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A Test of the Cognitive Self-Medication Hypothesis of Tobacco Smoking in Schizophrenia

Britta Hahn[1,*], **Alexander N. Harvey**[1], **Marta Concheiro-Guisan**[2], **Marilyn A. Huestis**[2], **Henry H. Holcomb**[1], and **James M. Gold**[1]

[1]University of Maryland School of Medicine, Maryland Psychiatric Research Center, P.O. box 21247, Baltimore, MD 21228

[2]National Institute on Drug Abuse – Intramural Research Program, Chemistry and Drug Metabolism Section 251 Bayview Blvd., Baltimore, MD 21224

Abstract

Background—Heavier tobacco smoking among people with schizophrenia (SCZ) has been suggested to reflect self-medication of cognitive deficits. The idea that cognitive-enhancing effects of nicotine are a primary motivator of tobacco consumption in SCZ and that abstinence would deprive SCZ of such beneficial effects may explain hesitation among providers to pursue smoking cessation in SCZ. This study tested predictions of the cognitive self-medication hypothesis.

Methods—In three counterbalanced sessions, 17 SCZ and 17 healthy control subjects (HCS), all smokers, were tested under *ad libitum* smoking, or 3.5 hours after abstaining and receiving a nicotine (14 mg/24 hrs) or placebo patch.

Results—Attention task performance was improved by transdermal nicotine relative to placebo, with intermediate performance by *ad libitum* smoking. These effects were of similar size in SCZ and HCS, and did not reflect remediation of functions disproportionately impaired in SCZ. Although more SCZ reported that the need to concentrate influenced their smoking, this was not reflected by these patients' actual behavior. Self-reported ability to concentrate changed with nicotine status in HCS but not SCZ, suggesting insensitivity of SCZ to nicotine-derived performance benefits. Nicotine plasma concentrations after *ad libitum* smoking were not associated with performance benefits but instead with the propensity to experience nicotine withdrawal upon abstinence. This association was seen selectively in SCZ, suggesting a possible reason for heavier smoking.

Conclusions—These findings suggest that subjective or objective attentional benefits are unlikely the primary driving force of tobacco consumption in SCZ and should not discourage providers from supporting quit attempts.

Keywords

schizophrenia; nicotine; smoking; self-medication; cognitive deficits; withdrawal

*Corresponding author: bhahn@mprc.umaryland.edu, Tel: 410-402-6112, Fax: 410-402-7198.

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Introduction

The prevalence of tobacco smoking among people with schizophrenia (SCZ) is 3-5 times higher than in the general population, higher even when compared with many other psychiatric diagnoses(1-3). SCZ also tend to smoke more heavily and have more difficulty quitting(3-5). Self-medication theories hypothesize that SCZ smoke more heavily because the ingested nicotine alleviates schizophrenia symptoms or medication side-effects. SCZ display attentional, short-term memory and executive control deficits that limit everyday functioning(6;7). The possibility that SCZ self-medicate such deficits is supported by findings that nicotine and other nicotinic acetylcholine receptor (nAChR) agonists enhance sensory, alerting, attentional and mnemonic processes in SCZ(8-21), mimicking effects in healthy subjects(22) and laboratory animals(23;24). Improved attention is a particularly robust finding(22;25;26) and may underlie effects on higher functions. In SCZ, attention appears to be particularly impaired when requiring top-down control(27-29) or being distributed broadly(30;31). The cognitive self-medication hypothesis gained momentum with findings that certain information processing deficits in SCZ may reflect nAChR hypofunction(1;32-37). Overlap between functions impaired in schizophrenia and enhanced by nicotine has been suggested based on reports of larger performance-enhancing effects of nicotine in SCZ than healthy control subjects (HCS)(8;12-14;20;21;38;39).

The NIMH Tobacco Use and Cessation in Psychiatric Disorders Workgroup voiced concerns that a narrow focus on self-medication hypotheses as the cause for high smoking rates in psychiatric populations “may result in insufficient attention to other plausible explanations and discourage efforts in mental health treatment settings to promote tobacco cessation”(40), p.1693). Despite significant morbidity and mortality from smoking in SCZ(40-42), there is indication that health care providers often assign low priority to nicotine dependence treatment in the mentally ill(43-45) and in particular SCZ(45). The perception that SCZ smoke to achieve better cognitive functioning may explain hesitation to treat tobacco dependence aggressively.

To date, only indirect evidence supports the cognitive self-medication hypothesis. While more pronounced benefits from nicotine were reported in SCZ than HCS on diverse cognitive measures, it is unclear whether these effects motivate SCZ to smoke and account for higher smoking prevalence and severity. Specific predictions can be derived from the self-medication hypothesis. Performance improvement should be more pronounced in SCZ than HCS, and more pronounced on functions impaired in SCZ. Tobacco smoking should be a similarly effective means of achieving such improvement as experimenter-administered nicotine. SCZ should smoke with the purpose of achieving these improvements. The subjective ability to concentrate should be enhanced acutely with smoking or other forms of nicotine administration. Finally, if performance improvement was a major force driving the heavier smoking in SCZ, one may expect heavier smoking to be associated with greater benefits. The present study was designed to test these predictions, focusing on the attention domain.

Methods and Materials

Participants

Seventeen patients meeting Diagnostic and Statistical Manual of Mental Disorders-IV(46) criteria for schizophrenia (N=5 paranoid, 9 undifferentiated, 2 residual) or schizoaffective disorder (N=1), and 17 HCS, all smokers of ≥5 cigarettes or cigarillos/day on ≥5 days/week, completed the study. Three SCZ were treated with first-generation and 13 with second-generation antipsychotics; one was stably unmedicated. Eight SCZ additionally received antidepressant and 6 anxiolytic medication. Groups were matched demographically but

differed in IQ (Table 1). Participants provided informed consent for a protocol approved by the University of Maryland Baltimore Institutional Review Board. For more detail, see Supplement 1.

Procedure

The study involved one training and three test sessions. During training, participants received instructions and practiced full versions of the attention tasks. They completed intelligence testing(47), the trait version of the State-Trait Anxiety Inventory (STAI(48); Supplement 1, Figure S2), the Fagerstrom Test for Nicotine Dependence (FTND(49)), questions related to nicotine use history, and a reasons-for-smoking questionnaire.

During test sessions, participants received in counterbalanced order (A) a transdermal nicotine patch (14 mg/24 hrs; Nicoderm CQ®, GlaxoSmithKline), (B) a placebo patch, or (C) could smoke as many of their cigarettes as they wished (*ad libitum* smoking). Participants and investigators were blind with regard to patch condition (see Supplement 1).

Participants were instructed to smoke as usual prior to study sessions. Upon arrival, a breath carbon monoxide (CO) reading (Micro Smokerlyzer) was taken. Participants completed the 8-item Minnesota Nicotine Withdrawal Scale (MNWS(50)), and a list of bidirectional scales sensitive to tobacco deprivation-induced mood changes(51); reported in Supplement 1). In the *ad libitum* smoking session, the attention tasks followed. In the two patch sessions, the patch was applied, participants abstained from smoking and spent a 3.5-hour absorption period watching TV or reading. After completing withdrawal questionnaires again, they performed the attention tasks. Participants could take short breaks during all testing sessions, but only in the *ad libitum* condition was smoking allowed. After task completion, participants again completed withdrawal questionnaires and the STAI state version (Supplement 1; Figure S2). Immediately after, a 5-mL venous blood sample was collected. Samples were centrifuged and plasma stored at −20° C until analysis. Nicotine, cotinine, trans-3′-hydroxycotinine and norcotinine were measured by liquid chromatography-tandem mass spectrometry (details in Supplement 1). Only nicotine and cotinine are reported here.

Cognitive tasks

In each session, participants completed two computerized tasks challenging aspects of attention impaired in SCZ.

The Spatial Attentional Resource Allocation Task (SARAT) is a stimulus detection task manipulating the size of the attentional focus(52). Participants fixated a central circle throughout (trials with eye movements were eliminated). First, a central cue was presented consisting of one, two, or four quarters of the fixation circle turning black (Figure 1A). After a 400-1300-ms stimulus-onset-asynchrony, a 500-ms peripheral target (high or low contrast) appeared in one of the corners of the screen, to which participants responded by button-press. The cue indicated the likely target quadrant(s). Fewer cued locations enable more precise prediction of the target location and a narrower attentional focus(52). Increasing the number of cued locations increases spatial uncertainty and the need to monitor broadly, which was shown to potentiate impairment of SCZ(30). The cue provided invalid information on 20% of trials with one or two cued locations (not analyzed). The cue was not followed by a target on 9.7% of trials, presented unpredictably, to discourage anticipatory responding (not analyzed). There were 336 valid, 56 invalid and 42 cue-only trials, tested over 14 blocks interspersed by rest periods. Trial types were randomized. Task completion took one hour.

The Singleton Detection Task was performed second. It manipulates the need to ignore salient distractors, a function impaired in SCZ(27;28). Circular search arrays were composed

of nine shape stimuli, each 3.40° from a central fixation cross (Figure 1B). Red stimuli were presented against a green background. The red and green were isoluminant, determined by a flicker fusion procedure prior to the task. The target was a shape singleton, i.e. circle among diamonds or diamond among circles. Each stimulus contained a line. The task was to press one of two buttons indicating whether the line in the shape singleton was vertical or horizontal (50% chance). On half the trials, all stimuli were red. On the other half, one of the non-target items was a black color and luminance singleton serving as a distractor. Participants were informed that the color singleton was never the target. Each array remained on display until response. A 500-ms blank interval preceded the next array. There were 576 trials in total with short breaks every 36 trials. The entire task procedure took ~45 min.

For greater detail, see Supplement 1.

Data analysis

Most dependent variables were analyzed by ANOVA including Group (SCZ, HCS) as a between-subject factor and Drug (placebo patch, nicotine patch, *ad libitum* smoking) as a within-subject factor. Additional within-subject factors compared within-session measurement time points or task conditions.

Results

Smoking variables (Table 1)

SCZ and HCS did not differ in years of smoking, cigarettes/day, age of starting smoking or smoking regularly, number of quit attempts, or FTND scores. The trend toward lower FTND scores in SCZ was driven by items affected by group home living (details in Supplement 1), suggested to lead to underestimation of dependence severity in SCZ(53). When two of these items with particularly low factor loadings in SCZ(53) were excluded, FTND scores were identical in SCZ (4.0 ±1.66) and HCS (4.0 ±1.46). Expired CO levels upon arrival trended to be higher in SCZ. However, there were no main effects or interaction in ANOVA with Group and Drug as factors.

Participants were asked to check those of five items that determined how much they smoked during a day (“my mood”, “how much money I have”, “if I have *to* be in places where I can't smoke”, “if I have to do things where I have to concentrate”, “if I am with other people who smoke”). Figure S1 shows the percentage of SCZ and HCS endorsing each item. A significant difference occurred for being with other smokers (χ^2 =5.10, P<0.03), suggesting that fewer SCZ smoke socially. A trend difference was seen for having to concentrate (χ^2 =3.11, P<0.078), which was endorsed by 9/17 SCZ and 4/17 HCS.

Nicotine plasma concentrations

Nicotine concentrations within drug conditions differed widely between participants (Figure 2). Overall, however, a main effect of Drug [F(2,64)=140, P<0.001] in two-factor ANOVA confirmed higher concentrations in the *ad libitum* smoking [t(33)=;8.81, P<0.001] and nicotine patch condition [t(33)=;10.9, P<0.001] as compared with placebo. The *ad libitum* smoking and nicotine patch conditions did not differ [P>0.5]. There was no main effect of Group [P>0.4] and no Group by Drug interaction [P>0.6], indicating that nicotine concentrations did not differ between SCZ and HCS. The same pattern was observed with cotinine.

Nicotine Withdrawal

Figure 3A shows MNWS scores. On patch days, withdrawal was measured upon arrival, prior to, and after the attention tasks. In the *ad libitum* smoking session, there were only two ratings because testing commenced shortly after arrival. Arrival scores did not differ between sessions; there was no main effect of Drug (P>0.4) or Drug × Group interaction (P>0.7) in 2-factor ANOVA. However, SCZ overall had higher scores than HCS [main effect of Group: F(1,31)=14.7, P<0.001].

Withdrawal within patch sessions was analyzed by 3-factor ANOVA with Group, Drug (nicotine, placebo) and Time (arrival, pre-test, post-test) as factors. Scores increased over time [Time main effect: F(2,60)=11.6, P<0.001], more so during placebo than nicotine patch sessions [Drug × Time interaction: F(2,60)=4.12, P<0.03]. In SCZ, scores were overall higher, but changes with time were blunted as compared with HCS [Group × Time: F(2,60)=3.61, P<0.04]. A significant increase from arrival was, however, still seen under placebo, and neither the Group × Drug (P>0.5) nor the Group × Drug × Time interaction (P>0.7) was significant. When exploring the items driving the Group × Time interaction, only “Difficulty Concentrating” was significant [F(2,60)=8.18, P<0.001]. Figure 3B shows large pre- to post-test increases in HCS, particularly under placebo. In contrast, “Difficulty Concentrating” in SCZ differed neither between drug conditions nor between within-session time points and appeared completely unaffected by nicotine status.

MNWS scores during *ad libitum* smoking resembled the nicotine patch condition (Figure 3A). Pre- and post-test scores (excluding arrival ratings in patch sessions) were compared between all three drug conditions by three-factor ANOVA. A main effect of Drug [F(2,62)=3.14, P=0.05] was due to a difference between placebo and transdermal nicotine [t(32)=2.31, P<0.03, paired t-test] with a trend difference also between placebo and *ad libitum* smoking (P=0.056), but not between transdermal nicotine and *ad libitum* smoking (P>0.9). There were main effects of Time (P<0.01) and Group (P<0.01), but no other significant effects. To test the prediction that smoking enhances SCZ's subjective ability to concentrate, we compared end-of-session “Difficulty Concentrating” between placebo and *ad libitum* smoking. There was a reduction in HCS [t(15)=2.32, P<0.04] but not SCZ [t(16)=1.07, P=0.3; Figure 3B].

Affect-related withdrawal scales were largely consistent with the above pattern (Supplement 1; Figure S3).

Behavioral Performance

SARAT—Performance was analyzed by four-factor ANOVA with Group, Drug, Number of Cued Locations (1,2,4), and Target Contrast (high, low) as factors.

Reaction time (RT) depended on task conditions as reported previously(30;52); see Supplement 1. Importantly, the slowing with greater spatial uncertainty was more pronounced for SCZ than HCS [Group × Number of Cued Locations: F(2,64)=4.16, P=0.02; Figure S4], replicating previous findings that SCZ are particularly impaired at distributing attention broadly(30).

A main effect of Drug [F(2,64)=5.70, P<0.005] was largely due to RT reduction with transdermal nicotine relative to placebo (Figure 4A). Effect sizes of this reduction were similar between groups: Cohen's d=0.49 in SCZ, and d=0.46 in HCS. *Ad libitum* smoking produced intermediate performance not significantly different from either transdermal nicotine or placebo. Effects of Drug did not interact with Group (P>0.7), Number of Cued Locations (P=0.16) or Target Contrast (P>0.9), and no three- or four-way interaction was

significant (Drug × Group × Cue: P=0.39), indicating that nicotine did not reverse specific impairment in SCZ.

Omission errors were low (2.5% overall). Both nicotine and *ad libitum* smoking reduced omissions, but the main effect of Drug failed significance [F(2,64)=2.96, P=0.059], probably due to floor effects. Task condition effects are reported in Supplement 1.

Singleton Detection Task—Due to color blindness, four SCZ could not perform this task, resulting in N=13. Performance was analyzed by 3-factor ANOVA with Group, Drug and Distractor (present,absent) as factors.

Accuracy was high (97.5% overall). The main effect of Drug was significant [F(2,56)=6.87, P=0.002], with both transdermal nicotine and *ad libitum* smoking significantly enhancing accuracy relative to the placebo patch. No other effects were significant.

RT (median across trials; responses >5 s were excluded) was slower in SCZ than HCS [Group main effect: F(1,28)=9.62, P<0.005], and slower with than without a distractor [Distractor: F(1,28)=33.5, P<0.001]. There was a main effect of Drug [F(2,56)=4.33, P<0.02]. Transdermal nicotine significantly reduced RT relative to placebo. Intermediate performance with *ad libitum* smoking did not significantly differ from the nicotine or placebo patch condition. There was a trend for the distractor effect to be larger in SCZ than HCS (Distractor × Group: P=0.094). However, there were no interactions involving Drug (Drug × Distractor: P=0.18; Drug × Group: P>0.7; Drug × Group × Distractor: P>0.4).

To test whether effects of nicotine would manifest more specificity when limiting distractor trials to those most challenging top-down attentional control, we repeated ANOVA including only the two closer distractor distances that produced the largest distractor effects (Supplement 1; Figure S5). There were again main effects of Group, Drug, and Distractor, but Drug now interacted with Distractor [F(2,56)=3.19, P<0.05], reflecting larger RT reduction with transdermal nicotine and *ad libitum* smoking in the presence than absence of a distractor (Figure 4B). However, there were no interactions involving Group (Distractor × Group P=0.25; Drug × Group P>0.8; Drug × Group × Distractor P>0.9], indicating that despite specificity of the drug effect, this occurred in both groups and did not reflect remediation of deficits in SCZ.

The Need to Concentrate as Reason for Smoking

Participants had completed the attention tasks at least once prior and were aware of the need to concentrate for two hours in testing sessions. Thus, we expected the 9 SCZ who had endorsed that their smoking amount depended on their need to concentrate to smoke more in the *ad libitum* condition than the remaining 8 SCZ. However, subgroups differed neither in nicotine plasma concentrations [t(15)=1.36, P=0.19; analyses of the increase relative to placebo yielded the same pattern; Supplement 1], nor in end-of-session MNWS self-ratings of difficulty concentrating [t(15)=1.74, P=0.1], nor in SARAT RT benefit relative to placebo [t(15)=1.46, P=0.16]. The trends actually reflected less smoking, greater difficulty concentrating, and less RT benefit in the *ad libitum* condition in SCZ endorsing this item, drawing into question the accuracy of their self-reports. Groups did not differ on smoking severity or demographics, except that SCZ endorsing this item had fewer years of education [t(15)=2.36, P<0.04] and lower IQ [P=0.066].

Correlations

If performance benefits drove the heavier tobacco consumption in SCZ, with or without awareness, then higher levels of smoking-derived nicotine should predict greater smoking-

induced performance benefits. This was tested by correlating nicotine plasma concentrations in the *ad libitum* smoking condition with SARAT RT reductions relative to placebo. A positive correlation would indicate that more smoking was associated with greater benefits. There was no such association in SCZ [R=-0.24, P>0.3; Pearson correlation] or HCS [R=-0.32, P>0.2]. The trends even suggest that lower nicotine concentrations were associated with greater improvement.

If, by contrast, nicotine withdrawal was a determinant of smoking, then the propensity to experience withdrawal in the absence of nicotine should predict smoking-derived nicotine intake. This was tested by correlating participants' MNWS increase from arrival to the end of the placebo session with nicotine concentrations in the *ad libitum* smoking session. A positive correlation was found for SCZ (R=0.68, P=0.003) but not HCS (R=-0.29, P=0.28); Figure 5. The correlations differed between groups (z=2.99, P<0.003), even after removing one outlier HCS (z=2.3, P<0.03). To test whether smoking-derived nicotine reduced withdrawal, nicotine concentrations in the *ad libitum* session were correlated with the decrease in end-of-session MNWS scores relative to placebo. A positive correlation would suggest that more smoking was associated with greater withdrawal reduction. This prediction was confirmed for SCZ [R=0.51, P<0.04] but not HCS (R=-0.31, P>0.24; difference between correlations: z=2.33, P<0.02; after removing outlier: z=1.91, P=0.056). Partial correlations controlling for IQ yielded almost identical results.

Discussion

This study tested predictions of the cognitive self-medication account for more prevalent and heavier tobacco smoking among SCZ. The prediction that SCZ derive greater cognitive improvement from nicotine than HCS, in particular on functions most impaired, is based on the idea that impairments resulted from nAChR hypofunction. In our attention paradigms, the effects of nicotine or *ad libitum* smoking did not differ between groups. We replicated disproportionately large impairment of SCZ spreading attention broadly(30), but the effects of nicotine or smoking were not more pronounced under these conditions. We identified a trend-impairment for SCZ to ignore salient distractors, but although effects of nicotine and smoking were more pronounced when these distractors were most disruptive, this was equally true for SCZ and HCS, yielding no evidence of larger benefits in SCZ or specific remediation of deficits. While there is always a possibility that critical interactions were missed due to lack of power, the complete absence of trends towards any interaction involving Group and Drug suggests that attention-enhancing effects of nicotine, although robust in SCZ, did not specifically ameliorate schizophrenia-related impairment.

The above was surprising in view of previous reports of larger effects of nicotine in SCZ. The functions showing this interaction differed between studies, ranging from information processing, sustained and selective attention and response inhibition to short-term memory and delayed recognition(8;12-14;20;21;38;39). With the exception of neurophysiological information processing indices, it is not always clear whether these improvements were specific to areas of disproportionate impairment in SCZ, and whether larger effects may have resulted from a lower baseline. Citation bias may also play a role; the effects of nicotine on the majority of tested performance indices did not differ between SCZ and HCS. Another factor differentiating the current study is that previous reports did not always match groups on smoking severity, and the majority tested smokers after at least overnight withdrawal. Thus, larger nicotine effects may in some cases reflect more pronounced withdrawal-induced deficits in SCZ.

If performance benefits are a significant driving force of tobacco smoking in SCZ, we would expect them to be similarly robust with smoking as with experimenter-administered

nicotine. We found that, across groups, smoking appeared to be a less effective means of achieving performance improvement than transdermal nicotine, despite similar end-of-session nicotine plasma concentrations. The pharmacokinetics associated with the delivery devices may explain this. Cigarette-derived nicotine is marked by rapid peaks but is also rapidly metabolized(54;55), and it is unlikely that nicotine concentrations optimal for performance improvement were present throughout the testing period. By contrast, protracted release of nicotine from the patch ensures more sustained and stable concentrations(56-58).

When asked, more SCZ than HCS endorsed that how much they smoke depended on their need to concentrate. This could be seen as direct support for cognitive self-medication. However, further analyses comparing nicotine intake in the *ad libitum* smoking session indicated that these self-reports did not reflect actual behavior. Despite the evident need to concentrate, SCZ indicating that they adjusted their smoking based on this need actually tended to have lower smoking-derived nicotine concentrations and less subjective and objective improvement in their ability to concentrate. Furthermore, in the full SCZ sample, self-reported difficulty concentrating did not vary with drug condition or time-since-withdrawal, as in HCS. SCZ's subjective difficulty concentrating was higher overall but appeared completely insensitive to their current nicotine status. SCZ appeared to have no awareness of acute beneficial effects of nicotine on their ability to concentrate, despite performance benefits comparable to HCS.

Subjective state generally was less influenced by nicotine or smoking status in SCZ than HCS. Breath CO levels upon arrival trended to be higher in SCZ, but SCZ had higher MNWS scores at all times including arrival. MNWS ratings in SCZ did not depend on current nicotine deprivation status as in HCS, with similar trends also on the affect-related withdrawal scales and STAI (Supplement 1). A likely explanation is that higher trait negative affect(59) and other symptoms associated with schizophrenia overshadowed the perhaps more subtle changes related to acute nicotine status. This suggests that nicotine or smoking may not significantly modulate disease-related negative affectivity, including subjective difficulty concentrating.

Performance-enhancing effects could reinforce tobacco consumption independent of awareness. However, if these effects were a main reason behind the heavier smoking in SCZ, then one would expect greater smoking-derived nicotine intake to be associated with greater performance improvement. This prediction was not confirmed. If anything, more smoking was associated with smaller performance benefits, consistent with an inverted U-shaped dose-response function(23;60) on which most participants had exceeded nicotine concentrations optimal for attentional benefits. This is difficult to reconcile with the hypothesis that such benefits account for heavier smoking in SCZ and suggests that other factors drive smoking amount. Indeed, smoking-derived nicotine intake in SCZ, but not HCS, was robustly associated with their propensity to experience nicotine withdrawal upon abstinence, and with acute withdrawal reduction relative to placebo. Thus, the one factor identified that could explain heavier tobacco consumption among SCZ was not related to cognitive effects of nicotine but reflected more classical dependence aspects. Overall, our results suggest that despite clearly demonstrable improvements in attentional performance, these benefits do not appear to be a primary motivator of tobacco smoking in schizophrenia.

Study limitations include a relatively modest sample size, and the fact that the *ad libitum* smoking session was not blinded and differed in timing from the patch sessions. However, it is difficult to explain smaller performance benefits by *ad libitum* smoking relative to placebo with expectation effects or the lack of an absorption period-equivalent. Our cognitive performance indices were restricted to attentional functions. This ensured robust effects of

nicotine and tested the most likely substrate of cognitive self-medication. Larger-scale studies should also probe mnemonic and executive control functions, but bearing in mind that effects may be secondary to effects on attention. We did not assess other “classical” aspects of dependence that may discriminate groups, such as positive reinforcement(61) or conditioned cue responses. Our study targeted a set of predictions derived from the cognitive self-medication hypothesis, and the complete absence of support is informative despite these limitations.

The results by no means diminish the therapeutic potential of nAChR agonists for cognitive deficits in schizophrenia. Attention-enhancing effects of transdermal nicotine were robust in SCZ and HCS. nAChR agonists given via a delivery system with similar temporal stability may improve everyday functioning in SCZ, especially long-term when coupled with cognitive challenges inherent in daily life or induced by training interventions(62). Although attention-enhancing effects of nicotine are likely not the primary driving force of tobacco consumption in SCZ, these effects may have therapeutic benefits when optimally harvested.

The clinical implication of our findings is that smoking cessation would not deprive SCZ of an efficacious means of self-medicating attentional deficits but equates overcoming an addiction. Together with findings that smoking cessation does not exacerbate psychosis(63;64) and that chronic tobacco smoking has negative neurobiological effects that may contribute to cognitive impairment(65), this should help remove hesitation to motivate quit attempts among SCZ and initiate adequate treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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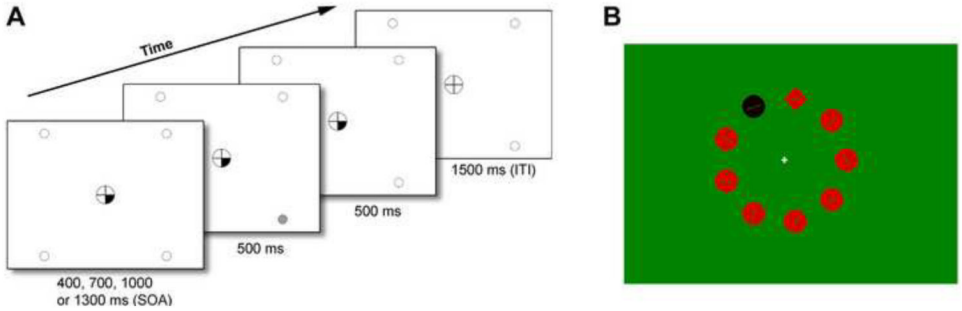

Figure 1.

(A) Components of a trial in the Spatial Attentional Resource Allocation Task. Onset of a central cue preceded target onset by a variable stimulus onset asynchrony (SOA) of 400, 700, 1000 or 1300 ms. The target was presented for 500 ms in the continuing presence of the cue, which remained on display until 500 ms after target offset. Only screen background was then presented for a 1500-ms intertrial interval (ITI) of. One, two, or all four target locations could be cued at the same time, thus varying the predictability of the target. (B) A stimulus display example during the Singleton Detection Task. The task was to indicate whether the line inside the shape singleton was vertical or horizontal. A black color singleton distractor was present on half of the trials.

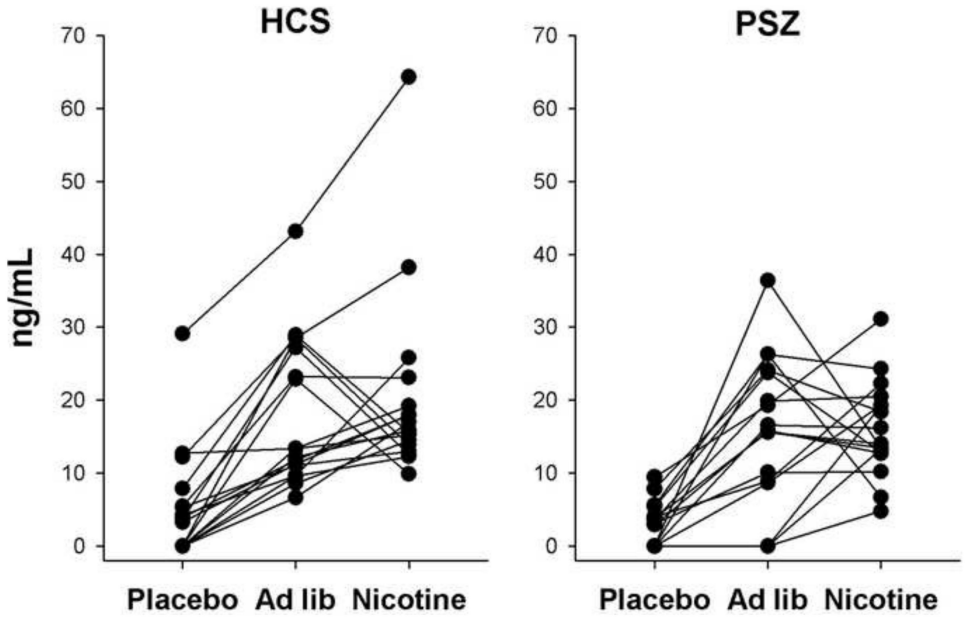

Figure 2.
Plasma nicotine concentrations of healthy control subjects (HCS) and people with schizophrenia (SCZ) at the end of cognitive test sessions per group and drug condition.

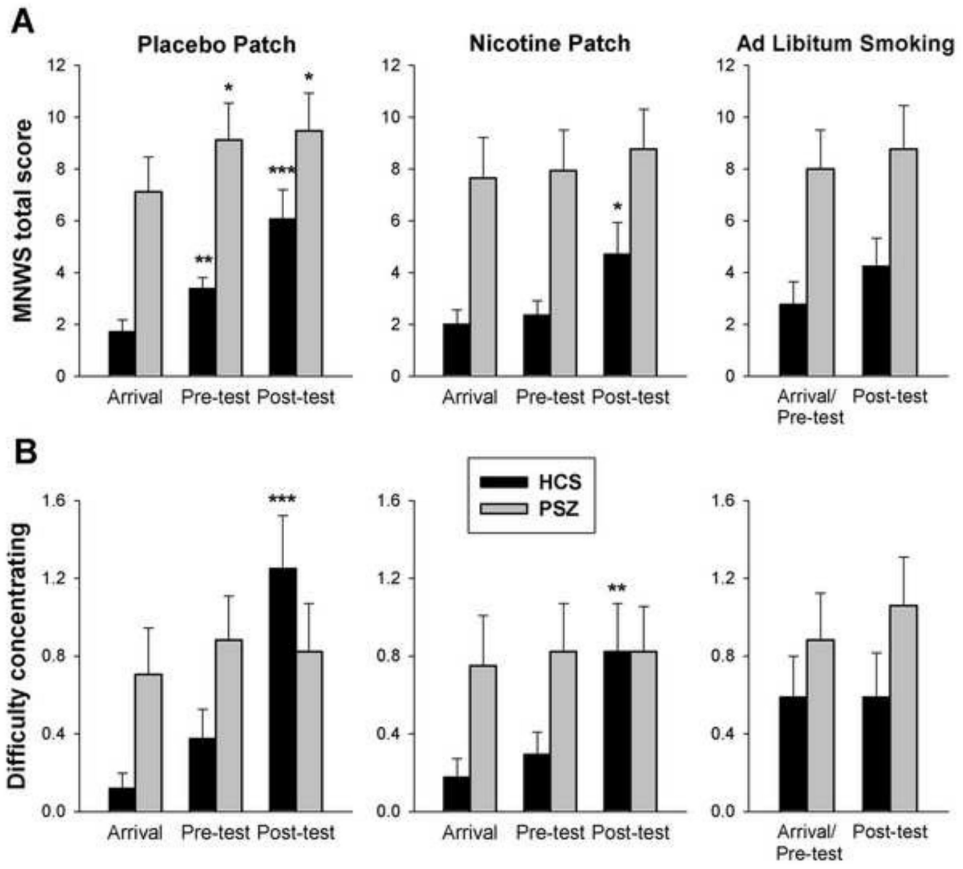

Figure 3.

Average (±SEM) scores on the Minnesota Nicotine Withdrawal Scale (MNWS) of 17 healthy control subjects (HCS) and 17 people with schizophrenia (SCZ). The scales were administered upon arrival, after the absorption period (pre-test), and after cognitive testing (post-test). In the *ad libitum* smoking condition, arrival and pre-test was identical. Figure 3A shows total MNWS scores, Figure 3B the "difficulty concentrating" subitem.

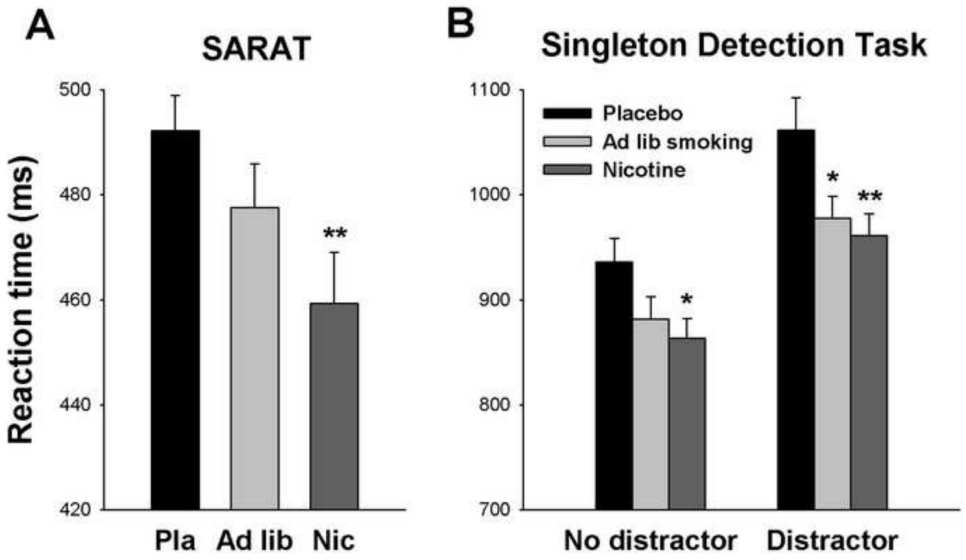

Figure 4.

Average reaction time in each of the three drug conditions. A: Reaction time in the Spatial Attentional Resource Allocation Task (SARAT) of 34 subjects, including 17 healthy controls and 17 people with schizophrenia. B: Reaction time in the Singleton Detection Task of 30 participants, including 17 healthy controls and 13 people with schizophrenia, in the presence and absence of a color singleton distractor. Error bars reflect the SEM adjusted to remove between-subject variability in average reaction time across drug conditions(66;67). * $P<0.05$, ** $P<0.01$, paired t-test comparison with placebo condition. Please note the difference in scales adopted in panels A and B.

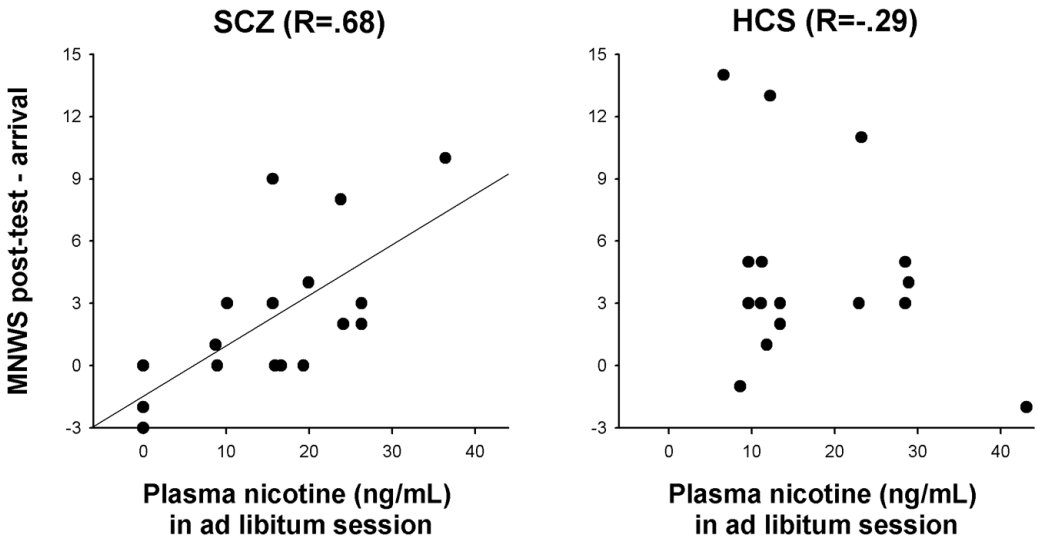

Figure 5.

Pearson correlations in people with schizophrenia (SCZ) and healthy control subjects (HCS) between the increase in Minnesota Nicotine Withdrawal Scale (MNWS) scores over the course of the placebo session and nicotine plasma concentrations in the *ad libitum* smoking session. A significant association between abstinence-induced withdrawal and smoking-derived nicotine intake was seen in SCZ but not HCS.

Table 1

	People with Schizophrenia (mean ± stdev)	Healthy Control Subjects (mean ± stdev)	Statistic	P-value
Age	43.1 ± 10.5 (range 22-53)	40.2 ±11.1 (range 25-52)	t(32)=.76	P>0.4
Male: Female	14 : 3	14 : 3	χ^2 =0	P=1
African American : Caucasian	5 : 12	8 : 9	χ^2 =1.12	P=0.29
Education (years)	12.1 ± 2.1	12.5 ± 1.2	t(32)=.70	P>0.4
Number of cigarettes/day	17.9 ± 8.4	16.6 ± 9.7	t(32)=.41	P>0.6
Years of Smoking	21.9 ± 11.3	21.8 ± 11.4	t(32)=.05	P>0.9
Number of quit attempts	3.7 ± 3.4	3.8 ± 7.6	t(32)=.06	P>0.9
Age start smoking	17.8 ± 4.8	15.4 ± 3.4	t(32)=1.64	P=0.11
Age smoking regularly	19.5 ± 4.3	18.8 ± 5.7	t(32)=.41	P>0.6
FTND[a] total score	4.6 ± 2.1	5.6 ± 1.8	t(32)=1.43	P=0.16
Arrival CO (ppm)[b]	29.5 ± 19.8	20.6 ± 6.8	t(32)=1.76	P=0.09
Estimated IQ[c]	97.9 ± 12.2	111.1 ± 14.0	t(32)=2.93	**P<0.01**
Brief Psychiatric Rating Scale	36.6 ± 8.0 (range 24-52)			
Scale for the Assessment of Negative Symptoms	37.9 ± 13.7 (range 15-64)			

[a] Fagerstrom Test for Nicotine Dependence

[b] Average over all three test sessions

[c] estimated by the vocabulary and matrix reasoning subscales of the Wechsler Abbreviated Scale of Intelligence(47)