Schizophrenia, smoking status, and performance on the matrics Cognitive Consensus Battery

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ABSTRACT

Cognitive deficits and high rates of nicotine dependence are consistently documented in the schizophrenia literature. However, there is currently no consensus about how regular smoking influences cognition in schizophrenia or which cognitive domains are most affected by chronic smoking. Previous studies have also failed to disambiguate the effects of chronic nicotine from those of acute exposure. The current study uses a novel approach to testing nicotine addicted patients at a time-point between acute enhancement and withdrawal and implements the MATRICS Cognitive Consensus Battery (MCCB) to compare the overall cognitive performance of regular smokers (n=40) and nonsmokers (n=36) with schizophrenia. Controlling for age, gender, and education, smokers with schizophrenia were significantly more impaired on a visual learning task, the Brief Visuospatial Memory Test-Revised (BVMT-R), than their nonsmoking peers. Among smokers, smoking behavior (i.e., exhaled carbon monoxide levels of smokers) predicted BVMT-R T score; greater smoking was associated with more impaired visual learning. Negative symptom severity was not predictive of greater visual learning deficits in smokers or nonsmokers. Future longitudinal research will be required to determine if there is a dose-response relationship between chronic nicotine and visual learning impairment in patients at various stages of psychotic illness.

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1. Introduction

Individuals with serious mental illness (SMI) abuse nicotine-containing tobacco products at high rates. Experts estimate that 65–90% of patients with schizophrenia are regular smokers (Aubin et al., 2012). The dramatic association between SMI and nicotine use has spurred research and debate over nicotine's effects on attention and cognition. Empirical investigations of both the short-term and long-term effects of nicotine on cognitive functions have yielded mixed results. One theory suggests that nicotine self-administration is a form of self-medication for the negative symptoms and cognitive deficits associated with psychotic disorders (Kumari and Postma, 2005; Evans and Drobes, 2009).

Acute nicotine can improve the performance of patients with schizophrenia on cognitive tasks including measures of novelty detection memory (Jubelt et al., 2008), spatial organization and verbal memory (Smith et al., 2002), and sustained attention (Barr et al., 2008). Withdrawal can induce cognitive impairments,

impacting sustained attention (Sacco et al., 2005) and visuospatial working memory (George et al., 2002).

However, the cognitive effects of chronic nicotine use in this population are less clear. Existing cross-sectional studies have crucial methodological and sampling differences. The definitions of "smoker," "nonsmoker," and "former smoker," change with each investigation. Studies have employed a wide range of cognitive batteries representing diverse cognitive domains, varying in duration, order of testing, and comparability. Differences between smoking and non-smoking groups on clinical measures of symptomology and severity of illness are inconsistent across studies. Additionally, when to allow the use of nicotine is critical and varies.

One of the first studies to compare the cognitive performance of smokers with schizophrenia (n =23, M_{age}=43.9) to non-smoking outpatients (n =8, M_{age}=41.5) was George et al. (2002). Smokers were determined to have a Fagerstrom Test for Nicotine Dependence (FTND) score greater than 5, carbon monoxide (CO) level greater than 10 ppm, cotinine levels of more than 150 ng/ml (plasma) and 600 ng/ml (urine), and reported smoking at least 20 cigarettes per day. Nonsmokers and smokers were evaluated on the computerized Stroop Color Word Test (SCWT) and the Visuospatial Working Memory (VSWM) task. At baseline evaluations,

it was unclear when the smokers had last smoked. Nonsmokers had significantly higher total scores on the Positive and Negative Syndrome Scale (PANSS) than smokers and significantly more negative symptoms. In contrast, smokers reported significantly more depression on the Beck Depression Inventory (BDI) than their nonsmoking peers. George et al. (2002) observed that smokers had better VSWM performance than nonsmokers. However, this difference failed to reach statistical significance ($p=0.20$). These results were negative, perhaps due to the small sample size of the non-smoking group.

To further clarify how chronic smoking affects cognitive functioning in adult outpatients with schizophrenia, Wing et al. (2011) compared the performance of current smokers (n $=38$, $Mage=41.9$), former smokers (n $=16$, $Mage=42.5$), and never smokers (n $=26$, $Mage=42.5$) on a neuropsychological battery. Current smokers had FTND scores of at least 5, CO level of greater than 10 ppm, and were smoking at least 10 cigarettes per day. Former smokers had quit smoking at least 6 months before study enrollment, and never smokers had smoked fewer than 100 lifetime cigarettes. Both former smokers and never smokers had CO levels that were less than 10 ppm. Importantly, current smokers were not deprived of nicotine more than 30 min throughout cognitive testing. The cognitive battery was composed of the Conners' Continuous Performance Test (CPT), the SCWT, and the Wisconsin Card Sorting Test (WCST) to examine sustained attention, response inhibition and processing speed, and cognitive flexibility respectively. Although the schizophrenia groups were similar in negative and positive symptoms, current smokers had significantly lower IQ than former smokers. Controlling for IQ, never smokers demonstrated lower CPT hit rate and slower reaction time on SCWT (across congruent, neutral, and incongruent trials) than former or current smokers. The authors came to the same conclusion as George et al. (2002), that never smokers with schizophrenia have more severe cognitive deficits than current or former smokers with this disorder (Wing et al., 2011). However, they did not replicate the neurocognitive findings as they selected different cognitive tests. Furthermore, there were disparate findings on the one task that was shared between studies (SCWT), possibly due to differences in sample size and clinical characteristics (differences between groups on depression, PANSS and negative symptoms).

A third study, Morisano et al. (2013), used the same criteria for their smoking and nonsmoking groups as Wing et al. (2011) except that smokers had at least 15 cigarettes per day. As in Wing et al. (2011), smokers (n $=32$, Mage $=41.3$) and nonsmokers (n $=15$, Mage $=39.9$) were similar for positive and negative symptoms, and smoking participants did not go longer than 30 min without smoking during the cognitive testing. The neurocognitive assessment included CPT, Trail Making Test, WCST, VSWM, Digit Span, and the California Verbal Learning Test (CVLT-II). Smoking patients outperformed nonsmoking patients on specific domains of the CVLT-II; smokers correctly recalled more items after short and long delays when semantic cues were provided and when a forced choice between words was offered (during recognition). Although Morisano et al. (2013) had similar design and sample to Wing et al. (2013), and demonstrated worse cognition in non-smokers with schizophrenia, they did not replicate the specific finding of lower CPT hit rate. The authors cite "methodological, statistical and population differences between this and other studies" to explain the discrepancies (Morisano et al., 2013, p. 51).

Cumulatively, the results of Morisano et al. (2013) Wing et al. (2011) and George et al. (2002) suggest chronic nicotine has positive effects on cognitive functioning in schizophrenia. However, some suggest that chronic nicotine may further impair cognitive deficits. In a large sample of male Han Chinese inpatients with schizophrenia, Zhang et al., (2002) compared the performance of nonsmokers with schizophrenia to smokers with schizophrenia on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Current smokers (n $=456$) were defined as individuals who smoked at least one cigarette per day for at least a year. Nonsmokers (n $=124$) were made up of former smokers (n $=20$) (individuals who had previously smoked at least one cigarette per day and successfully quit for at least a year) and never smokers (n $=104$) (participants who reported smoking less than 100 lifetime cigarettes). Smokers ($Mage=48.6$) were significantly older than nonsmokers $(Mage=46.3)$. Current smokers were allowed to smoke before testing and were offered smoking breaks during the test session. As in George et al. (2002), Zhang et al. (2012) found that their nonsmokers had significantly more negative symptoms than their smoker group. However, the study's primary finding was that smokers scored significantly lower than nonsmokers on the RBANS total score and two subscales: Visuospatial /Constructional and Immediate Memory. The performance differences on the RBANS total score and on the Visuospatial/Constructional index remained significant even when the authors controlled for differences in age, number of hospitalizations, PANSS total score, negative symptoms, antipsychotic drugs, and anticholinergic drugs. These findings are incompatible with George et al. (2002), in which smokers outperformed nonsmokers on visuospatial memory tasks.

Further investigations comparing smokers with schizophrenia to nonsmokers with schizophrenia include a study by Iasevoli et al. (2013) which examined cognitive differences in outpatients with treatment resistant schizophrenia (TRS). TRS patients were defined as individuals who had not responded to, "at least two or three antipsychotic agents" (Iasevoli et al., 2013, p 1114). Their nonsmoking group (n $=28$) smoked less than 100 lifetime cigarettes and less than one cigarette per day at the time of enrollment and their smoker group (n $=31$) smoked more than one cigarette each day for more than one year. Smokers (Mage $=37.61$) and nonsmokers (Mage $=36.67$) enrolled were slightly younger than previously tested groups. Smoker TRS patients had significantly higher scores on the total PANSS than nonsmokers. This difference was driven by high negative symptom ratings in the smoker TRS patients. Although the authors state that all smoking participants had their last cigarette, "within 1 h from assessments," (Iasevoli et al., 2013, p1115) the PANSS and the Personal and Social Performance Scale (PSP) were completed before the cognitive testing, which was assessed with the Brief Assessment of Cognition in Schizophrenia (BACS). Cognitive domains assessed by the BACS were the following: verbal memory by the List Learning task, working memory by the Digit Sequencing task, verbal fluency by the Category Instances task, processing speed by the Symbol Coding task, problem solving by the Tower of London task, and motor speed by the Token Motor task. Smokers and nonsmokers with TRS performed similarly on the BACS with an important exception; smokers performed significantly worse than nonsmokers in the problem solving domain. Across both the nonsmoker and smoker groups, poorer cognitive performance was associated with more severe negative symptoms. The authors state their results may indicate that smokers with TRS schizophrenia are more cognitively impaired than TRS nonsmokers. Although this is a similar finding to Zhang (2012), of more severe deficits in smokers, the samples differed in the distribution of negative symptoms between groups and highlighted different domains where cognitive deficits were most pronounced.

Based on the current literature, it is unclear how chronic smoking influences cognition in schizophrenia. There is also little consensus over which cognitive domains are most affected by chronic nicotine abuse and how chronic smoking relates to clinical symptomology. Most prior studies targeting these questions have allowed patients to smoke before or during testing to avoid testing