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***In vivo* evidence for β_2 nicotinic acetylcholine receptor subunit upregulation in smokers as compared to nonsmokers with schizophrenia**

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Abstract

Background: Schizophrenia is associated with very high rates of tobacco smoking. The latter may be related to an attempt to “self-medicate” symptoms and/or to alterations in function of high affinity nicotinic acetylcholine receptors (β_2^* -nAChRs).

Methods: Smoking and nonsmoking subjects with schizophrenia (n=31) and age-, smoking- and sex-matched comparison subjects (n=31) participated in one [¹²³I]5-IA-85380 single photon emission computed tomography (SPECT) scan to quantify β_2^* -nAChR availability. Psychiatric, cognitive, nicotine craving and mood assessments were obtained during active smoking as well as smoking abstinence.

Results: There were no differences in smoking characteristics between smokers with and without schizophrenia. Subjects with schizophrenia had lower β_2^* -nAChR availability relative to comparison group, and nonsmokers had lower β_2^* -nAChR availability relative to smokers. However, there was no smoking by diagnosis interaction. Relative to nonsmokers with schizophrenia, smokers with schizophrenia had higher β_2^* -nAChR availability in limited brain regions. In smokers with schizophrenia, higher β_2^* -nAChR availability was associated with lower negative symptoms of schizophrenia and better performance on tests of executive control. Chronic exposure to antipsychotic drugs was not associated with changes in β_2^* -nAChR availability in schizophrenia.

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Conclusions: Although subjects with schizophrenia have lower β_2^* -nAChR availability as compared to comparison group, smokers with schizophrenia appear to upregulate in the cortical regions. Lower receptor availability in smokers with schizophrenia in the cortical regions is associated with a greater number of negative symptoms and worse performance on tests of executive function; suggesting smoking subjects with schizophrenia who upregulate to a lesser degree may be at risk for poorer outcomes.

Keywords

nicotinic acetylcholine receptors; psychosis; tobacco smoking; negative symptoms; executive control; SPECT

Introduction

Schizophrenia is associated with very high rates of tobacco addiction (80%) relative to the general population (20%) (1, 2). Compared to typical smokers from the general population, individuals with schizophrenia are reported to extract higher amounts of nicotine per cigarette and higher rates of smoking-related cardiovascular disease, pulmonary disease and associated mortality (3, 4). The high rate of tobacco smoking may reflect an attempt to “self-medicate” the negative symptoms, cognitive dysfunction, and antipsychotic-related side-effects associated with schizophrenia (1, 5-9). Therefore, understanding the basis for high rates smoking in this population, a modifiable risk factor, might lead to increased life expectancy and quality of life, and may also provide the basis for developing drugs to target the symptoms of schizophrenia.

Nicotine, the primary addictive and reinforcing constituent in cigarettes, has high affinity for the beta2-subunit containing nicotinic acetylcholine receptors (β_2^* -nAChRs). Evidence from postmortem (10), preclinical (11), and clinical (12, 13) studies demonstrates that chronic administration of nicotine and tobacco smoking increases the number of β_2^* -nAChRs in most brain regions (12, 14), a process that is commonly referred to as “upregulation”. However, results from a post-mortem study suggests that smokers with schizophrenia fail to upregulate β_2^* -nAChRs to the same extent as comparison smokers. This post mortem study that controlled for smoking status showed that while nonsmokers with and without schizophrenia have similar binding of [3 H]-nicotine (symbolizing similar availability of β_2^* -nAChRs), smokers with schizophrenia have lower [3 H]-nicotine binding than smokers without schizophrenia. Taken together these findings suggested that smokers with schizophrenia do not upregulate nAChRs to the same extent as smokers without schizophrenia (15). We confirmed *in vivo* the postmortem findings of Breese et al. that smokers with schizophrenia had lower β_2^* -nAChR availability relative to smokers without schizophrenia (16). Furthermore, we showed that β_2^* -nAChR availability in individuals with schizophrenia correlated with negative symptoms (16). However, because our initial study did not include nonsmokers with schizophrenia, we were unable to determine whether smoker with schizophrenia do not upregulate nAChRs.

The overarching goal of the current study was to determine the role of β_2^* -nAChRs in schizophrenia-associated symptomatology. β_2^* -nAChRs have been previously quantified

with high affinity radioligand [^{123}I]-5 -iodo-3-[2(S)-2-azetidylmethoxy]pyridine ([^{123}I]5-IA) (17) and SPECT (18). in a range of clinical samples including individuals with nicotine addiction (19, 20), alcohol use disorders (21), major depressive disorder (22), bipolar disorder (23), and schizophrenia (16)) [^{123}I]5-IA has slow dissociation from the receptor–ligand complex, a good specific to nonspecific binding ratio, and high selectivity for β_2^* -nAChRs (18, 24). We hypothesized that although there would be overall lower β_2^* -nAChR availability in individuals with vs. without schizophrenia, we would observe higher β_2^* -nAChR availability in smokers vs. nonsmokers with schizophrenia in the cortex, hippocampus, and striatum based on previous postmortem findings (15). Second, we hypothesized that the lower β_2^* -nAChR availability, the more severe the schizophrenia-associated symptoms. Third, we hypothesized that the lower β_2^* -nAChR availability, the more severe the cognitive deficits. Finally, an exploratory aim was to determine the influence of chronic antipsychotic treatment on β_2^* -nAChR availability in schizophrenia.

Methods

Approvals

This study was approved by the Yale University and VA Connecticut Healthcare System Institutional Review Boards. All participating subjects signed informed consent after the study was explained to them in detail (see supplement).

Subjects

Thirty one subjects with schizophrenia (2 women smokers; 22 smokers, 4 of whom were unmedicated; 9 nonsmokers 2 of whom were unmedicated) and 31 age- and sex-matched comparison subjects (2 women smokers; 22 smokers, 9 nonsmokers) completed the study and were included in the analyses. Data from the previous sample of smoking subjects with and without schizophrenia (16) are included here as part of this study. Thus, 11 medicated smokers with schizophrenia and 11 smoking controls are included from the previously sample in order to test the hypothesis of higher β_2^* -nAChR availability in smokers.

Subjects completed a comprehensive screening process (see supplement. A psychiatric, medical and neurological evaluation was completed by a research physician. A structured clinical interview for DSM-IV (SCID) to verify the primary diagnoses of schizophrenia (or lack thereof for comparison group) was conducted. In addition, for the schizophrenia group, information collected by clinical evaluation, SCID data, review of the medical record and contact with the patient's clinician was used to confirm the diagnosis and to exclude subjects with any other disorders other than nicotine dependence. Comparison subjects were excluded for lifetime exposure to psychiatric medication, except for smoking cessation attempts (and none in the past year). Nicotine dependence was evaluated with the Fagerström Test for Nicotine Dependence (20). Smoking status at screening was verified by a plasma cotinine level > 150 ng/ml, urine cotinine level > 100 ng/ml, and carbon monoxide (CO) level > 11 ppm at baseline. Nonsmoking status was ascertained by self-report, plasma cotinine level < 15 ng/ml, breath CO levels < 8 ppm at baseline and scan day, and urine cotinine levels < 50 ng/ml. All nonsmokers were *never* smokers. Lifetime history of and

current substance use disorders was ascertained by psychiatric interview, chart review (only in schizophrenia patients), SCID, 30-day Timeline Follow Back and urine toxicology.

In the schizophrenia group only clinically stable subjects were included. Those schizophrenia taking antipsychotic medications were required to be taking a stable dose for the past 12 weeks. Benzodiazepines were permitted on an as-needed basis for subjects with schizophrenia, but not within 12 hours of testing. Subjects taking tricyclic antidepressants, anticholinergics, or selective serotonin reuptake inhibitors were excluded because there is some evidence that these drugs interfere with [123 I]5-IA binding.

Smoking Cessation

Approximately 1 week of abstinence from tobacco smoking is required to clear nicotine from the brain so that it will not interfere with [123 I]5-IA binding (21). To help the subjects abstain from smoking for at least 5 days before the SPECT scan day, they were given brief behavioral counseling based on clinical practice guidelines and contingency management (16). Eligible smokers with schizophrenia were hospitalized on a smoke-free unit and were not allowed to use drugs for smoking cessation, since these could alter [123 I]5-IA binding. Abstinence from smoking and other nicotine products was confirmed by daily monitoring of breath carbon monoxide (CO) and dipstick measurement of urinary cotinine. The CO and urine cut off on scan day were < 8ppm and < 50 ng/ml, respectively. Nicotine craving and withdrawal were evaluated using the Tiffany Urge to Smoke Questionnaire (22) and the Minnesota Nicotine Withdrawal Scale (23), respectively, at intake, during smoking cessation, and on the SPECT scan day. Two factors of Tiffany Smoking Urges Questionnaire were employed: desire (positive symptoms associated with wanting a cigarette; e.g., “I have an urge to smoke”) and relief (withdrawal relief expected if cigarette is smoked; e.g., “Nothing would be better than smoking a cigarette right now”).

Behavioral Testing

Positive, negative, and general symptoms of schizophrenia were measured by the Positive and Negative Syndrome Scale (PANSS) (24) and the Scale for the Assessment of Negative Symptoms (SANS) (25). Depressive symptoms were assessed by the Montgomery-Åsberg Depression Scale (MADRS) (26), and involuntary movements were evaluated with the Abnormal Involuntary Movement Scale (AIMS) (27).

Cognitive testing

Executive control was assessed using the Stroop Color-Word Test (25) and Wechsler Digit Symbol Test (this test assesses several functions including executive control and processing speed; (26)). Subjects participated in cognitive testing: 1) at baseline to familiarize them with cognitive testing (baseline 1), 2) a second baseline to obtain measures of cognitive performance without the factor of novelty (baseline 2), 3) one day after smoking cessation, and 4) on SPECT scan day (after 1 week of smoking abstinence). Nonsmoking subjects were administered cognitive testing at the same time points.

Magnetic Resonance Imaging

Each subject participated in one magnetic resonance imaging (MRI) scan prior to SPECT scanning on a Signa 1.5T system (General Electric Co, Milwaukee, Wis) as described previously (27).

SPECT Imaging

[¹²³I]5IA was synthesized (28) and administered through a venous catheter using a bolus-plus-constant-infusion paradigm with a ratio of 7.0 ± 0.03 h for the smokers with schizophrenia, 7.0 ± 0.03 h for the nonsmokers with schizophrenia, 7.0 ± 0.02 h for the comparison smokers, and 7.0 ± 0.04 h for the comparison nonsmokers. SPECT emissions (3×30 -min static emissions) and transmission scans were collected 6-8 hrs after initiation of [¹²³I]5IA administration as described previously (13, 16). Total injected dose (accounting for decay) of 345.0 ± 31.3 MBq for the smokers with schizophrenia, 355.7 ± 33.9 MBq nonsmokers with schizophrenia, 332.2 ± 41.9 MBq comparison smokers, and 352.2 ± 49.6 MBq for the comparison nonsmokers. Blood was drawn prior to injection and in the middle of the emission scans for analysis of plasma total parent and free fraction of parent tracer in plasma (f_p , free fraction). The chemical fate of [¹²³I]5-IA post injection was assessed in plasma as previously described (29).

SPECT Image Analysis

SPECT emission images were analyzed as described previously (16). A co-registered MR image was used to guide the placement of standard 2-dimensional region of interest (ROI) templates using MEDx software (Medical Numerics, Inc.). A 3D volume of interest was generated for each region and transferred to the co-registered SPECT image to determine regional radioactive densities. The chosen regions contain β_2^* -nAChRs and have been examined in the postmortem study and included the frontal and parietal cortices, thalamus, striatum (an average of caudate and putamen), and hippocampus. Regional [¹²³I]5IA uptake was determined by V_T/f_p where V_T is volume of distribution and f_p is free plasma fraction (calculated as regional activity divided by free plasma parent between 6 and 8 hours of infusion), was used to correct for possible differences in radiotracer metabolism or plasma protein binding between groups and subjects (30).

Statistical analyses

Statistical analysis was performed using IBM SPSS v19.0 (Armonk, New York). Statistical significance was set at $p < 0.05$, two-tailed. Two (diagnosis) by two (smoking status) multivariate analysis of variance was used to measure differences in receptor availability between experimental groups. Differences between cognitive and clinical outcomes at different time points were evaluated within groups using two-tailed, paired t-tests. Spearman correlation coefficient was employed to measure associations between receptor availability and clinical and cognitive variables.

Results

Demographic characteristics for all groups are listed in Table 1. There were no significant differences in age between any of the groups ($p > 0.2$). There were no significant differences

in any smoking characteristics between smokers with and without schizophrenia for the number of cigarettes smoked daily, nicotine dependence, relief, desire or withdrawal at baseline or on scan day ($p>0.21$). There were no significant differences in CO or urine cotinine levels on the day of the scan between smokers with and without schizophrenia ($p>0.36$).

V_T/f_p

There were no significant differences in f_p between subjects with and without schizophrenia (scz f_p 0.35 ± 0.05 ; control f_p 0.36 ± 0.05 ; $p=0.47$). There was a significant effect of smoking status (Hotelling's trace $F=3.2$, $p=0.01$) and diagnosis of schizophrenia (Hotelling's trace, $F=7.4$, $p=0.00$) but no significant interaction between smoking and schizophrenia ($p=0.67$) on β_2^* -nAChR availability. Overall, smokers had higher V_T/f_p as compared to nonsmokers in all the regions assessed: frontal $F(1,59)=5.4$, $p=0.02$) and parietal ($F(1,59)=4.4$, $p=0.04$) cortices, thalamus ($F(1,59)=8.3$, $p=0.006$), striatum ($F(1,59)=18.0$, $p=0.000$) and hippocampus ($F(1,59)=5.9$, $p=0.02$). Subjects with schizophrenia had significantly lower (13%) V_T/f_p as compared to comparison group in the frontal ($F(1,59)=5.4$, $p=0.02$) and parietal ($F(1,59)=4.4$, $p=.04$) cortices, but not in the subcortical regions where the differences were 2-5% ($p>.42$) (Figure 1, Table 2).

To explore whether the difference in V_T/f_p between smokers and nonsmokers was the same between groups, a secondary analysis (MANOVA) was conducted dividing the groups into subjects with and without schizophrenia. This revealed a statistically significant effect of smoking in the comparison group (Hotelling's Trace $F=4.2$, $p=0.006$), and with significant differences in all the regions assessed (frontal $F(1,30)=7.8$, $p=0.009$) and parietal ($F(1,30)=10.3$, $p=0.003$) cortices, thalamus $F(1,30)=5.4$, $p=0.027$), striatum ($F(1,30)=11.3$, $p=0.002$) and hippocampus ($F(1,30)=4.4$, $p=0.044$). In the schizophrenia group, there was a statistically significant effect of smoking (Hotelling's Trace $F=4.2$, $p=0.007$), and the difference was significant in the frontal $F(1,30)=10.4$, $p=0.003$) and parietal ($F(1,30)=8.2$, $p=0.008$) cortices, and striatum ($F(1,30)=7.1$, $p=0.012$), but not in the thalamus ($F(1,30)=3.0$, $p=0.092$) or hippocampus ($F(1,30)=2.0$, $p=0.165$).

Symptoms Measures and V_T/f_p

There were no differences in the positive symptoms (PANSS), depression (MADRS) or dyskinesia (AIMS) scores between smokers and nonsmokers with schizophrenia at baseline or on scan day (after smokers abstained from smoking) ($p>0.25$) (Table 1). There were no significant changes in depressive, positive or negative symptoms in smokers on scan day (smoking abstinence) as compared to baseline. At baseline and on scan day, compared to nonsmokers with schizophrenia, smokers with schizophrenia had lower negative symptoms scores measured by the PANSS negative symptoms subscale scores (baseline PANSS $F(1,27)=5.1$, $p=0.03$; scan day PANSS ($F(1,26)=6.4$, $p=0.018$) and SANS (baseline SANS $F(1,27)=3.1$, $p=0.09$).

A negative correlation between negative symptoms measured by both the PANSS negative symptom subscale and SANS and V_T/f_p was observed in the frontal and parietal cortices and striatum in the overall sample of subjects with schizophrenia at baseline and on scan day

(Figure 2). This effect appears to be driven by smokers because a subsequent subgroup (smokers vs. nonsmokers) analysis revealed a significant negative correlation between negative symptoms and V_T/f_p only in smokers with schizophrenia (Figure 2). No significant correlations were observed between MADRS depression scores and V_T/f_p .

Executive control and V_T/f_p

There were no differences in performance on cognitive measures between smokers and nonsmokers with schizophrenia at any time points. In smokers with schizophrenia, there was a positive correlation between performance on the Stroop Color-Word test (Interference score) and V_T/f_p in the frontal ($r=0.59$, $n=17$, $p=0.012$) and parietal cortices ($r=0.59$, $n=17$, $p=0.013$) (Figure 3), and between Digit Symbol score and V_T/f_p in the frontal ($r=0.48$, $n=21$, $p=0.027$) and parietal cortices ($r=0.44$, $n=21$, $p=0.047$).

Smoking characteristics and V_T/f_p

There were no significant associations between receptor availability and any smoking characteristics in smokers with schizophrenia (all $p>0.17$), including nicotine dependence, years and numbers of cigarettes smoked. Further, there were no significant associations between cigarette craving and V_T/f_p on scan day ($p>0.11$).

Antipsychotic Medication and V_T/f_p

Exploratory analyses (22 smokers, 4 of whom were unmedicated; 9 nonsmokers 2 of whom were unmedicated) were conducted to examine whether treatment with antipsychotic medication was related to V_T/f_p in subjects with schizophrenia. Since there was a significant age difference between medicated and unmedicated subjects with schizophrenia ($F(1,28)=4.7$, $p=0.039$), age was entered as a covariate. We did not observe statistically significant effect of antipsychotic medication status ($p=0.235$).

Discussion

This study examined the effect of smoking and schizophrenia on an *in vivo* measure of V_T/f_p . First, we detected lower regional V_T/f_p in schizophrenia regardless of smoking status. Second, we observed that smokers with schizophrenia have significantly higher V_T/f_p than nonsmokers in several brain regions. Third, we extend the findings of a negative correlation between V_T/f_p and negative symptoms in smokers with schizophrenia in a larger sample. Fourth, performance on tests of executive control is positively correlated with V_T/f_p . Fifth, chronic treatment with antipsychotic medications does not appear to influence V_T/f_p .

Effect of Diagnosis on V_T/f_p

Individuals with schizophrenia have significantly lower V_T/f_p in cortical regions as compared to those without schizophrenia; however, smokers with schizophrenia show region-specific upregulation of these receptors. We had previously reported lower V_T/f_p in a small sample ($n=11$) of smoking subjects with schizophrenia as compared to comparison smokers (16). Here, we extend these findings to a larger sample of smokers with schizophrenia as well as nonsmokers with schizophrenia and show lower V_T/f_p across smoking groups. The lower V_T/f_p observed in schizophrenia might contribute to the

increased smoking observed in this population. Higher V_T/f_p in smokers is believed to partially represent greater numbers of desensitized and inactivated nAChRs (31, 32), therefore, the lower V_T/f_p in schizophrenia may reflect altered receptor functionality, since maintained nAChR desensitization may be important for relieving nicotine withdrawal in human smokers (33).

Effect of Smoking Status on V_T/f_p

In order to determine whether smokers with schizophrenia upregulate their β_2^* -nAChRs, and to determine the role this system plays in smoking in schizophrenia, nonsmokers with the illness were included in this study. An effect of schizophrenia and smoking status was observed on V_T/f_p but not a diagnosis by smoking interaction: as a group, individuals with schizophrenia have lower V_T/f_p as compared to those without schizophrenia and all smokers regardless of having a diagnosis of schizophrenia have higher V_T/f_p . While the lack of diagnosis by smoking interaction suggests that the degree of upregulation is not significantly different between the schizophrenia and control groups, in the patient group, the degree of upregulation was significant only in the frontal and parietal cortices, and striatum, but not thalamus or hippocampus. These data suggest that smokers with schizophrenia show a different pattern of nAChR upregulation than the general population.

Relationship between Schizophrenia Symptoms and V_T/f_p

There was a specific and robust inverse relationship between V_T/f_p and negative symptoms in smokers with schizophrenia (16). Regardless of the measure of negative symptoms (SANS or PANSS) used, patients with lower V_T/f_p reported greater number negative symptoms. This finding is consistent with a recent report of a negative correlation between negative symptoms and [3H]-nicotine binding to nAChRs in the lymphoblast model ((34). It is tempting to speculate whether schizophrenia patients smoke to alleviate negative symptoms. Some studies report that schizophrenic patients who smoked heavily had the lowest number of negative symptoms (35). However it should be noted that studies on the association between symptom domains and smoking have yielded conflicting results, with studies suggesting a positive correlation between smoking variables and negative symptoms, a negative correlation between smoking variables and negative symptoms, or no relationship between smoking variables and symptoms ((35-51). Smoking high nicotine cigarettes decreases negative symptoms to a greater extent than smoking denicotinized cigarettes (52). Similarly, some but not other clinical trials have demonstrated beneficial effects of nAChR agonists on negative symptoms (53-56). Interestingly, the nAChR agonist TC-5619 had stronger effects on reducing negative symptoms in smokers with schizophrenia (56) a finding that is consistent with our observation that the relationship between β_2^* -nAChR availability and negative symptoms is present only in smokers. While admittedly speculative, one mechanism through which nicotine could reduce negative symptoms may be related to the ability of nicotine to increase burst-firing of dopaminergic neurons and increase dopamine release (57-59), thereby correcting the cortical hypodopaminergia that may mediate negative symptoms (60). Thus, treatments based on a β_2^* -nAChR mechanism may be useful for treating negative symptoms in smokers with schizophrenia, and would likely contribute to improved smoking cessation treatments in these individuals.

Relationship between Executive Function and V_T/f_p

There was a positive association between V_T/f_p in the frontal and parietal cortices and performance on tests related to executive control (Stroop Color-Word test and Digit Symbol subtest) in smokers with schizophrenia. Thus, smokers with schizophrenia who have higher V_T/f_p may have better executive control. The frontal and parietal cortices both regulate executive functioning (61), and these findings support the idea that a balance of cholinergic neurotransmission is required for normal cognition. Regional V_T/f_p may therefore play a critical role in these brain areas in those with and without psychiatric illness; however, despite evidence implicating the cholinergic system in the neurobiology of cognitive dysfunction of schizophrenia (62, 63), the effects of drugs targeting nAChRs for cognitive deficits associated with schizophrenia have been mixed. For example, nicotine preferentially enhanced attentional processing in individuals with schizophrenia and their first-degree relatives as compared to typical individuals (8, 64) and tobacco smoking cessation impaired visuospatial working memory in smokers with schizophrenia but not in smokers without schizophrenia (8); however, augmentation with the selective $\alpha_4\beta_2$ -nAChR agonist AZD3480 failed to improve performance on the MATRICS and Integneuro battery in schizophrenia patients ($n > 400$) who were receiving typical antipsychotics (65). The effects of varenicline, an $\alpha_4\beta_2$ -nAChR partial agonist and a low affinity α_7 -nAChR agonist (66), are also mixed. Some studies have demonstrated improvements in executive control in smokers with schizophrenia (66, 67) and another found varenicline improved verbal learning and memory but not attentional or visuospatial indices (52). The varied outcome measures used makes a collective interpretation of these studies challenging, especially since these studies are further confounded by subjects' smoking status. It is likely that in smokers, high affinity nAChRs are fully occupied by nicotine derived from smoking and additional nAChR agonists may, therefore, not produce any effects. In trials testing nAChR agonists in acutely abstinent smokers, it is difficult to tease out the procognitive effects of nAChR agonists from the effects of reversing nicotine withdrawal. Investigations are currently underway which may provide further evidence for beneficial effects of varenicline and other drugs that act at β_2^* -nAChR for cognitive dysfunction in schizophrenia.

Relationship between Antipsychotic Exposure and β_2^* -nAChR availability

Consistent with preclinical data (68), in this study chronic exposure to dopamine D2 receptor antagonist antipsychotic medications was not significantly related to V_T/f_p . This would suggest that group differences in V_T/f_p cannot be explained by an effect of chronic exposure to antipsychotic medications. The limited number of unmedicated subjects studied limits evaluation of medication by smoking interaction, but should be evaluated in future studies.

Effect of Smoking Cessation on Symptoms

Consistent with our previous study (16), in this extended sample of smokers with schizophrenia, smoking cessation and short-term abstinence had no significant effects on positive symptoms, negative symptoms or depression ratings. These data do not support the "self-medication" hypothesis according to which individuals with schizophrenia smoke to alleviate positive and negative symptoms and depression. Nevertheless, in this larger

sample, most smokers with schizophrenia resumed smoking immediately after completing the SPECT scan, which supports the facts that it is so much more difficult for them to quit smoking, and thus much more effective treatments and more behavioral support is needed in this population.

Limitations and future directions:

There were some limitations to this study. First, the smoking sample included subjects from previously published study (16); however, inclusion of that sample was important in order to evaluate whether smokers with schizophrenia show β_2^* -nAChR upregulation. Second, the sample was composed primarily of male subjects. Since we previously showed sex-specific differences in β_2^* -nAChR upregulation in non-psychiatric subjects (69), it is possible that a larger cohort of female smokers may reveal different results. Third, given that sample of unmedicated individuals with schizophrenia was limited and the groups were less than ideally matched, the interactions between V_T/f_p and antipsychotic treatment should be interpreted cautiously. Fourth, whether the lower V_T/f_p is present at the onset of the illness or is a consequence of the illness and/or treatment cannot be established without studying unmedicated prodromal patients. Showing abnormalities in V_T/f_p in prodromal patients might provide one explanation for the higher rates of smoking in individuals who go on to develop schizophrenia. Fifth, illness duration was not well matched between nonsmoking and smoking subjects with schizophrenia and could influence the observed differences in V_T/f_p . Sixth, region volumes were not checked, and therefore we cannot rule out the possibility that regional volume differences with resultant partial volume effects contributed to the measurements. Finally, cognitive tasks that preferentially load prefrontal cortical function will be used in future studies to link β_2^* -nAChR availability, prefrontal cortical function and negative symptoms.

To conclude, we extended our previous findings to show that although V_T/f_p is lower in individuals with schizophrenia, smokers with schizophrenia have higher V_T/f_p compared to nonsmokers, suggesting an upregulation of β_2^* -nAChRs. Lower V_T/f_p in subjects with schizophrenic might contribute to the vulnerability to smoking in this population. Furthermore, this system may play a role in negative symptoms and executive dysfunction: two important symptom domains in schizophrenia for which existing treatments have limited efficacy. These data support targeted development of nAChR agonists to treat negative symptoms and executive dysfunction in smokers with schizophrenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Scatter plot of V_T/f_p in the parietal and frontal cortices, thalamus, striatum and hippocampus in subjects with schizophrenia who are smokers (closed circles) and nonsmokers (open circles), comparison subjects who are smokers (closed diamonds) and nonsmokers (open diamonds), all subjects with schizophrenia (closed triangles), and all comparison (open triangles). We observed a main effect of smoking (Hotelling's trace $F=3.2$, $p=.01$) and diagnosis of schizophrenia (Hotelling's trace, $F=7.4$, $p=.00$) but no significant interaction of smoking by schizophrenia ($p=.67$) on V_T/f_p . Overall, smoking subjects had greater receptor availability as compared to nonsmokers, and subjects with schizophrenia had lower receptor availability as compared to those without schizophrenia.

Fig. 2.

Negative association between V_T/f_p and negative symptoms were observed in the total sample of subjects with schizophrenia on the PANSS and SANS in the parietal (shown here) and frontal cortices and striatum. Total sample: Frontal (PANSS $r=-0.52$, $n=31$, $p=0.003$; SANSS $r=-0.40$, $n=31$, $p=0.03$) and parietal (PANSS $r=-0.55$, $n=31$, $p=0.002$; SANSS $r=-0.53$, $n=31$, $p=0.003$) cortices and striatum (PANSS $r=-0.40$, $n=31$, $p=0.03$; SANSS $r=-0.38$, $n=31$, $p=0.04$). However, when we stratified the sample by smoking, this observation persisted in the smoking sample only. Frontal: PANSS $r=-0.45$, $n=22$, $p=0.04$ and parietal (PANSS $r=-0.53$, $n=22$, $p=0.01$ SANSS $r=-0.50$, $n=22$, $p=0.02$).

Fig. 3.

Significant positive associations were observed between V_T/f_p and performance on tests of executive control in the group of smokers with schizophrenia (Stroop Color-Word test shown here): in the frontal ($r=.59$, $n=17$, $p=.012$) and parietal cortices ($r=.59$, $n=17$, $p=.013$).

Table 1

Subject characteristics.

	SezS (n=22)		SezNS (n=9)		CS (n=22)		CNS (n=9)		All Sez (n=31)		All Control (n=31)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	42.1	11.1	38.5	14.8	39.7	10.9	35.1	12.1	41.1	12.0	38.3	11.3
Yrs smoking	25.6	12.7			19.3	11.0						
Cig/day	20.7	7.0			18.9	8.1						
Age of diagnosis	23.9	7.5	25.9	9.4					24.4	7.9		
Yrs diagnosed	17.3	10.4	10.6	10.4					15.6	10.6		
Baseline assessments												
FTND	5.7	1.9			4.9	2.8						
MSWQ	7.7	5.9			4.9	7.1						
Tiffany QSU Desire	34.5	13.8			33.2	14.3						
Tiffany QSU Relief	32.7	11.0			26.3	11.5						
PANSS positive	19.2	4.3	18.3	2.7					18.9	3.8		
PANSS negative	35.0	5.7	36.3	7.5					20.5	5.3		
PANSS total	73.0	9.6	79.2	11.7					74.8	10.4		
SANS	30.4	14.8	44.1	21.5					34.4	17.8		
Scan day assessments												
MSWQ	4.4	4.5			2.7	4.1						
Tiffany QSU Desire	26.9	11.2			19.0	10.4						
Tiffany QSU Relief	26.8	10.3			17.9	8.7						
PANSS positive	19.6	4.0	17.9	2.3					19.2	3.7		
PANSS negative	18.5	4.7	23.3	3.3					19.7	4.9		
PANSS total	74.7	9.3	76.4	10.8					75.2	9.6		
SANS	32.3	16.1	48.5	18.0					36.6	17.9		

SezS – smokers with schizophrenia; SezNS – nonsmoker with schizophrenia; CS – control smoker; CNS – control nonsmoker.

Table 2

 V_T/f_P by group

Region	SczS (n=22)		SczNS (n=9)		CS (n=22)		CNS (n=9)		All Scz (n=31)		All Control (n=31)		% dif Scz vs Control	P
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Parietal	47.1	14.0	33.4	5.0	54.2	12.9	40.0	7.9	43.1	13.5	49.8	13.2	13.4	.04
Frontal	51.1	14.4	35.2	3.8	58.2	13.7	44.7	11.3	46.5	14.3	53.9	14.4	13.8	.02
Thalamus	120.1	30.7	101.5	12.1	128.9	28.5	105.3	29.8	114.7	27.8	120.9	30.9	5.1	>.10
Striatum	75.1	19.5	56.8	8.9	78.0	16.7	58.9	13.6	69.8	19.0	71.7	18.2	2.7	>.10
Hippocampus	78.5	24.9	65.8	13.9	74.7	16.6	62.7	20.5	74.8	22.8	70.3	18.8	-6.4	>.10

SczS – smokers with schizophrenia; SczNS – nonsmoker with schizophrenia; CS – control smoker; CNS – control nonsmoker