patch and provided no comparisons between types of nicotine delivery devices. Future investigations are warranted to both explore potential dose effects and compare the influence of the type of nicotine delivery device. Most importantly, negative studies may indicate that nicotine use in schizophrenia cannot be entirely explained by the enhancing effects of nicotine on cognition. This would corroborate the *shared vulnerability* model, which involves shared neurobiological dysfunctions between nicotine consumption and schizophrenia, but not necessarily an alleviation of the manifestations through nicotine intake (Chambers, 2009; Chambers et al., 2001).

Another caveat is the condition variability of nicotine intake and measurements across studies. To eliminate all the nicotine from chronic smoking in smokers, the vast majority of studies started the nicotine administration and assessments during withdrawal states. This introduces the confound of the early sensory and cognitive disturbances induced by lack of nicotine. It is therefore not possible in these cases to determine to what extent the effects of acute nicotine intake are, in fact, the alleviation of the withdrawal syndrome (Snyder et al., 1989). Furthermore, withdrawal state and efficacy of nicotine replenishment after acute administration may also vary depending on withdrawal time period and the duration/intensity of smoking, which differed across studies. Nevertheless, improvements observed in schizophrenia non-smokers suggest a genuine increase in performance after nicotine intake, rather than a recovery from a withdrawal effect (Avila et al., 2003; Barr et al., 2008; Fisher et al., 2012; Harris et al., 2004; Jubelt et al., 2008; Petrovsky et al., 2013; Quisenbary et al., 2014; Sherr et al., 2002; Tregellas et al., 2005). More specifically, studies observed that nicotine depletion has greater adverse effects on cognitive performance in schizophrenia participants than in non-schizophrenia controls, and that nicotine replenishment ameliorates the deficits to the levels of controls (AhnAllen et al., 2008; Myers et al., 2004).

Furthermore, the studies included in this review assessed the short-term effects of a single administration of nicotine. It is thus difficult to infer the effects of chronic tobacco use from the results of these studies, which presented acute effects of nicotine observed within an



experimental framework. Furthermore, the observed improvements in cognitive and early sensory pathophysiological processes stand in contradiction to the more severe clinical pictures and outcomes commonly observed in chronic nicotine users with schizophrenia (Aguilar et al., 2005; Dixon et al., 2007; Hickling et al., 2017; Iasevoli et al., 2013; Krishnadas et al., 2012; Medici et al., 2016; Patkar et al., 2002; Yee et al., 2015). One potential explanation is that chronic nicotine use induces cognitive and early sensory impairments that supersede some initial benefits provided by nicotine use. To address this complex question, further studies are warranted to compare the effects of post acute administration vs. follow-up and vs. chronic nicotine intake in individuals with schizophrenia, including chronic nicotine users who are not tobacco smokers, for example, users of e-cigarettes. Interestingly, it was observed that chronic nicotine administration reverses hypofrontality in animal models of addiction and schizophrenia, a finding that supports the self-medication hypothesis (Koukouli et al., 2017).

Finally, no quantitative analyses were applicable due to the high heterogeneity of studies included in this systematic review. To date, no nicotinic drug developed to target nAChRs has conducted a successful phase 3 clinical trial in schizophrenia (Tregellas and Wylie, 2019). Given the clinical importance of cognitive and early sensory outcomes, further quantitative comparisons of acute nicotine effects in schizophrenia non-smokers vs. smokers may help to determine which populations are more likely to be aided by these drugs.

#### 4.4. Conclusion and further implications

Nicotine addiction is among the most burdensome comorbidities of schizophrenia. However, the specific impact of nicotine on core physiopathological aspects of the disorder is not clear. Here, we reviewed the specific effects of nicotine on cognitive and early sensory processes in schizophrenia. We observed that both aspects could be improved in these subjects after an acute administration of a single dose of nicotine, but this improvement varies depending on assessments and nicotine intake conditions. Importantly, these effects can reflect nicotine activity not only in cholinergic nAChR but also its action towards other neurotransmitter sites that are implicated in cognitive and early sensory functions. Further studies are required to better clarify the molecular mechanisms that mediate the improvements observed in the reviewed studies. Cognitive and early sensory impairments are thought to have direct implications in the outcome of individuals with schizophrenia. Although the deficits may not be the driving force of nicotine consumption in schizophrenia, current findings suggest the need to consider the potential decrease of cognitive and early sensory

performance when these individuals quit smoking. For instance, smoking-cessation could be coupled with remediative and training interventions (Hahn et al., 2013a; Hahn et al., 2019). Finally, future investigations are warranted to investigate the effectiveness of adjunctive nicotine agents on the preservation of cognitive and early sensory functions.

## AUTHOR CONTRIBUTION

CD designed the study and wrote the first draft of the manuscript. FH supervised the study. BR, JB, CC and MM provided critical inputs to the manuscript. All authors reviewed and approved the manuscript in its final form.

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## CONFLICT OF INTEREST

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This study was not funded.

## Figure Captions

**Figure 1:** PRISMA Flow diagram for the systematic review.

Medline, Embase, ScienceDirect and Clinical Trials databases were searched using the following Medical Subject Heading (MeSH) terms with no publication date restrictions until December 2019: *(nicotine) AND (cognition OR cognitive OR attention OR vigilance OR memory OR “executive function” OR “social cognition” OR sensory OR visual OR auditory) AND (schizophrenia OR psychosis OR psychotic).*

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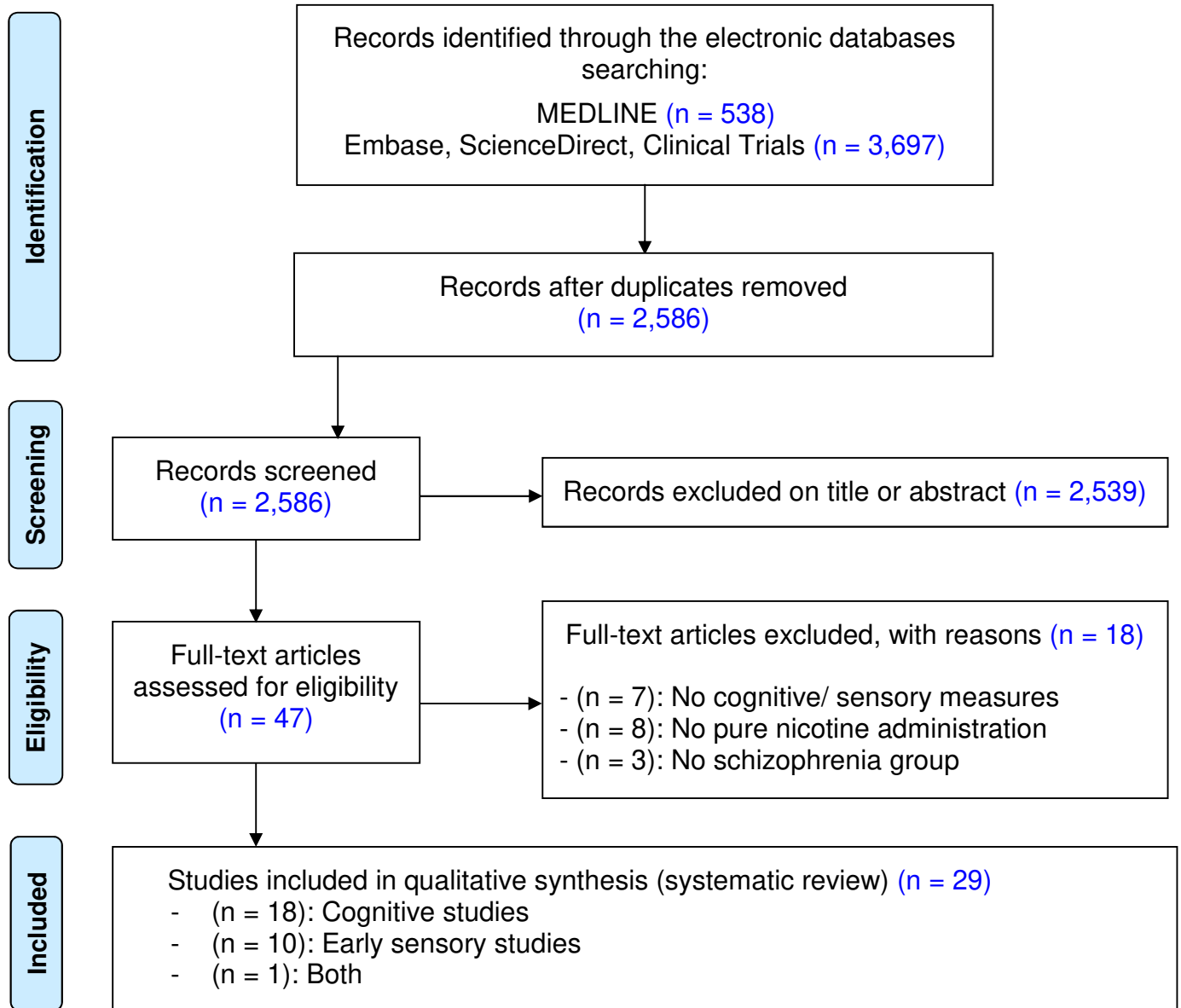
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Study	Sample	Measure time point(s)	Experimental and control condition(s)	Outcome (tool)	Key findings
<i>schizophrenia vs. non-schizophrenia placebo-controlled crossover</i>					
<i>Dépatie 2002</i>	15 schizophrenia smokers 14 control smokers	<b>T0:</b> nicotine intake after 1-night withdrawal	Transdermal nicotine patch (14-mg) vs. placebo patch	<b>Processing Speed</b> ( <i>CPT-IP reaction time</i> ) sustained <b>Attention</b> ( <i>CPT-IP</i> )	<b>T0:</b> Greater Attention under nicotine vs. placebo in the schizophrenia group relative to control. No changes in Processing Speed.
<i>Jacobsen, 2004</i>	13 schizophrenia smokers 13 control smokers	<b>T0:</b> nicotine intake after 15-h withdrawal	Transdermal nicotine patch (28-35-mg) vs. placebo patch	<b>Processing Speed</b> ( <i>auditory n-back reaction time</i> ) verbal <b>Working Memory</b> ( <i>auditory n-back</i> )	<b>T0:</b> Greater verbal Working Memory under nicotine vs. placebo in schizophrenia relative to lower in control. No changes in Processing Speed. <b>Neuroimaging (MRI):</b> Under nicotine, greater thalamo-cortical functional connectivity in schizophrenia than control during verbal Working Memory task.
<i>Hong, 2011</i>	20 schizophrenia smokers 24 control smokers	<b>T0:</b> nicotine intake after 4-h withdrawal	Transdermal nicotine patch (21-35mg) vs. placebo patch.	<b>Processing Speed</b> ( <i>RVIP reaction time</i> ) sustained <b>Attention</b> ( <i>RVIP</i> )	<b>T0:</b> Greater Attention and Processing Speed under nicotine vs. placebo in both groups. <b>Neuroimaging (MRI):</b> During placebo, Attention task-related reduced activation in frontal, parietal, cingulate and thalamic regions in schizophrenia relative to control. During nicotine, no changes observed in this pattern.
<i>Hahn, 2013</i>	17 schizophrenia smokers 17 control smokers	<b>T0:</b> nicotine intake after 3.5-h withdrawal (except for <i>ad libitum</i> smoking condition)	Transdermal nicotine patch (14-mg) vs. placebo patch vs. <i>ad libitum</i> smoking	<b>Processing Speed</b> ( <i>SARAT reaction time</i> ) selective <b>Attention</b> ( <i>SA</i> )	<b>T0:</b> Greater Attention under nicotine and <i>ad libitum</i> vs. placebo in both groups. Greater Processing Speed under nicotine vs. placebo and <i>ad libitum</i> smoking in both groups.
<i>Kochunov 2013</i>	20 schizophrenia smokers 19 control smokers	<b>T0:</b> nicotine intake after 3-h withdrawal	Transdermal nicotine patch (21-mg) vs. placebo patch	<b>Processing Speed</b> ( <i>RVIP reaction time</i> ) sustained <b>Attention</b> ( <i>RVIP</i> )	<b>T0:</b> No changes in Attention and Processing speed . <b>Neuroimaging (MRI):</b> Fraction anisotropy enhancement (corpus callosum genu) in both groups vs. placebo. This enhancement is correlated with Attention in the schizophrenia group, relative to control.
<i>AhnAllen, 2015</i>	29 schizophrenia smokers 28 control smokers	<b>T0:</b> nicotine intake after 5-h of usual smoking	Very low nicotine content cigarette smoking (VLNPC) + Transdermal nicotine patch (42-mg) vs. VLNPC + placebo patch vs. usual brand	<b>Processing Speed</b> ( <i>CPT-II/RVIP reaction time</i> ) sustained <b>Attention</b> ( <i>CPT-II/RVIP</i> ) <b>Visual Memory</b> ( <i>DMS-12</i> )	<b>T0:</b> Greater Attention and Processing Speed under nicotine vs. placebo and usual brand in both groups. No changes in Visual Memory.
<i>Barr, 2008</i>	28 schizophrenia non-smokers 32 control non-smokers	<b>T0:</b> baseline <b>T1:</b> 3-h after nicotine intake <b>T0-T1 interval:</b> 1-2 weeks	Transdermal nicotine patch (14-mg) vs. placebo patch	<b>Processing Speed</b> ( <i>Stroop reaction time</i> ) sustained <b>Attention</b> ( <i>CPT-IP</i> ) verbal <b>Working Memory</b> ( <i>LNS</i> ) inhibitory control <b>Executive Functions</b> ( <i>Stroop</i> )	<b>T0-T1:</b> Greater improvement of Attention and EF vs. placebo in schizophrenia relative to control. No changes in verbal Working Memory and Processing Speed.
<i>Jubelt 2008</i>	10 schizophrenia non-smokers 12 control non-smokers	<b>T0:</b> baseline <b>T1:</b> 4-h after nicotine intake <b>T0-T1 interval:</b> few-hours	Transdermal nicotine patch (14-mg) vs. placebo patch.	<b>Processing Speed</b> ( <i>episodic memory paradigm reaction time</i> ) <b>Verbal Memory</b> ( <i>episodic memory paradigm</i> )	<b>T0-T1:</b> Improvements in Verbal Memory and Processing Speed under nicotine vs. placebo in both groups.

<i>Smucny 2016a, 2016b</i>	17 schizophrenia non-smokers 20 control non-smokers	<b>T0:</b> baseline	Transdermal nicotine patch (7-mg) vs. placebo patch.	<b>Processing Speed</b> ( <i>SART reaction time</i> ) sustained <b>Attention</b> ( <i>SART</i> )	<b>T0:</b> No changes in Attention and Processing speed . <b>Neuroimaging (MRI):</b> Under placebo, Attention task increased activity in the ventral parietal cortex (VPC) and hippocampus, and reduced connectivity between the VPC and the left-inferior frontal gyrus in schizophrenia relative to control. Under nicotine, this pattern tends to be normalized in schizophrenia.
<b><i>schizophrenia vs. non-schizophrenia uncontrolled</i></b>					
<i>Myers 2004</i>	15 schizophrenia smokers 14 schizophrenia non-smokers 15 control-S 12 control non-smokers	<b>T0:</b> +2-h withdrawal <b>T1:</b> nicotine intake <b>T0-T1 interval:</b> 1-h	Nicotine nasal spray (1 mg)	<b>Processing Speed</b> ( <i>DMS for faces reaction time</i> ) <b>Visual Memory</b> ( <i>DMS for faces</i> )	<b>T0-T1:</b> Improvement of Visual Memory in schizophrenia smokers only. No changes in Processing speed and visual Working Memory.
<i>AhnAllen, 2008</i>	22 schizophrenia smokers 16 control smokers	<b>T0:</b> 1-h withdrawal <b>T1:</b> nicotine intake after 8-h withdrawal <b>T2:</b> 3-h after nicotine intake	Transdermal nicotine patch (21-mg)	<b>Processing Speed</b> ( <i>ANT reaction time</i> ) selective <b>Attention</b> ( <i>ANT</i> )	<b>T0-T2:</b> Greater improvement of Processing Speed in schizophrenia relative to control. No changes in Attention.
<b><i>schizophrenia placebo-controlled crossover</i></b>					
<i>Levin 1996</i>	15 schizophrenia smokers	<b>T0:</b> nicotine intake after 1-night withdrawal	Transdermal nicotine patch (7-mg) vs. 14-mg patch vs. 21-mg patch vs. placebo patch	<b>Processing Speed</b> ( <i>Simple/complex reaction time</i> ) sustained <b>Attention</b> ( <i>CPT</i> ) visual <b>Working Memory</b> ( <i>DMS</i> ) verbal <b>Working Memory</b> ( <i>Sternberg Memory Test</i> )	<b>T0:</b> Improvement of Attention and visual Working Memory in nicotine conditions vs. placebo. No changes in Processing Speed and verbal Working Memory.
<i>Smith 2002</i>	31 schizophrenia smokers	<b>T0:</b> 1-night withdrawal <b>T1:</b> 2-h after nicotine intake	High-nicotine cigarettes (HNC, 3.8-mg) vs. very-low-nicotine-cigarettes (VLNC, 0.2-mg) vs. nicotine nasal spray (20-40-mg/ml) vs. placebo spray.	<b>Processing Speed</b> ( <i>two-choice reaction time</i> ) visual <b>Working Memory</b> ( <i>Spatial organisation test</i> ) <b>Verbal Memory</b> ( <i>RANDT memory test</i> ) <b>Verbal Fluency</b> ( <i>Letter fluency test</i> )	<b>T0-T1:</b> Greater improvement of Processing Speed, Verbal Fluency, visual Working Memory and Verbal Memory after both cigarette conditions vs. nasal spray and placebo. Greater improvement of Verbal Memory and Visual Memory after nasal spray vs. placebo spray, and under HNC vs. VLNC.
<i>Smith 2006</i>	27 schizophrenia smokers	<b>T0:</b> nicotine intake after 12-h withdrawal <b>T1:</b> 30-min after nicotine intake	Nicotine nasal spray vs. placebo spray	<b>Processing Speed</b> ( <i>two-choice reaction time</i> ) sustained <b>Attention</b> ( <i>CPT</i> ) visual <b>Working Memory</b> ( <i>Spatial organisation test and visuospatial memory -probe task</i> ) <b>Verbal Memory</b> ( <i>Randt memory test</i> )	<b>T0-T1:</b> Greater improvement of Attention and visual Working Memory under nicotine vs. placebo. No changes in Processing Speed and Verbal Memory.
<i>Boggs, 2013</i>	9 schizophrenia smokers (7 for nicotine conditions)	<b>T0:</b> nicotine intake after 12-h withdrawal <b>T1:</b> 45-min after nicotine intake <b>T2:</b> 135-min after nicotine intake	IV nicotine low-dose vs. IV medium-dose vs. IV placebo	sustained <b>Attention</b> ( <i>CPT</i> ) inhibitory control <b>Executive Functions</b> ( <i>Stroop</i> )	<b>T0-T2:</b> No changes in Attention and Executive Functions.
<i>Ghiasi 2013</i>	45 schizophrenia smokers	<b>T0:</b> baseline <b>T1:</b> nicotine intake after 1-night	Transdermal nicotine patch (21-mg) vs. no patch	<b>Visual Memory</b> ( <i>BVMT-R</i> )	<b>T0-T1:</b> Decrease in Visual Memory in the no patch group relative to other groups.

		withdrawal for nicotine condition <b>T0-T1 interval:</b> 1-night	vs. <i>ad libitum</i> smoking		
<i>Harris 2004</i>	10 schizophrenia smokers 10 schizophrenia non-smokers	<b>T0:</b> nicotine intake after 2-h withdrawal (for schizophrenia smokers)	Nicotine gum (6-mg) vs. placebo gum	Sustained <b>Attention</b> ( <i>digit span test</i> ) Selective <b>Attention</b> ( <i>timed coding test</i> ) <b>Verbal Fluency</b> ( <i>Word fluency test</i> ) <b>Verbal Memory</b> ( <i>Immediate Memory Index</i> ) visual <b>Working Memory</b> ( <i>visuo-spatial organisation test</i> )	<b>T0:</b> Greater sustained and selective Attention after nicotine intake vs. placebo in schizophrenia non-smokers relative to schizophrenia smokers. No changes in Verbal Fluency, Verbal Memory and visual Working Memory.
<i>Quisenberts 2014</i>	16 schizophrenia smokers 16 schizophrenia non-smokers	<b>T0:</b> nicotine intake after 2-h withdrawal (for schizophrenia smokers)	Nicotine nasal spray 1-mg vs. Nicotine nasal spray 2-mg vs. placebo spray.	<b>Processing Speed</b> ( <i>Symbol Digit Substitution Test reaction time</i> ) sustained <b>Attention</b> ( <i>CPT</i> ) verbal <b>Working Memory</b> ( <i>LNS</i> ) <b>Visual Memory</b> ( <i>BVRT</i> ) theory of mind <b>Social Cognition</b> ( <i>Reading the Mind in the Eyes test</i> )	<b>T0:</b> Greater Attention/ Vigilance under 2-mg spray vs. placebo in schizophrenia smokers, relative to no effect in schizophrenia non-smokers. No changes in Processing Speed, Visual Memory, verbal Working Memory and Social Cognition.

**Table 1:** Studies investigating nicotine impact on cognition in schizophrenia.

ANT= Attentional Network Task; BVRT= Benton Visual Retention Test; CPT= Continuous Performance Test; CPT-II: Continuous Performance Test version II; CTP-IP= Continuous Performance Test, identical pairs version; DMS= Delayed match-to-sample; fMRI= functional Magnetic Resonance Imaging; LNS= Letter Number Sequencing; PS= processing speed; RVIP= Rapid Visual Information Processing; SARAT= Spatial Attentional Resource Allocation Task; SART= Sustained Attention to Response Test.

Outcome	Smokers: significant (nicotine > placebo) * (schizophrenia > control) improvement	Non-smokers: Significant (nicotine > placebo) * (schizophrenia > control) improvement	Significant (nicotine > placebo) * (schizophrenia smokers > schizophrenia non-smokers) improvement	Significant (nicotine > placebo) improvement in schizophrenia smokers
<b>Speed of processing</b>	<b>0/ 6</b>	<b>0/ 3</b>	0/ 0	<b>1/ 3</b>
<b>Attention/ Vigilance</b>	<b>1/ 5</b>	<b>1/ 2</b>	<b>3/ 3</b>	<b>2/ 4</b>
Sustained	1/ 4	1/ 2	2/ 2	2/ 3
Selective	0/ 1	0/ 0	1/ 1	0/ 0
<b>Working Memory</b>	<b>1/ 1</b>	<b>0/ 1</b>	<b>0/ 2</b>	<b>3/ 4</b>
Visual	0/ 0	0/ 0	0/ 1	3/ 3
Verbal	1/ 1	0/ 1	0/ 1	0/ 1
<b>Verbal memory</b>	<b>0/ 0</b>	<b>0/ 1</b>	<b>0/ 1</b>	<b>1/2</b>
<b>Verbal fluency</b>	<b>0/ 0</b>	<b>0/ 0</b>	<b>0/ 1</b>	<b>0/ 1</b>
<b>Visual memory</b>	<b>0/ 1</b>	<b>0/ 0</b>	<b>0/ 1</b>	<b>1/1</b>
<b>Executive functions</b>	<b>0/ 0</b>	<b>1/ 1</b>	<b>0/ 0</b>	<b>0/ 1</b>
<b>Social cognition</b>	<b>0/ 0</b>	<b>0/ 0</b>	<b>0/ 1</b>	<b>0/ 0</b>

**Table 2:** Summary of experiments showing significant cognitive improvement after nicotine intake in placebo-controlled studies.

Study	Sample	Design and measure time points	Experimental and control conditions	Outcome	Key findings
<i>Mobascher 2012</i>	15 schizophrenia smokers 14 control smokers	<b>Design:</b> randomized, double-blind, placebo-controlled, crossover. fMRI scan during task. <b>Measures:</b> baseline, +1-night of withdrawal	Nicotine nasal spray (1 mg) at +1-night vs. placebo spray at +1-night	ERP-P300-informed fMRI activation ERP-P300 amplitude and latency (electrodes Cz, Pz, CP1, CP2) elicited by visual oddball deviants	No changes for ERP measures. More fMRI activations (anterior cingulate and adjacent medial frontal cortex) in both groups.
<i>Dulude 2010</i>	12 schizophrenia smokers	<b>Design:</b> randomized, double-blind, placebo-controlled, crossover. <b>Measures:</b> +3-hours nicotine withdrawal	Nicotine gum (8mg) vs. placebo gum at +3-hours	ERPs amplitude and latency (electrode Fz, Cz, Pz) elicited by frequency and duration auditory oddball deviants (MMN) and standards (N1).	Improvement of Fz-MMN amplitude under nicotine vs. placebo for duration deviants but not for frequency deviants No changes for Fz-MMN latency and Fz-N1 amplitude and latency.
<i>Fisher 2012</i>	12 schizophrenia non-smokers	<b>Design:</b> randomized, double-blind, placebo-controlled, crossover. <b>Measures:</b> baseline	Nicotine gum (6-mg) vs. placebo gum	ERP-MMN amplitude (electrode Fz) and latency (electrodes Fz, F3, F4) elicited by auditory oddball deviants	Improvement of MMN latency under nicotine vs. placebo for intensity deviants but not frequency and duration deviants. No changes for MMN amplitude.
<i>Inami 2007</i>	10 schizophrenia non-smokers (including 1 schizophrenia smokers) 10 control non-smokers (including 2 control smokers)	<b>Design:</b> randomized, placebo-controlled, crossover. <b>Measures:</b> baseline, 24-h washout	Transdermal nicotine patch (16-mg) vs. placebo patch	ERP-MMN amplitude and latency (electrode Fz) elicited by auditory oddball deviants	Improvement of MMN latency under nicotine vs. placebo latency for frequency deviants in control but no difference in schizophrenia.
<i>Inami 2019</i>	8 schizophrenia smokers 10 schizophrenia non-smokers 11 control smokers 11 control non-smokers	<b>Design:</b> non-randomized, placebo-controlled, crossover. <b>Measures:</b> baseline, 24-h washout	Placebo patch vs. (followed by) Transdermal nicotine patch (35-mg)	ERP-MMN latency elicited by auditory oddball deviants (electrodes Fz, Cz)	Improvement of MMN latency under nicotine vs. placebo for frequency deviants in both control groups. No change in schizophrenia non-smokers. In schizophrenia smokers, withdrawal led to prolonged MMN latencies that returned to baseline after nicotine administration.
<i>Petrovsky 2013</i>	12 schizophrenia smokers 10 schizophrenia non-smokers 14 control smokers 12 control non-smokers	<b>Design:</b> randomized, double-blind, placebo-controlled, crossover. <b>Measures:</b> +15-hours nicotine withdrawal (for	Transdermal nicotine patch (14-mg for smokers, 7-mg for non-smokers) vs. placebo patch at +12-hours nicotine	Eye tracking: Latencies of pro- and anti-saccades to peripheral visual targets, using both standard and delayed trials.	Improvement of anti-saccades latencies for standard trials in all groups. No changes for pro-saccade latencies.



		smokers)	withdrawal (for smokers)		
<i>Sherr 2002</i>	15 schizophrenia smokers 14 schizophrenia non-smokers 15 control smokers 14 control non-smokers	<b>Design:</b> open-label, uncontrolled <b>Measures:</b> baseline, +2-hours withdrawal	Nicotine nasal spray (1 mg) at +2-hours	Eye tracking: latency, accuracy and acceleration of pro-saccades during 3 phases of moving visual targets smooth pursuit (initiation, maintenance and prediction).	Improvement of acceleration during pursuit initiation in both schizophrenia relative to both control. Improvement of saccades during maintenance and prediction for all groups.
<i>Larrison-Faucher 2004</i>	8 schizophrenia smokers 8 control smokers	<b>Design:</b> open-label, placebo-controlled <b>Measures:</b> baseline	Nicotine gum (4mg) vs. Nicotine gum (6mg) vs. placebo gum vs. no gum at baseline	Eye tracking: Latencies of pro- and anti-saccades to peripheral visual target using standard trials.	Under nicotine 6-mg, improvement of anti-saccades latencies in a schizophrenia subgroup that showed a baseline deficit relative to control. No changes for saccade latencies.
<i>Tregellas 2005</i>	5 schizophrenia smokers 4 schizophrenia non-smokers	<b>Design:</b> randomized, placebo-controlled, crossover. fMRI scan during task. <b>Measures:</b> baseline (2-hours withdrawal for smokers), after gum administration	Nicotine gum (6-mg for smokers, 4-mg for non-smokers) vs. placebo gum	Eye tracking: accuracy of smooth pursuit to moving visual targets.	Improvement in accuracy vs. placebo in both schizophrenia groups. Greater activity (cingulate gyri, precuneus, area extrastriate visual cortex) and less activity (parietal eyes fields, hippocampus) vs. placebo in both groups.
<i>Avila 2003</i>	14 schizophrenia smokers 13 schizophrenia non-smokers 14 control smokers 11 control- NS	<b>Design:</b> open-label, uncontrolled <b>Measures:</b> baseline, +2h withdrawal	Nicotine nasal spray (1-mg) at +2-hours	Eye tracking: accuracy and acceleration of pro-saccades to moving visual targets.	Improvement in accuracy and latency vs. placebo in both schizophrenia groups relative to control. Improvement more pronounced in schizophrenia non-smokers
<i>Dépatie 2002</i>	15 schizophrenia smokers 14 control smokers	<b>Design:</b> randomized, double-blind, placebo-controlled, crossover <b>Measures:</b> +1-night of withdrawal	Transdermal nicotine patch (14-mg) vs. placebo patch	Eye tracking: Accuracy of pro- and anti-saccades to peripheral visual targets, using both standard and delayed trials. Accuracy of smooth pursuit to moving visual targets.	Improvement in anti-saccades and smooth pursuit accuracy in nicotine vs. placebo in both groups

**Table 3:** Studies investigating nicotine impact on sensory processes in schizophrenia.

ERP= event-related potential; fMRI= functional Magnetic Resonance Imaging; MMN= mismatch negativity; NS= non-smokers; S=smokers;