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# Neuropsychological deficits in nonsmokers with schizophrenia: Effects of a nicotinic antagonist

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**Abstract**

*Background:* Biochemical, physiological and genetic evidence suggests dysregulation of central nicotinic acetylcholine receptor (nAChR) systems in schizophrenia, which may contribute to neuropsychological dysfunction and the high rates of smoking in this disorder. To evaluate the effects of nAChR blockade on neuropsychological performance in schizophrenia without the confounding effects of cigarette smoking, we compared neuropsychological performance in schizophrenia and healthy control nonsmokers after pre-treatment with the centrally-acting nAChR antagonist mecamylamine (MEC).
*Methods:* Using a within-subjects, counterbalanced design, schizophrenia ($n=14$) and control ($n=15$) nonsmokers were pre-treated for 3 days with MEC (0.0, 5.0, and 10.0 mg/day). Subjects performed repeated neuropsychological assessments including visuospatial working memory (VSWM), Continuous Performance Test (CPT), Wisconsin Card Sorting Test (WCST), Word Serial Position Test (WSPT) and Stroop Color Word Test (SCWT) during three sequential test sessions per week over three test weeks.
*Results:* We found significant main effects of schizophrenia diagnosis on: VSWM 30 and 60 delays ($p$'s $<0.01$), CPT (% Hit Rate, Reaction Time, Variability Index; $p<0.01$ for all outcomes), WCST ($p<0.01$ for all outcomes) and Word Serial Position Test ($p<0.01$). However, there were no main effects of repeated test administration (Session) or MEC dose on any of these outcomes, and no significant 3-way (Diagnosis × Session × MEC dose) interactions.
*Conclusions:* Our results suggest that there are a broad range of neuropsychological deficits in nonsmokers with schizophrenia. Furthermore, pretreatment with a centrally-acting nAChR antagonist did not alter neuropsychological performance in either nonsmoking patients with schizophrenia or controls.


*Keywords:* Nicotinic receptor; Schizophrenia; Cognition; Neuropsychological testing; Nonsmokers; Mecamylamine; Antagonist; Human laboratory study

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## 1. Introduction

Patients with schizophrenia have been shown to have high rates of smoking (58–88%) as compared to the general population (de Leon et al., 1995; Dalack et al., 1998; Kalman et al., 2005). One potential biological factor that may make these patients vulnerable to tobacco addiction are deficits in cognitive performance in schizophrenia, including attention, verbal learning and memory, executive function and spatial working memory (Park and Holzman, 1992; Keefe et al., 1995). Nicotine administration through cigarette smoking may remediate deficits in reaction time, working memory and attention in patients with schizophrenia (Levin et al., 1996; Depatie et al., 2002; George et al., 2002a; Sacco et al., 2005). However, most studies of nAChR function and neurocognitive performance to date have been confounded by effects of chronic cigarette smoking and tobacco abstinence effects. Our recent work has suggested that cigarette smoking selectively modulates spatial working memory and sustained attentional deficits associated with schizophrenia and that such effects are mediated by central nAChR stimulation (Sacco et al., 2005).

Little is known, however, about functional effects of nAChR modulation on cognitive deficits in schizophrenia independent of cigarette smoking effects. It has been demonstrated that there is an increase in the numbers of nAChRs with tobacco exposure in nonpsychiatric smokers as compared to control nonsmokers (Benhammou et al., 2000), and pre-clinical studies suggest that nicotine produces an upregulation of the central nAChR (Picciotto, 2003). Interestingly, one study in patients with schizophrenia (Breese et al., 2000) suggests the presence of comparable levels of nAChRs in post-mortem brains of nonsmokers in comparison to smokers with schizophrenia. This finding implies a failure to upregulate nAChRs in response to nicotine and tobacco exposure in smokers with schizophrenia. Thus, nAChR receptor dynamics appear to be altered in schizophrenia.

To determine the contribution of nAChRs to neurocognitive dysfunction in patients with schizophrenia independent of the confounding effects of nicotine and tobacco exposure, we studied the effects of treatment with three doses (0.0, 5.0 and 10.0 mg/day) of the centrally-acting nAChR antagonist mecamylamine (Inversine®) on neuropsychological performance in patients with schizophrenia and nonpsychiatric controls who are biochemically-verified nonsmokers. We hypothesized that an nAChR antagonist such as MEC would further impair neuropsychological deficits in nonsmokers with schizophrenia, compared to nonpsychiatric control nonsmokers.

## 2. Methods

### 2.1. Subjects

Nonsmoking schizophrenia patients and nonpsychiatric controls were recruited as comparison groups to schizophrenia and control cigarette smokers for a study of cigarette smoking effects on cognitive function in schizophrenia, and the role of nicotinic receptor mechanisms in smoking-related cognitive enhancement using the nAChR antagonist mecamylamine hydrochloride (Sacco et al., 2005). Twenty-nine schizophrenia nonsmokers (SNS) and 43 nonpsychiatric control nonsmokers (CNS) were screened for participation in this study. Fourteen subjects with schizophrenia and 23 nonpsychiatric controls were excluded for the following reasons: unwillingness to participate (SNS, $n=4$; CNS, $n=11$), scheduling difficulties preventing participation (SNS, $n=1$; CNS, $n=4$), diagnostic ineligibility (SNS, $n=1$; CNS, $n=2$), IQ score below minimum requirements (SNS, $n=1$; CNS, $n=2$), positive urine toxicology screen for illicit substances (SNS, $n=2$; CNS, $n=0$), medical exclusions (SNS, $n=1$; CNS, $n=1$), excessive use of alcohol (SNS, $n=0$; CNS, $n=2$), inability to give informed consent (SNS, $n=2$; CNS, $n=0$), psychiatrically unstable (SNS, $n=2$; CNS, $n=0$), and the presence of cigarette smoking despite reporting nonsmoking status (SNS, $n=0$; CNS, $n=1$). A total of 15 schizophrenia and 20 control nonsmokers were randomized into the study, and of those patients randomized, 14 schizophrenia and 15 control nonsmokers completed the entire study. Patients were recruited from the Connecticut Mental Health Center in New Haven, CT, while controls were recruited from the community using newspaper advertisements and flyers. Written informed consent was obtained from all participants and the protocol was approved by the Human Investigation Committee at Yale Medical