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Minimal effects of prolonged smoking abstinence or resumption on cognitive performance challenge the “self-medication” hypothesis in schizophrenia

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ABSTRACT

One prominent, long-standing view is that individuals with schizophrenia smoke cigarettes more than the general population to “self-medicate” cognitive deficits and other symptoms. This study tested the self-medication hypothesis by examining the effects of smoking abstinence and resumption on cognition in patients with schizophrenia. Nicotine-dependent smokers with schizophrenia ($n = 26$) were trained on a cognitive battery and then hospitalized to achieve and maintain confirmed abstinence from smoking for ~1 week. Cognition was tested while smoking as usual (baseline), one day after smoking cessation (early abstinence), ~1 week later (extended abstinence), and within ~3 weeks of resuming smoking (resumption). The test battery included measures of processing speed, attention, conflict resolution, verbal memory, working memory, verbal fluency, and executive function to evaluate multiple cognitive domains affected by schizophrenia. Positive and negative symptoms of schizophrenia, depressive symptoms, and dyskinesia were also measured at baseline and after prolonged abstinence. There were no significant changes in global cognitive test performance with smoking cessation, abstinence, or resumption. There were small decreases in a measure of processing speed and delayed verbal recall with abstinence, but these findings failed to survive adjustments for multiple comparisons. Surprisingly, in this within subject “On-Off-Off-On” design, there were no significant effects of early or prolonged abstinence from smoking on cognitive and behavioral measures in smokers with schizophrenia. The results of this study challenge the widely held “self-medication” hypothesis of smoking and schizophrenia, question the extent of pro-cognitive effects of smoking and nicotine in schizophrenia, and support encouraging smoking cessation in schizophrenia.

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1. Introduction

The rates of tobacco use and nicotine addiction in schizophrenia are extremely high, with a recent study showing 70–80% prevalence (Hartz et al., 2014) and some studies showing near 90% prevalence (de Leon and Diaz, 2005; Hughes et al., 1986). Smokers with schizophrenia have reduced smoking cessation rates, extract more nicotine per cigarette and smoke higher numbers of stronger cigarettes, all indicators of greater nicotine dependence than other smokers (Dalack et al., 1998; de Leon and Diaz, 2005; Hughes et al., 1986). One widely-held theory about smoking behavior in schizophrenia is the “self-medication hypothesis” according to which patients smoke tobacco to attenuate positive, negative, depressive or cognitive symptoms or antipsychotic

medication side effects (Kumari and Postma, 2005; Leonard et al., 2007; Wing et al., 2012). Nicotine or tobacco smoking, however, does not seem to improve positive psychotic symptoms (Smith et al., 2002), and psychotic symptoms do not worsen during nicotine withdrawal (Dalack et al., 1999; Yang et al., 2002). More research interest has been focused on the effects of nicotine on the very disabling negative symptoms and cognitive deficits of schizophrenia (Smucny et al., 2016; Yee et al., 2015), but the evidence has been mixed.

Some literature suggests that there are schizophrenia-specific beneficial effects of nicotine and nicotinic cholinergic agents on some cognitive deficits, electrophysiologic measures of early information processing, oculomotor dysfunction and affect (Dépatie et al., 2002; George et al., 2002; Olincy et al., 2000). Studies of nicotine administration and tobacco smoking on cognitive test performance in schizophrenia have yielded conflicting results with some reporting improvements in processing speed, working memory and executive function while others found no significant improvements (Boggs et al., 2013; Hahn et

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al., 2013; Harris et al., 2004; Smith et al., 2002; Wing et al., 2011). Some of this variability may be due to methodological differences or subject characteristics in these studies. Studies of acute, overnight, short-term (hours) withdrawal followed by resumption of smoking suggest that nicotine improves visuospatial working memory in schizophrenia (George et al., 2002; Sacco et al., 2005). Although several studies suggest that nicotine acutely improves attention in schizophrenia, whether it improves other cognitive domains, overall cognition, or confers long-term benefits is unclear (Boggs et al., 2014). Furthermore, though other nicotinic acetylcholine receptor (nAChR) ligands have been pursued for treating the cognitive deficits of schizophrenia, unfortunately standardized cognitive test batteries have failed to capture consistent improvements from these drugs (Boggs et al., 2014). If the self-medication hypothesis explained the increased smoking in schizophrenia, we would expect smokers with schizophrenia to have more cognitive gains from smoking and greater cognitive costs of smoking cessation than otherwise healthy smokers. Instead, smoking cessation and withdrawal from nicotine has been reported to precipitate neurocognitive deficits, such as impaired working memory, in healthy smokers without psychiatric illness (Mendrek et al., 2006; Patterson et al., 2010), and nicotine withdrawal or smoking resumption does not result in specific changes in attention in schizophrenia beyond the healthy smokers, as would be predicted by the self-medication hypothesis (AhnAllen et al., 2015; Hahn et al., 2013). However, the benefits of nicotine use for global cognition in schizophrenia during long-term abstinence, rather than acute withdrawal, is not well known. To our knowledge, there are no studies in smokers with schizophrenia assessing global cognitive test performance following a longer period of confirmed abstinence— a period that extends beyond the acute withdrawal stage. We studied the impact of confirmed early (1 day) and extended abstinence (~1 week) from smoking on cognitive test performance across several cognitive domains in smokers with schizophrenia. Furthermore, we investigated the effects of smoking resumption on cognitive test performance in the same subjects. Demonstrating that early and extended abstinence impairs, while resumption of smoking improves, global cognitive test performance might explain why smokers with schizophrenia find it harder to quit and why they are more likely to resume smoking. Given the widely held “self-medication” hypothesis of smoking and schizophrenia, we also studied the effects of smoking cessation on the core symptoms of schizophrenia, depression symptoms and dyskinesia. Finally, we studied the effects of smoking cessation on nicotine craving and nicotine withdrawal. We hypothesized early and extended smoking abstinence would be responsible for decreased global cognitive performance that would reverse during smoking resumption.

2. Methods

2.1. Subjects

Data reported here were obtained from subjects who participated in a single- photon emission computerized tomography (SPECT) imaging study of $\beta 2^*$ -nAChR availability in schizophrenia (D'Souza et al., 2012; Esterlis et al., 2014) that required confirmed inpatient abstinence from tobacco smoking for ~1 week (mean admission 5.8 days, SD 0.6, range 5–7 days, with reason for variability being coordinating participants' scheduling with schedule of imaging procedures reported elsewhere). While some of the methods and the results of $\beta 2^*$ -nAChR availability are reported elsewhere (D'Souza et al., 2012; Esterlis et al., 2014), the principal findings reported here have not been published elsewhere. Eligibility criteria included: 1) age 18–70 years old; 2) schizophrenia diagnosis confirmed based on DSM-IV criteria, clinical records, clinician input, and use of the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1997); and 3) cigarette smokers who smoked at least 10 cigarettes a day, verified at baseline by a plasma cotinine level > 150 ng/ml, urine cotinine level > 100 ng/ml (NicAlert™ by Nymox Pharmaceutical Corporation), and carbon monoxide (CO) level > 11 ppm

(MicroDirect-Micro CO meter (Cat. No. MC02). Exclusion criteria included 1) any other current axis I diagnosis besides schizophrenia; 2) diagnosis of substance abuse in the past month or substance dependence in the previous 6 months (excluding nicotine and caffeine); 3) treatment with selective serotonin re-uptake inhibitors and/or tetra/tricyclic antidepressants; and 4) psychiatric or medical instability. Lifetime history of and/or current substance use disorders were ascertained by psychiatric interview, chart review, SCID-I/P, 30-day Timeline Followback, and urine toxicology.

2.2. Study procedures

2.2.1. Regulatory approvals and consent process

Both the Yale University and VA Connecticut Healthcare System Institutional Review Boards approved this study. All subjects signed informed consent after the study was explained to them in detail as described elsewhere (D'Souza et al., 2012; Esterlis et al., 2014).

2.2.2. Screening

Methods for some aspects of this study have been reported previously (D'Souza et al., 2012; Esterlis et al., 2014). Subjects who met study criteria had screening assessments conducted including demographic data, clinical history, clinical ratings including the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987), Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982), Montgomery-Asberg Depression Scale (MADRS) (Montgomery, 1979), Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976b), cigarette usage, and degree of nicotine dependence measured by the Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al., 1991).

2.2.3. Smoking cessation

Eligible smokers with schizophrenia were hospitalized on a smoke-free research unit to achieve and maintain abstinence from smoking for at least 5 days. Subjects were not allowed to receive any drugs that could facilitate smoking abstinence, including varenicline, bupropion, and nicotine replacement. Trained research staff counseled subjects daily to cope with withdrawal symptoms. Counseling was paired with contingency management: the latter has been shown to reduce cigarette smoking in smokers with schizophrenia in short-term studies (D'Souza et al., 2012; Roll et al., 1998; Tidey et al., 1999; Tidey et al., 2011). Subjects were paid \$25 for the first day of inpatient abstinence, and payments were escalated by \$25 for every inpatient day. Thus, if subjects were able to complete the entire inpatient abstinence period of at least 5 days, they were eligible to receive up to \$375. Abstinence from smoking or any other nicotine products was confirmed by daily breath CO monitoring (cutoff <8 ppm) and urinary cotinine (cutoff <50 ng/ml) [NicAlert, (Nymox)] (see Supplemental Table 1 for interpretation of assays). In addition, plasma cotinine was assayed while smoking as usual and after ~1 week of abstinence. Finally, subjects were aware that failure to abstain triggered discharge from the study.

2.2.4. Cognitive test battery

Multiple domains of cognitive function were tested using a battery of tests that have been shown to be sensitive to nicotine administration, withdrawal, and or abstinence in smokers with and without schizophrenia (reviewed in Boggs et al., 2014) and normal controls (reviewed in Heishman et al., 2010; Heishman et al., 1993). Furthermore, the cognitive domains tested, executive functioning, verbal working memory, processing speed, inhibition, and attention, have been shown to be consistently impaired in schizophrenia, and thus domains to monitor for sensitivity to nicotine or smoking effects to test the self-medication hypothesis of smoking in this disorder (Green et al., 2004; Westerhausen et al., 2011). To minimize practice effects and novelty of cognitive assessments, subjects were administered the cognitive battery twice on the same day ~2 weeks prior to smoking cessation (Goldberg et al., 2010; Lees et al., 2015). Executive control and cognitive inhibition

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