Published in final edited form as:
Drug Alcohol Depend. 2011 November 1; 118(0): 313–319. doi:10.1016/j.drugalcdep.2011.04.009.

Shorter interpuff interval is associated with higher nicotine intake in smokers with schizophrenia

Jill M. Williams[a,b,*], **Kunal K. Gandhi**[a,b], **Shou-En Lu**[b,a], **Supriya Kumar**[a], **Marc L. Steinberg**[a,b], **Brett Cottler**[a], and **Neal L. Benowitz**[c]

[a]UMDNJ-Robert Wood Johnson Medical School, United States

[b]UMDNJ-School of Public Health, United States

[c]University of California San Francisco, United States

Abstract

Background—People with schizophrenia are frequent and heavy smokers.

Methods—The objective of this study was to measure serum nicotine levels and ad libitum smoking behavior for 24 + 2h using the CReSS micro topography device in 75 smokers with schizophrenia (SCZ) and compare these to 86 control smokers (CON) without mental illness. Mean values of repeatedly measured topography variables were compared using three-level nested linear models to adjust for between subject differences and the double nested data.

Results—Smokers with SCZ smoked more cigarettes in the 24 h period and took an average of 2.8 more puffs per cigarette than CON ($p < 0.001$). The time between puffs, or interpuff interval (IPI), was shorter in SCZ by an average of 6.5 s ($p < 0.001$). The peak flow rate was higher in SCZ by an average of 4.9 ml/s ($p < 0.05$). Smokers with SCZ spent an average of 1.0 min less time smoking a single cigarette vs. CON ($p < 0.001$). Smokers with SCZ also had shorter IPI and more puffs per cigarette in an analysis of first cigarette of the day. For all subjects, a decrease in IPI by 1s was associated with an increase in serum nicotine of 0.19 ng/ml and in cotinine of 5.01 ng/ml (both $p < 0.05$). After controlling for diagnosis group, higher craving scores on QSU Factor 2 (urgent desire to smoke) were associated with shorter IPI.

Discussion—Smokers with schizophrenia demonstrate more intense cigarette puffing that is associated with greater nicotine intake. This pattern may provide insight into other heavily dependent smokers.

Keywords

Nicotine; Schizophrenia; Smoking; Cotinine

[*]Corresponding author at: UMDNJ-Robert Wood Johnson Medical School, 317 George Street, Suite 105, New Brunswick, NJ 08901-2008, United States. Tel.: +1 732 235 4341; fax: +1 732 235 4277. jill.williams@umdnj.edu (J.M. Williams).

Conflict of interest

Jill Williams and Marc Steinberg have received research and grant support from Pfizer. Jill Williams is also a consultant of Pfizer. Neal Benowitz has been a paid consultant to pharmaceutical companies that market or are developing smoking cessation medications, including Pfizer, GlaxoSmithKline, Novartis, Sanofi-Aventis, Accrux and Aradigm. Neal Benowitz has served as a paid expert witness in litigation against tobacco companies regarding tobacco addiction.
Kunal K. Gandhi, Supriya Kumar, Shou-En Lu, and Brett Cottler: no conflict declared.

1. Introduction

People with schizophrenia smoke at higher rates than the general population in both U.S. and international studies (Lasser et al., 2000; de Leon and Diaz, 2005). There is also evidence of high nicotine dependence in this group measured as heavy smoking (de Leon and Diaz, 2005), higher scores on structured nicotine dependence scales (Weinberger et al., 2007) or other indicators including higher carbon monoxide boost (Tidey et al., 2008) or waking at night to smoke (Prochaska et al., 2007). Not surprisingly, smoking-related diseases are common and individuals with schizophrenia suffer increased cardiovascular and respiratory diseases as well as reduced life expectancy (Curkendall et al., 2004; Brown et al., 2000; Capasso et al., 2008). Smoking cessation rates in this group are also lower compared to the general population (Lasser et al., 2000; Covey et al., 1994).

In addition to being heavy smokers, there is evidence that smokers with schizophrenia take in more nicotine per cigarette than smokers without this disorder as measured by levels of nicotine and cotinine, a nicotine metabolite (Olincy et al., 1997; Williams et al., 2005). Our prior work showed that smokers with schizophrenia have 1.3 times higher serum nicotine and cotinine levels compared to controls with no mental illness. Smokers with schizophrenia have no differences in rates of oxidative metabolism of nicotine based on a ratio of 3-hydoxycotinine (3HC) to cotinine (COT; Williams et al., 2005). 3HC/COT is a useful biomarker of CYP2A6 metabolic activity and measure of the rate of nicotine metabolism (Benowitz et al., 2003; Dempsey et al., 2004).

Higher nicotine intake from smoking a single cigarette (after a period of overnight abstinence) has been demonstrated in smokers with schizophrenia compared to controls (Williams et al., 2010). The increase in levels of blood nicotine that occur from smoking a single cigarette is referred to as “nicotine boost” which averages about 10 ng/ml per cigarette in non-psychiatrically ill smokers (Russell et al., 1981; Foulds et al., 1992; Patterson et al., 2003). Average levels of nicotine boost were 28 ng/ml in smokers with schizophrenia. Smokers with schizophrenia reached the nicotine peak earlier (4.8 min vs. 6.4 min) than control smokers and had a greater total nicotine intake (measured as area under the serum nicotine concentration–time curve) from a single cigarette (Williams et al., 2010).

Most studies of nicotine intake in schizophrenia have failed to include assessments of smoking topography to characterize differences in cigarette puffing behavior. Topography studies are important since the way in which cigarettes are smoked, rather than the physical characteristics of the cigarette, is the most important determinant of nicotine in take (Kozlowski et al., 2001). Smoking topography methodology is a valuable tool for assessing cigarette smoke self-administration and technological advances allow for these studies to be done in naturalistic settings, outside of the laboratory. A concern in interpreting prior laboratory-based topography studies has been that the setting and/or device might influence the smoking behavior (Scherer, 1999; Tobin and Sackner, 1982). Although all topography measurements are limited, at least to some degree, by the artificial act of smoking while using a device or smoking through a mouthpiece, these smaller portable devices are easy to use outside of the laboratory setting to capture more naturalistic smoking and allow for less intrusion from the research environment. The filter end of a cigarette is inserted into the topography instrument and smoke flows through the device into a sterilized mouthpiece from which the smoker inhales. A differential pressure flow sensor device measures the pressure differential generated by each puff on the mouthpiece. All of the other variables are derived from the basic measurements of flow and time (Hammond et al., 2005).

Tidey et al. (2005) published a study comparing topography measurements in 20 smokers with schizophrenia (SCZ) to 20 matched controls (CON) using a laboratory based

topography device. Participants underwent two assessments of smoking topography taken during 90 min of ad libitum smoking on separate days. The study did not collect blood nicotine levels, but subjects did provide a saliva sample for cotinine level. SCZ subjects smoked significantly more total puffs, more puffs per cigarette, had larger total puff volume and had shorter inter-puff interval than CON. Test-retest reliabilities were good to excellent between smoking session and the authors concluded that smoking behavior in schizophrenia is reliable when assessed with topography. McKee et al. (2009) conducted a pilot study in 14 smokers that showed no difference in smoking topography measures between smokers with SCZ and controls.

The objective of this current study was to measure smoking topography and serum nicotine levels in smokers with schizophrenia and compare these to control smokers without mental illness. We were also interested in looking at puffing patterns for the first cigarette of the day smoked since it is a predictor of daily nicotine uptake, and nicotine dependence (Muscat et al., 2009).

By evaluating smoking puffing behavior and nicotine intake concurrently we hoped to examine associations between puff characteristics and nicotine levels measured in the same day. Identifying cigarette puffing parameters that determine nicotine intake is essential to understanding tobacco use in schizophrenia and can be used to develop better treatments and improve cessation outcomes for smokers with schizophrenia.

2. Methods

2.1. Subjects

This study was approved by the IRB at UMDNJ-Robert Wood Johnson Medical School. Subjects were recruited from the UMDNJ-University Behavioral Health Care System and other outpatient behavioral health care agencies. A community sample of healthy volunteer smokers without mental illness was recruited through advertisements to participate in the study. All subjects with schizophrenia were enrolled in mental health treatment, stable on antipsychotic medications and had their diagnosis confirmed with the Structured Clinical Interview for DSM-IV (SCID; Spitzer and Williams, 1985). Individuals with schizoaffective disorder or serious cognitive impairment (assessed as a Mini-Mental Status exam score of less than 22; Folstein et al., 1975) were excluded. Controls smokers had to be without any mental illness within the last year (SCID confirmed) and could not be taking an antidepressant, mood stabilizer or anxiolytic for any reason within the previous 6 months. All subjects were ≥18 years of age, smoked 10 or more cigarettes per day (CPD), and had a baseline expired carbon monoxide (CO) level greater than 8 parts per million (ppm). CO levels were assessed by having participants take a deep breath and hold it for 15s before exhaling into a hand held carbon monoxide monitor (EC-50 Smokerlyzer, Bedfont Scientific). Subjects using tobacco products other than cigarettes, pregnant smokers or anyone with an active substance use problem (as defined by the Drug Abuse Screening Test; Gavin et al., 1989 or Alcohol Use Disorders Identification Test; Babor et al., 1992) were excluded. Use of any tobacco treatment medications was also an exclusion. Participants were paid $15 for baseline assessments and $85 for the completion of all measurements on Day 3.

From these recruitment efforts, 606 potential participants were screened for eligibility although most were screen failures for not meeting diagnostic criteria. One hundred and eighty-eight who met eligibility gave signed informed consent to participate, consisting of 88 smokers with schizophrenia (SCZ) and 100 controls (CON). Data from some participants was later excluded for subjects not meeting eligibility ($n = 7$), being lost to follow-up/not completing study ($n = 10$), violating research protocol ($n = 4$), and one participant wanted

their data and blood specimens discarded. An additional 5 subjects are not included in the analyses because they did not have a complete dataset (lacking topography or serum nicotine measures). Therefore, for the purpose of this study, analyses were conducted on 161 participants who completed all study procedures: SCZ ($n = 75$), and CON ($n = 86$).

2.2. Procedures

After signing of the consent form, subjects completed an assessment battery including a smoking history, an expired CO reading, demographic and medication questionnaires, and the Fagerstrom Test for Nicotine Dependence (FTND; Heatherton et al., 1991). Weight, body mass index, and vital signs were collected and a urine pregnancy test given to female subjects of childbearing age to rule out pregnancy. Psychological symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1989), and the Montgomery Asberg Depression Rating Scale (MADRS; Montgomery et al., 1985) in schizophrenia subjects only. Subjects were required to bring their own cigarettes for all study procedures which took place on three consecutive days.

Following completion of the questionnaires, participants were trained on the proper use of the topography device and were observed smoking with the device during practice topography sessions on Day 1–2. The Clinical Research Support System (CReSS) Micro Smoking Topography device (Plowshare/Borgwaldt-KC, Richmond, VA)is a battery-operated device that measures a full complement of smoking behaviors, including puff volume, quantity of puffs, puff duration, average flow, interpuff interval, time and date. Although this device uses a mouthpiece, cigarette smoking does not change as a function of smoking through a mouthpiece (Blank et al., 2009; Lee et al., 2003). The CReSS micro detects cigarette insertion and removal and automatically measures all puff measurements. Following study procedures, the data are transferred from the handheld device to a desktop computer program.

Subjects were then scheduled for a final study day (Day 3) during which time they would have an all day assessment of smoking topography and nicotine blood levels. On the afternoon prior to Day 3 subjects had a brief appointment to review instructions. They took the topography device home with them and began using it for all cigarettes smoked ad libitum, starting around 3 pm in the afternoon. They were also instructed to use the device for all cigarettes smoked upon awakening the next day, including the first cigarette of the day, prior to returning to the lab for a 9:00 am appointment.

Subjects arrived at the lab at 9:00 am on Day 3 and were not allowed to smoke from 9 am to 10 am to standardize time for the first blood collection. Subjects completed brief questionnaires assessing their urges to smoke (Questionnaire of Smoking Urges Brief Form, QSU; Cox et al., 2001), and mood states (Positive and Negative Affect Schedule, PANAS; Watson et al., 1988). At 10:00 am, subjects had a baseline (pre-cigarette) expired CO reading and a pre-cigarette venous blood draw. Following this, subjects were instructed to smoke one of their own cigarettes. Immediately after smoking, subjects had a repeat (post-cigarette) CO reading and blood draw. Patients were then instructed to use the topography device for all cigarettes they smoked that day (unsupervised) and to return to the lab at 3pm for a third blood draw and final CO reading. Collection of nicotine levels at three time points was done to measure both the nicotine intake that occurs from smoking a single morning cigarettes as well as assess nicotine intake throughout the day and compare these with topography measures at different time points throughout the day. Studies of nicotine regulation show that during ad-lib smoking, nicotine gradually rises through the morning hours, plateaus around noon and remains relatively stable until bedtime, making 3 pm an ideal collection time (Benowitz and Jacob, 1984). 10 ml (2–3 teaspoons) of blood was collected at each time point in a serum tube, centrifuged for 15 min and frozen at −20°C for

later analysis. Specimens were sent to the Clinical Pharmacology Laboratory at the University of San Francisco for analysis of nicotine, cotinine, caffeine and 3-hydroxycotinine, which were quantified using liquid chromatography–mass spectrometry. Data retrieval and sanitization from the CReSS Micro was performed as per manufacturer instructions.

2.3. Statistical analysis

Independent sample *t*-tests and Chi-square tests were used to compare the baseline differences in socio-demographic variables and symptom scores between groups. The ratio of 3-hydroxycotinine to cotinine (3HC/COT), a biomarker of the rate of nicotine metabolism, was calculated. Antipsychotic medication dose was converted to chlorpromazine equivalents to standardize dose across different medications (CPZ; Woods, 2003). Baseline CO (in ppm), average number of cigarettes per day (CPD) and serum nicotine values were compared between groups using independent sample *t*-test. Serum cotinine values as well as the 3HC/COT ratios were compared between groups using the nonparametric Wilcoxon test.

We used a data cleaning procedure (Plowshare Technologies) to identify and delete erroneous puffs/cigarettes, which are beyond the normal physiologic measures and can result from movement artifact. The criteria for false puffs includes puff volume greater than 150 ml, average flow rate less than 15 ml/s, peak flow rate less than 16 ml/s and duration greater than 2800 m sec. We also considered puffs with an IPI of greater than 90 s to be aberrant and these were deleted from the analysis (this represented 0.3% of the dataset). Less than 5% of puffs were defined as aberrant based on any of the above criteria. In addition to the values derived by the topography machine we calculated several additional variables. Total cigarette puff volume (ml) was derived by multiplying the puff count by the mean puff volume per cigarette. Total cigarette puff rate (puffs/min) was derived by dividing the total number of puffs per cigarette by the total time taken to finish that cigarette.

Mean values of repeatedly measured topography variables of IPI, average flow, peak flow, puff duration, puff volume, total volume and puff count were estimated and compared using a random effects nested linear model analysis (Littell et al., 2006) in which the random effects component was used to model the different variation in the SCZ and COsN subjects and in the double nested structure of data (puffs within cigarettes and cigarettes within subjects). Random effects model analysis was also used to estimate and compare the mean values of repeatedly measured puff counts per cigarette and total cigarette volume to examine cigarettes within subjects.

To assess the association between topography variables (IPI, average flow, peak flow, puff duration, average puff volume, total volume and puff count) and changes in nicotine intake at different time points, we used a two step regression model procedure. First we estimated for each subject the mean values of each repeatedly measured smoke topography variable and its standard error using mixed model analysis (Step 1). In Step 2, we applied a weighted linear regression analysis to assess the change in nicotine levels with each mean smoke topography measure estimated in Step 1. The weighted analysis was used to account for the variation between repeatedly measured topography data. Specifically, we used the inverse of the standard errors obtained in Step 1 as the weight such that the mean measures with better precision received bigger weight in this regression analysis. Different analyses were completed using different time points for nicotine or cotinine collection or topography measurements.

Separate backward stepwise linear regression analyses were conducted to identify predictors of serum nicotine and cotinine levels. The variables entered into the initial model were age,

gender, race, cigarettes per day, years smoked, time of blood draw, number of past quit attempts, smoking menthol cigarettes, QSU Factors 1 and 2, and PANAS positive and negative scores.

Analyses were performed using SAS Proc Mixed and SAS Proc Genmod that produced sandwich-type variance estimate as a conservative approach. p-values less than 0.05 were considered to be statistically significant. Bonferroni corrections were applied to adjust for type I error rates resulting from multiple comparisons, as appropriate. All statistical analyses were performed using SPSS v17.0 and SAS v9.1.

3. Results

3.1. Demographics

No differences were found between SCZ versus CON on cigarettes smoked per day (CPD), FTND total score, age of first smoking, number of past quit attempts, race/ethnicity and education (see Table 1). Smokers with SCZ had higher baseline expired CO (23.1 vs. 19.5; $p < 0.05$) and were older and more likely to be men compared to CON (both $p < 0.01$). CON were more likely to report waking up at night to smoke (89.5% vs. 77.3%; $p < 0.05$) although groups were not different in reporting time to first cigarette (within the first 30 min of awakening), indicating that overall the groups were well matched on levels of nicotine dependence.

3.2. Comparison between smoking topography measures during 24 h smoking session

During the 24±2 h assessment period, a total of 2966 cigarettes were smoked. This included data on 38691 individual puffs. Smokers with SCZ differed significantly from CON in several measures of smoking topography (see Table 2). Smokers with SCZ smoked more cigarettes in the 24h testing session (mean 21.0 SCZ vs. 16.0 CON) and took an average of 2.8 more puffs per cigarette than CON ($p < 0.001$). The time between puffs, or interpuff interval (IPI) was shorter in SCZ by an average of 6.5s ($p < 0.001$). The peak flow rate was higher in SCZ by an average of 4.9 ml/s ($p < 0.05$). Smokers with SCZ spent an average of 1.0min less total time smoking a single cigarette compared to CON ($p < 0.001$). The time to peak, which measures the time within the puff at which the peak flow was measured, was an average of 0.07s shorter in SCZ ($p < 0.01$). Smokers with SCZ had greater total puff volume than CON ($p < 0.001$). Smokers with SCZ had a faster average cigarette puff rate ($p < 0.001$).

3.3. Comparison between smoking topography measures from first cigarette of the day smoked

We determined the first cigarette of the day by first defining periods of sleep. Sleep was labeled as the longest period without smoking in the 24±2 h period of topography measurement (with a minimum of 4h), similar to other investigators (Grainge et al., 2009). The average time spent in sleep was not different between groups (SCZ 6.6 h vs. CON 8.1 h). The average time of the first cigarette of the day smoked was 7:32 am for the whole sample (not different between groups). Seven smokers with SCZ and 3 CON were excluded from this analysis because they did not meet the criteria of having at least 4h of sleep; an additional 2 were missing the first cigarette of the day due to data cleaning procedures leaving 149 subjects for analysis. This included data on 1850 puffs. Smokers with SCZ again differed significantly from CON in measures of smoking topography for the first cigarette of the day (see Table 3). Smokers with SCZ took an average of 3.3 more puffs per cigarette than CON ($p < 0.01$). The time between puffs, or interpuff interval (IPI) was shorter in SCZ by an average of 5.4 s ($p < 0.001$). The total cigarette puff volume (ml) was

an average of 130.3 ml greater in smokers with SCZ than CON (p <0.01). Smokers with SCZ had a faster average cigarette puff rate of 1.3 puffs/min (p < 0.001).

3.4. Comparison of serum nicotine and nicotine metabolite levels

Nicotine levels were measured 3 times on study Day 3: before (PRE) and after (POST) smoking a single timed morning cigarette at approximately 10 am and again at 3 pm. Smokers with SCZ had significantly higher serum nicotine levels at all time points, compared to the corresponding values for CON (see Table 1). At 3 pm, serum nicotine levels were 31.3 ng/ml for SCZ compared to 24.4 ng/ml for CON. Serum cotinine was also significantly higher for SCZ vs. CON (3 pm values shown; 450.9 ng/ml vs. 303.9 ng/ml; p <0.001), and as expected did not vary much throughout the day. Mean 3HC/cotinine ratios were not different between groups (mean 0.54 vs. 0.49; p =0.487). Separate backward stepwise linear regression analyses were conducted to identify the predictors of nicotine and cotinine levels. Having a diagnosis of schizophrenia and a higher PANAS positive score significantly predicted nicotine and cotinine level (all p <0.05). Higher PANAS positive scores predicted higher nicotine and cotinine levels in the whole sample with no differences between groups.

3.5. Associations between topography variables and nicotine intake

We conducted analyses to examine mean changes in nicotine intake biomarkers (nicotine and cotinine) for association with changes in smoking topography variables. Analyses were conducted within the whole group unless noted. We first examined these associations for the first cigarette of the day topography dataset and the 10 am (PRE) serum nicotine level. For all subjects (SCZ and CON), a decrease in IPI by 1s was associated with an increase in nicotine level of 0.19 ng/ml (mean= −0.19; SE=0.09; 95%CI= −0.36, −0.06; p < 0.05). No other topography variables were significantly associated with nicotine levels in this analysis. We also examined the associations for the first cigarette of the day topography dataset and the 10am serum cotinine level. For all subjects (SCZ and CON), a decrease in IPI by 1 s was associated withan increase in cotinine level of 5.01 ng/ml (mean= −5.01; SE=1.58; 95% CI= −8.14, −1.88; p < 0.01). No other topography variables were significantly associated with cotinine levels in this analysis although there was a trend for time to peak and total cigarette puff volume.

We then examined the associations for the 24h topography dataset and the 3 pm serum cotinine level. For all subjects (SCZ and CON), a decrease in IPI by 1 s was associated with an increase in cotinine level of 5.04 ng/ml (mean= −5.04; SE=1.92; 95%CI= −8.83, −1.25; p < 0.01). No other topography variables were significantly associated with cotinine levels in this analysis. Notopography variables were significantly associated with nicotine levels at 3 pm.

We isolated the 10 am cigarette smoked between the 10 am PRE and POST blood draws in order to examine the associations for the topography of this cigarette and the difference in nicotine level between POST and PRE. No topography variables were significantly associated with the change in nicotine levels in this analysis.

3.6. Associations between Interpuff Interval and expired CO

We conducted exploratory analyses to examine mean changes in expired CO at 3pm with changes in IPI in the 24h topography dataset. We found that (for all subjects), a decrease in IPI by 1 s was significantly associated with an increase in expired CO by 0.34 ppm (mean= −0.34; SE=0.12; 95%CI= −0.58, −0.10; p < 0.01).

3.7. Craving and affective states

Items from the QSU were analyzed as two factors: “intention to smoke” (Factor 1) and “anticipation of relief from withdrawal” (Factor 2; Tiffany and Drobes, 1991). Smokers with SCZ had higher subscale scores on Factor 2 (39.0 vs. 20.6, $p < 0.001$) but no differences for QSU general factor (i.e., average of both factors) or Factor 1 scores. Groups differed significantly in PANAS scores. Smokers with SCZ had higher PANAS negative scores (7.7 vs. 5.2, $p < 0.05$) and lower PANAS positive scores (22.5 vs. 27.0, $p < 0.01$) as compared to CON.

We repeated the two step regression model to assess the association between IPI and scores on the PANAS negative scale and QSU (Factor 2) since the groups differed on these measures. After controlling for diagnosis group (SCZ vs. CON), higher QSU Factor 2 score was associated with shorter IPI. The mean IPI decreased by 0.68s for every 10 unit increase in QSU Factor 2 score (95%CI: −0.12, −0.02; $p < 0.01$) with no difference between groups. PANAS negative score was not associated with IPI.

4. Discussion

In this study, smokers with SCZ differed from smokers without this disorder in that they took more frequent puffs per cigarette and waited less time between puffs. Topography results from the 24h smoking session were remarkably similar to the first cigarette of the day for measures of puff count and interpuff interval. Smoking more cigarettes before and during the study period could have biased the results towards the control group by reducing the impact of nicotine intake from a single cigarette in SCZ. Indeed, studies have shown that smokers who smoke more cigarettes per day have longer time between puffs (IPI) and lower smoke intake per cigarette (Hammond et al., 2005). We found the opposite in SCZ; despite smoking more cigarettes in 24h, individuals with SCZ still demonstrated more intensive puffing, even on the first cigarette of the day. Although the time to first puff was not different between groups, the time to peak, which measures the time to maximum puff velocity and the peak flow rate was faster in SCZ. The average time spent smoking each cigarette was also shorter in smokers with schizophrenia. These data suggest that short IPI is the mechanism for achieving higher serum nicotine levels per cigarette. This study also replicates prior findings of higher nicotine and cotinine levels in schizophrenia with no evidence of difference in nicotine metabolism via CYP2A6. Although other investigators have found an association between the metabolic ratio and topography variables (Moolchan et al., 2009), we did not. Although we hoped to compare topography and nicotine intake measurements from the same morning cigarette (POST-PRE) we were unable to find any associations between topography variables and the change in nicotine levels in this analysis. This may have been due to the fact that smokers with schizophrenia had smoked more cigarettes that morning since awakening compared to controls (mean 7.7 cigarettes vs. 4.7 cigarettes, SCZ vs. CON, prior to 10 am). In a separate study we have confirmed higher nicotine intake in SCZ vs. CON from a single cigarette smoked after a period of overnight abstinence (Williams et al., 2010).

Our findings are consistent with those reported by Tidey et al. (2005) who also found more puffs per cigarette, and shorter IPI in smokers with schizophrenia. Tidey et al. also found significantly higher total puff volume in smokers with schizophrenia. Total puff volume per cigarette is a function of puff number and volume per puff and is a good index of the ”work” the smoker performs in smoking the cigarette (Kozlowski et al., 2001). We also found greater total puff volume in schizophrenia which is primarily due to the increased number of puffs per cigarette. Estimates of total smoke exposure are essential to understanding differential toxic chemical exposures that result from smoking (Djordjevic et al., 2000). Strengths of our study include the 24 h smoking period, measurement of both topography

and biomarkers of smoking (nicotine and cotinine levels) and larger sample size than prior studies. From this evidence, it seems that the CReSS micro can be used effectively to examine questions about smoking topography in schizophrenia; no study subjects had difficulty using the topography device.

Perhaps more important than merely quantifying differences in puff parameters, this is the first study to demonstrate that specific puffing differences (i.e., decreases in IPI) are associated with increases in nicotine intake in both smokers with schizophrenia and controls. We found that shorter IPI was associated with nicotine intake both in the first cigarette of the day and the 24 h smoking period. Shorter IPI was also associated with higher cotinine levels. Other investigators have also found that an association between short inter-puff interval and increases in blood nicotine level in the general population (Bridges et al., 1990), suggesting that this effect is not unique to schizophrenia but is a mechanism associated with an intensity of cigarette smoking.

Smokers with SCZ report higher levels of negative affect (NA), less positive affect (PA) a greater anticipation that smoking will relieve NA (QSU Factor 2), and smoke with a pattern of rapid puffs and shorter IPI. QSU Factor 2 scores (anticipation that smoking will relieve negative affect) in this study were independently related to IPI. This suggests that smoking more intensely (i.e., more frequent puffing and reduced IPI) may be in response to having less ability to tolerate negative affect. Since NA, as measured by the Minnesota Nicotine Withdrawal Scale, increases in smokers with schizophrenia after only a 2h period of smoking abstinence, it is possible that they experience heightened sensitivity to the effects of nicotine withdrawal (i.e., experience more negative affect) which subsequently drives smoking behavior and reduces their likelihood of quitting smoking (Tidey et al., 2005; Tidey and Williams, 2007). This is also consistent with the finding that smokers with schizophrenia have reduced task persistence than smokers without this disorder, which is a measure of behavioral persistence when confronted with distress (Steinberg et al., 2010). Further investigation of negative affect and craving relief in schizophrenia are important to study since they are predictors of abstinence and probability of relapse in smoking cessation studies (Baker et al., 2004; Cappelleri et al., 2007). We also found that positive affect (PA) was a significant predictor of nicotine levels, which is consistent with other investigators (Patterson et al., 2003) but some what unexpected given that PA was lower in SCZ.

Topography measurements may yield valuable insights as they help to understand the behaviors related to increased nicotine intake and nicotine addiction. Since rate of delivery of drug or onset of action of drug is an essential aspect of understanding addiction, differences in cigarette puffing behavior measured via topography may yield clues about drug reward and reinforcements and warrants further study. Certain puffing behaviors signifying lower smoking consumption (decreased puff volumes and increased interpuff interval) predicted abstinence in quit smoking trials of both adults and adolescents (Strasser et al., 2004; Franken et al., 2006). In this study, experiencing an urgent desire to smoke was associated with a more intense behavioral response as measured by more puffs and shorter time between puffs in smoking topography. Urgency or intensity to smoke as defined by craving scores or more rapid time to first cigarette have been recently investigated as sensitive measures of nicotine dependence, linked to higher cotinine levels in the general population (Muscat et al., 2009). Urgency to smoke in schizophrenia as measured by greater nicotine intake from a single cigarette or more intense puffing behavior suggests greater nicotine dependence that may be missed when relaying only on assessments such as the FTND, which may be less useful in schizophrenia (Steinberg et al., 2005).

The reasons for higher nicotine intake in smokers with schizophrenia are still poorly understood. There is considerable support for a self-medication hypothesis that links

schizophrenia to nicotinic receptors (Freedman et al., 2000; Rippoll et al., 2004). These theories link nicotine levels in schizophrenia to a potential cognitive or other illness-enhancing aspect with evidence from studies of electrophysiology and cognitive functioning in schizophrenia (Adler et al., 1993; Olincy et al., 1998; George et al., 2002; Smith et al., 2002). Nicotine is theorized to enhance effects of dopamine in the prefrontal cortex and thus enhance cognition in relevant areas of executive function. An alternative hypothesis is that individuals with schizophrenia smoke in greater quantities due to alterations in brain dopaminergic systems (Chambers et al., 2001). This effect could increase the sensitivity to positive reinforcement (Spring et al., 2003). Alternatively individuals with schizophrenia who experience anhedonia, from illness and antipsychotic medications, could be seeking pleasure more often through substance use. This effect helps explain high use of other substances in schizophrenia, particularly stimulants, including caffeine (Gandhi et al., 2010; Dixon et al., 1991). More studies are needed to understand differences in this high risk smoking population.

Acknowledgments

This work was supported by grants to JMW from the National Institute of Mental Health (MH076672-01A1 to JMW) and from the National Institute on Drug Abuse (DA12393, NLB).

References

Adler LE, Hoffer LD, Wiser A, Freedman R. Normalization of auditory physiology by cigarette smoking in schizophrenic patients. Am. J. Psychiatry. 1993; 150:1856–1861. [PubMed: 8238642]

Babor, TF.; de la Fuentes, JR.; Saunders, J.; Grant, M. The alcohol use disorders identification test. Geneva, Switzerland: Guidelines for Use in Primary Health Care. World Health Organization; 1992. AUDIT.

Baker TB, Piper ME, McCarthy DE, Majeskie MR, Fiore MC. Addiction motivation reformulated: an affective processing model of negative reinforcement. Psychol. Rev. 2004; 111:33–51. [PubMed: 14756584]

Benowitz NL, Jacob P. Daily intake of nicotine during cigarette smoking. Clin. Pharmacol. Ther. 1984; 35:499–504. [PubMed: 6705448]

Benowitz NL, Pomerleau OF, Pomerleau CS, Jacob P 3rd. Nicotine metabolite ratio as a predictor of cigarette consumption. Nicotine Tob. Res. 2003; 5:621–624. [PubMed: 14577978]

Blank MD, Disharoon S, Eissenberg T. Comparison of methods for measurement of smoking behavior: mouthpiece-based computerized devices versus direct observation. Nicotine Tob. Res. 2009; 11:896–903. [PubMed: 19525207]

Bridges RB, Combs JG, Humble JW, Turbek JA, Rehm SR, Haley NJ. Puffing topography as a determinant of smoke exposure. Pharmacol. Biochem. Behav. 1990; 37:29–39. [PubMed: 2263664]

Brown S, Inskip H, Barraclough B. Causes of the excess mortality of schizophrenia. Br. J. Psychiatry. 2000; 177:212–217. [PubMed: 11040880]

Capasso RM, Lineberry TW, Bostwick JM, Decker PA, StSauver J. Mortality in schizophrenia and schizoaffective disorder: an Olmsted County, Minnesota cohort: 1950–2005. Schizophr. Res. 2008; 98:287–294. [PubMed: 18031996]

Cappelleri JC, Bushmakin AG, Baker CL, Merikle E, Olufade AO, Gilbert DG. Multivariate framework of the brief questionnaire of smoking urges. Drug Alcohol Depend. 2007; 90:234–242. [PubMed: 17482773]

Chambers RA, Krystal JH, Self DW. A neurobiological basis for substance abuse comorbidity in schizophrenia. Biol. Psychiatry. 2001; 50:71–83. [PubMed: 11526998]

Covey LS, Hughes DC, Glassman AH, Blazer DG, George LK. Ever-smoking, quitting, and psychiatric disorders: evidence from the Durham, North Carolina, epidemiologic catchment area. Tob. Control. 1994; 3:222–227.

Cox LS, Tiffany ST, Christen AG. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. Nicotine Tob. Res. 2001; 3:7–16. [PubMed: 11260806]

Curkendall SM, Mo J, Glasser DB, Rose Stang M, Jones JK. Cardiovascular disease in patients with schizophrenia in Saskatchewan. Can. J. Clin. Psychiatry. 2004; 65:715–720.

de Leon J, Diaz FJ. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. Schizophr. Res. 2005; 76:135–157. [PubMed: 15949648]

Dempsey D, Tutka P, Jacob P 3rd, Allen F, Schoedel K, Tyndale RF, Benowitz NL. Nicotine metabolite ratio as an index of cytochrome P450 2A6 metabolic activity. Clin. Pharmacol. Ther. 2004; 76:64–72. [PubMed: 15229465]

Dixon L, Haas G, Weiden PJ, Sweeney J, Frances AJ. Drug abuse in schizophrenic patients: clinical correlates and reasons for use. Am. J. Psychiatry. 1991; 148:224–230. [PubMed: 1987823]

Djordjevic MV, Stellman SD, Zang E. Doses of nicotine and lung carcinogens delivered to cigarette smokers. J. Natl. Cancer Inst. 2000; 92:106–111. [PubMed: 10639511]

Folstein MF, Folstein SE, McHugh PR. Mini-mental state a practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 1975; 12:89–98.

Foulds J, Stapleton J, Feyerabend C, Vesey C, Jarvis M, Russell MA. Effect of transdermal nicotine patches on cigarette smoking: a double blind crossover study. Psychopharmacology (Berl.). 1992; 106:421–427. [PubMed: 1570391]

Franken FH, Pickworth WB, Epstein DH, Moolchan ET. Smoking rates and topography predict adolescent smoking cessation following treatment with nicotine replacement therapy. Cancer Epidemiol. Biomarkers Prev. 2006; 15:154–157. [PubMed: 16434603]

Freedman R, Adams CE, Leonard S. The alpha7-nicotinic acetylcholine receptor and the pathology of hippocampal interneurons in schizophrenia. J. Chem. Neuroanat. 2000; 20:299–306. [PubMed: 11207427]

Gandhi KK, Williams JM, Menza M, Galazyn M, Benowitz NL. Serum caffeine in smokers with schizophrenia compared to smoking controls. Drug Alcohol Depend. 2010; 110:151–155. [PubMed: 20227198]

Gavin DR, Ross HE, Skinner HA. Diagnostic validity of the drug abuse screening test in the assessment of DSM-III drug disorders. Br. J. Addict. 1989; 84:301–307. [PubMed: 2650770]

George TP, Vessicchio JC, Termine A, Sahady DM, Head CA, Pepper WT, Kosten TR, Wexler BE. Effects of smoking abstinence on visuospatial working memory functionin schizophrenia. Neuropsychopharmacol. 2002; 26:75–85.

Grainge MJ, Shahab L, Hammond D, O'Connor RJ, McNeill A. First cigarette on waking and time of day as predictors of puffing behaviour in UK adult smokers. Drug Alcohol Depend. 2009; 101:191–195. [PubMed: 19264427]

Hammond D, Fong GT, Cummings KM, Hyland A. Smoking topography, brand switching, and nicotine delivery: an in vivo trial. Cancer Epidemiol. Biomarkers Prev. 2005; 14:1370–1375. [PubMed: 15941943]

Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom test for nicotine dependence: a revision of the Fagerstrom tolerance questionnaire. Br. J. Addict. 1991; 86:1119–1127. [PubMed: 1932883]

Kay SR, Opler LA, Lindenmayer JP. The Positive and Negative Syndrome Scale (PANSS): rationale and standardisation. Br. J. Psychiatry. 1989; (Suppl. 7):59–67.

Kozlowski, LT.; O'Connor, RJ.; Sweeney, CT. Risks Associated with Smoking Cigarettes with Low Machine Measured Yields of Tar and Nicotine. Bethesda, MD: Smoking and Tobacco Control Monograph No. 13. USDDHS, National Institutes of Health, National Cancer Institute; 2001. Cigarette design. (NIH Pub. No. 02-5074).

Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: a population-based prevalence study. JAMA. 2000; 284:2606–2610. [PubMed: 11086367]

Lee EM, Malson JL, Waters AJ, Moolchan ET, Pickworth WB. Smoking topography: reliability and validity in dependent smokers. Nicotine Tob. Res. 2003; 5:673–679. [PubMed: 14577984]

Littell, RC.; Milliken, GA.; Stroup, WW.; Wolfinger, RD.; Schabenberger, O. SAS for Mixed Models. 2nd. SAS Institute Inc: Cary NC; 2006.

McKee SA, Weinberger AH, Harrison EL, Coppola S, George TP. Effects of the nicotinic receptor antagonist mecamylamine on ad-lib smoking behavior, topography, and nicotine levels in smokers

with and without schizophrenia: a preliminary study. Schizophr. Res. 2009; 115:317–324. [PubMed: 19700263]

Montgomery SA, Smeyatsky N, de Ruiter M, Montgomery DB. Profiles of antidepressant activity with the Montgomery-Asberg Depression Rating Scale. Acta Psychiatr. Scand. 1985; (Suppl. 320):38–42.

Moolchan ET, Parzynski CS, Jaszyna-Gasior M, Collins CC, Leff MK, Zimmerman DL. A link between adolescent nicotine metabolism and smoking topography. Cancer Epidemiol. Biomarkers Prev. 2009; 18:1578–1583. [PubMed: 19423535]

Muscat JE, Stellman SD, Caraballo RS, Richie JP Jr. Time to first cigarette after waking predicts cotinine levels. Cancer Epidemiol. Biomarkers Prev. 2009; 18:3415–3420. [PubMed: 19959690]

Olincy A, Ross RG, Young DA, Roath M, Freedman R. Improvement in smooth pursuit eye movements after cigarette smoking in schizophrenic patients. Neuropsychopharmacol. 1998; 18:175–185.

Olincy A, Young DA, Freedman R. Increased levels of the nicotine metabolite cotinine in schizophrenic smokers compared to other smokers. Biol. Psychiatry. 1997; 42:1–5. [PubMed: 9193735]

Patterson F, Benowitz N, Shields P, Kaufmann V, Jepson C, Wileyto P, Kucharski S, Lerman C. Individual differences in nicotine intake per cigarette. Cancer Epidemiol. Biomarkers Prev. 2003; 12:468–471. [PubMed: 12750245]

Prochaska JJ, Leek DN, Hall SE, Hall SM. Cognitive interviews for measurement evaluation of the Fagerström Test for Nicotine Dependence (FTND) in smokers with schizophrenia spectrum disorders. Addict. Behav. 2007; 32:793–802. [PubMed: 16839695]

Rippoll N, Bronnec M, Bourin M. Nicotinic receptors and schizophrenia. Curr. Med. Res. Opin. 2004; 20:1057–1074. [PubMed: 15265251]

Russell MA, Jarvis MJ, Devitt G, Feyerabend C. Nicotine intake by snuff users. Br. Med. J. (Clin. Res. Ed.). 1981; 283:814–817.

Scherer G. Smoking behaviour and compensation: a review of the literature. Psychopharmacology. 1999; 145:1–20. [PubMed: 10445368]

Smith R, Singh A, Infante M, Khandat A, Kloos A. Effects of cigarette smoking and nicotine nasal spray on psychiatric symptoms and cognition in schizophrenia. Neuropsychopharmacol. 2002; 27:479–497.

Spitzer, RL.; Williams, JBW. Biometrics Research Department. New York, NY: New York State Psychiatric Institute; 1985. Structured Clinical Interview for DSM-III-R.

Spring B, Pingitore R, McChargue DE. Reward value of cigarette smoking for comparably heavy smoking schizophrenic, depressed, and nonpatient smokers. Am. J. Psychiatry. 2003; 160:316–322. [PubMed: 12562579]

Steinberg ML, Williams JM, Steinberg HR, Krejci JA, Ziedonis DM. Applicability of the Fagerström Test for Nicotine Dependence in smokers with schizophrenia. Addict. Behav. 2005; 30:49–59. [PubMed: 15561448]

Steinberg ML, Williams JM, Gandhi KK, Foulds J, Brandon TH. Lower task persistence in smokers with schizophrenia as compared to non-psychiatric control smokers. Psychol. Addict. Behav. 2010; 24:724–729. [PubMed: 21198231]

Strasser AA, Pickworth WB, Patterson F, Lerman C. Smoking topography predicts abstinence following treatment with nicotine replacement therapy. Cancer Epidemiol. Biomarkers Prev. 2004; 13:1800–1804. [PubMed: 15533910]

Tidey JW, Rohsenow DJ, Kaplan GB, Swift RM. Cigarette smoking topography in smokers with schizophrenia and matched non-psychiatric controls. Drug Alcohol Depend. 2005; 80:259–265. [PubMed: 15869844]

Tidey JW, Rohsenow DJ, Kaplan GB, Swift RM, Adolfo AB. Effects of smoking abstinence, smoking cues and nicotine replacement in smokers with schizophrenia and controls. Nicotine Tob. Res. 2008; 10:1047–1056. [PubMed: 18584468]

Tidey JW, Williams JM. Clinical indices of tobacco use among people with schizophrenia. J. Dual Diagn. 2007; 3:79–98.

Tiffany ST, Drobes DJ. The development and initial validation of a questionnaire on smoking urges. Br. J. Addict. 1991; 86:1467–1476. [PubMed: 1777741]

Tobin MJ, Sackner MA. Monitoring smoking patterns of low and high tar cigarettes with inductive plethysmography. Am. Rev. Respir. Dis. 1982; 126:258–264. [PubMed: 7103252]

Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J. Pers. Soc. Psychol. 1988; 54:1063–1070. [PubMed: 3397865]

Weinberger AH, Sacco KA, Creeden CL, Vessicchio JC, Jatlow PI, George TP. Effects of acute abstinence, reinstatement, and mecamylamine on biochemical and behavioral measures of cigarette smoking in schizophrenia. Schizophr. Res. 2007; 91:217–225. [PubMed: 17293085]

Williams JM, Gandhi KK, Lu SE, Kumar S, Shen J, Foulds J, Kipen H, Benowitz NL. Higher nicotine levels in schizophrenia compared with controls after smoking a single cigarette. Nicotine Tob. Res. 2010; 12:855–859. [PubMed: 20584771]

Williams JM, Ziedonis DM, Abanyie F, Steinberg ML, Foulds J, Benowitz NL. Increased nicotine and cotinine levels in smokers with schizophrenia and schizoaffective disorder is not a metabolic effect. Schizophr. Res. 2005; 79:323–335. [PubMed: 15961287]

Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. J. Clin. Psychiatry. 2003; 64:663–667. [PubMed: 12823080]

Table 1

Baseline characteristics of smokers with schizophrenia and control smokers (n =161).

	SCZ (n =75)	CON (n =86)	p-Value[a]
Mean (SD)			
Cigarettes per day	22.3 (11.5)	20.0 (7.7)	0.125
Baseline CO (ppm)	23.1 (12.2)	19.5 (7.6)	**0.026**
FTND	5.9 (2.0)	5.5 (1.9)	0.184
Age of first smoking	14.7 (5.2)	14.7 (3.7)	0.971
Past quit attempts	3.3 (4.1)	4.2 (16.8)	0.624
Age	45.7 (10.5)	38.0 (12.0)	<**0.001**
Count (%)			
Gender			<**0.01**
Male	55 (73.3)	44 (51.2)	
Female	20 (26.7)	42 (48.8)	
Race/Ethnicity			0.056
African-American	35 (46.7)	25 (29.1)	
Caucasian	33 (44.0)	45 (52.3)	
Hispanic	4 (5.3)	13 (13.1)	
Other	3 (4.0)	3 (3.5)	
Education			0.238
No High school	23 (30.7)	15 (17.4)	
High school/GED	31 (41.3)	41 (47.7)	
Some college	17 (22.7)	26 (30.2)	
Bachelors degree or higher	4 (5.3)	4 (4.7)	
Use of atypical antipsychotic			
Yes	65 (86.7)	-	
No	10 (13.3)	-	
Mean (SD)			
TTFC (30 min)	71 (95)	73 (85)	0.070
Woke during night to smoke			<**0.05**
Yes	58 (77.3)	77 (89.5)	
No	17 (22.7)	9 (10.5)	
Serum PRE nicotine (ng/ml)	22.0 (12.1)	16.3 (8.2)	<**0.01**
CO PRE (ppm)	21.9 (11.6)	17.7 (8)	<**0.01**
Serum POST nicotine (ng/ml)	35.2 (16.3)	30.6 (10.5)	<**0.05**
CO POST (ppm)	24.8 (11.5)	21.6 (7.8)	<**0.05**
Serum 3PM nicotine (ng/ml)	31.3 (12.1)	24.4 (10.6)	<**0.001**
Serum 3PM cotinine (ng/ml)	450.9 (199.1)	303.9 (128.1)	<**0.001**
CO 3PM (ppm)	27.4 (12.2)	23.0 (9.3)	<**0.05**
3HC/cotinine ratio	0.54 (0.38)	0.49 (0.31)	0.487
CPZ equivalents	505.5 (494.9)	-	
PANSS Positive Score	18.4 (6.1)	-	

	SCZ (*n* =75)	**CON (*n* =86)**	***p*-Value[a]**
PANSS Negative Score	18.7 (6.1)	-	
PANSS General Psychopathology Score	34.1 (9.8)	-	
MADRS Scale	10.2 (8.0)	-	
QSU Factor 1 Scale	53.9 (32.9)	50.5 (33.5)	0.514
QSU Factor 2 Scale	39.0 (31.1)	20.6 (24.2)	<**0.001**
QSU General Factor	49.65 (30.58)	37.85 (27.42)	0.077
PANAS Negative	7.7 (7.5)	5.2 (7.0)	0.031
PANAS Positive	22.5 (9.5)	27.0(7.5)	**0.001**

[a]Independent sample *t*-test Mann–Whitney or Chi-square test.

Table 2

Summary of topography results using CReSSMicro for 24h (n =161).

	SCZ (n =75)		CON (n =86)		SCZ–CON				
	Mean[a]	**SE**[a]	**Mean**[a]	**SE**[a]	**Mean**[a]	**SE**[a]	**df**	***t*-Value**	***p*-Value**
Puffs per cigarette (puff count)	15.8	0.20	12.3	0.15	2.8	0.81	2805	3.41	<**0.001**
Inter-puff interval (s)	14.0	0.90	21.0	0.14	−6.5	1.27	36E3	−5.15	<**0.001**
Time to first puff (s)	14.9	0.73	18.6	0.97	−3.1	1.90	2805	−1.60	0.109
Mean puff volume (ml)	46.3	0.14	46.2	0.15	1.4	2.52	36E3	0.54	0.593
Mean puff duration (s)	1.3	0.00	1.3	0.01	−0.04	0.07	36E3	−0.61	0.545
Time to peak (s)	0.39	0.02	0.45	0.017	−0.069	0.024	36E3	−2.72	<**0.01**
Peak flow (ml/s)	56.0	0.14	52.6	0.15	4.9	2.39	36E3	2.05	<**0.05**
Average flow (ml/s)	38.0	0.08	37.9	0.10	1.1	1.43	36E3	0.79	0.429
Total cigarette puff volume (ml)[b]	681.8	9.15	540.5	7.01	123.2	36.31	2805	3.39	<**0.001**
Total time to finish cigarette (min)	4.5	0.06	5.5	0.07	−1.0	0.23	2805	−4.06	<**0.001**
Total cigarette puff rate (per min)	4.3	0.07	2.7	0.04	1.4	0.26	2805	5.44	<**0.001**

[a]Mean and SE (standard errors) were estimated and compared using the random effects linear regression analysis.

[b]Derived by multiplying the puff count by the mean puff volume per cigarette.

Table 3

Summary of topography results using CReSSMicro for first cigarette of day (n=149).

	SCZ (*n* = 67)		CON (*n* = 82)		SCZ–CON				
	Mean[a]	**SE**[a]	**Mean**[a]	**SE**[a]	**Mean**[a]	**SE**[a]	**df**	**t-Value**	***p*-Value**
Puffs per cigarette (puff count)	15.4	0.79	12.0	0.71	3.3	1.06	214	3.12	<**0.01**
Inter-puff interval (s)	16.5	1.47	21.9	0.56	−5.4	1.57	1684	−3.42	<**0.001**
Time to first puff (s)	22.5	4.16	16.5	3.76	6.0	5.60	214	1.06	0.289
Mean puff volume (ml)	48.3	1.91	45.8	0.66	2.6	2.02	1790	1.27	0.205
Mean puff duration (s)	1.4	0.05	1.4	0.02	0.1	0.06	1790	0.92	0.357
Time to peak (s)	0.39	0.02	0.46	0.02	−0.069	0.029	1701	−2.37	<**0.05**
Peak flow (ml/s)	51.8	2.14	50.0	0.67	1.8	2.24	1790	0.80	0.423
Average flow (ml/s)	35.4	1.23	36.2	0.40	−0.8	1.30	1790	−0.61	0.544
Total cigarette puff volume (ml)[b]	644.5	35.12	514.3	31.75	130.3	47.34	214	2.75	<**0.01**
Total time to finish cigarette (min)	4.6	0.29	5.4	0.26	−0.8	0.39	214	−1.95	0.053
Total cigarette puff rate (per min)	3.9	0.2	2.5	0.19	1.3	0.28	214	4.76	<**0.001**

[a]Mean and SE (standard errors) were estimated and compared using the random effects linear regression analysis.

[b]Derived by multiplying the puff count by the mean puff volume per cigarette.

Drug Alcohol Depend. Author manuscript; available in PMC 2013 May 16.