Supplemental Text

Regulatory approvals: This study was conducted with the approval of the institutional review boards of the Yale University School of Medicine and the Veterans Affairs Connecticut Healthcare System. The use of the radioactive isotope was approved by the Yale Radiation Safety Committee. Magnetic resonance imaging (MRI) was performed with the approval of the Yale Magnetic Resonance Research Center. The radiotracer was administered under IND 61,156.

Consent process in smokers with schizophrenia: Before signing the consent form, subjects had several meetings with study staff where detailed information was provided to ensure that they understood the study and were suitable candidates. Subjects were required to pass a questionnaire about the key risks of the study. Parents, other family members, and nonresearch clinicians were involved in the process when available. The patient's primary clinician (i.e., nonresearch clinician) was required to assent to the patient's participation.

Inclusion/exclusion criteria for smokers with schizophrenia: Only subjects with a primary diagnosis of schizophrenia were included. Diagnosis was confirmed by Structured Clinical Interview for DSM-IV conducted by a research assistant and evaluation by a research psychiatrist. Subjects with a diagnosis of substance abuse within the past month or substance dependence (with the exception of nicotine or caffeine) within the past 6 months prior to screening evaluation were excluded. Smoking status was confirmed by plasma cotinine levels > 150 ng/mL, urine cotinine levels > 100 ng/mL, and carbon monoxide levels > 11 parts per million (ppm) at baseline. Nicotine dependence was evaluated using the Fagerström Test for Nicotine Dependence (1).

Additional screening: Subjects were also screened to ensure clinical stability; this screening included a chart review and review of medications and evaluation by a research psychiatrist. Subjects who were deemed clinically unstable as evidenced by recent psychiatric hospitalization or emergency room visits, increase in clinic visits due to psychiatric symptoms, homicidality, suicidality, and/or grave disability were excluded. Subjects needed to be taking stable doses of antipsychotic medications for at least 12 weeks.

Subjects were screened for any MRI exclusions, such as ferrous metal in the body, cardiac pacemaker, or severe claustrophobia. If a potential subject had any experience working with metal or had any eye injury involving metal, orbital x-rays were performed.

Description of contingency management: Contingency management has been shown to reduce cigarette smoking in smokers with schizophrenia in several short-term studies (2-4). Several methods have been used to monitor smoking behavior to verify smoking abstinence in contingency management studies. Breath carbon monoxide levels have a short half life, reflect only recent smoking, and therefore require frequent breath testing to confirm continuous abstinence (5). Urine, plasma, or salivary levels of cotinine, a principal metabolite of nicotine, have also been used to monitor abstinence (6); cotinine has a longer half-life (16 hours) than carbon monoxide. In this study we used the combination of daily carbon monoxide and urinary cotinine monitoring in real time, and plasma collected for cotinine levels was assayed later.

Subjects received escalating payments according to the schedule tabulated below. Subjects were told that the payments were for being hospitalized to achieve and maintain abstinence from smoking. However, subjects were told that if they showed evidence of having smoked (breath carbon monoxide level ≥ 11 ppm or urine cotinine level > 200 ng/ml) on the day of the SPECT scan, the scan would be cancelled and they would not be paid for the scan day

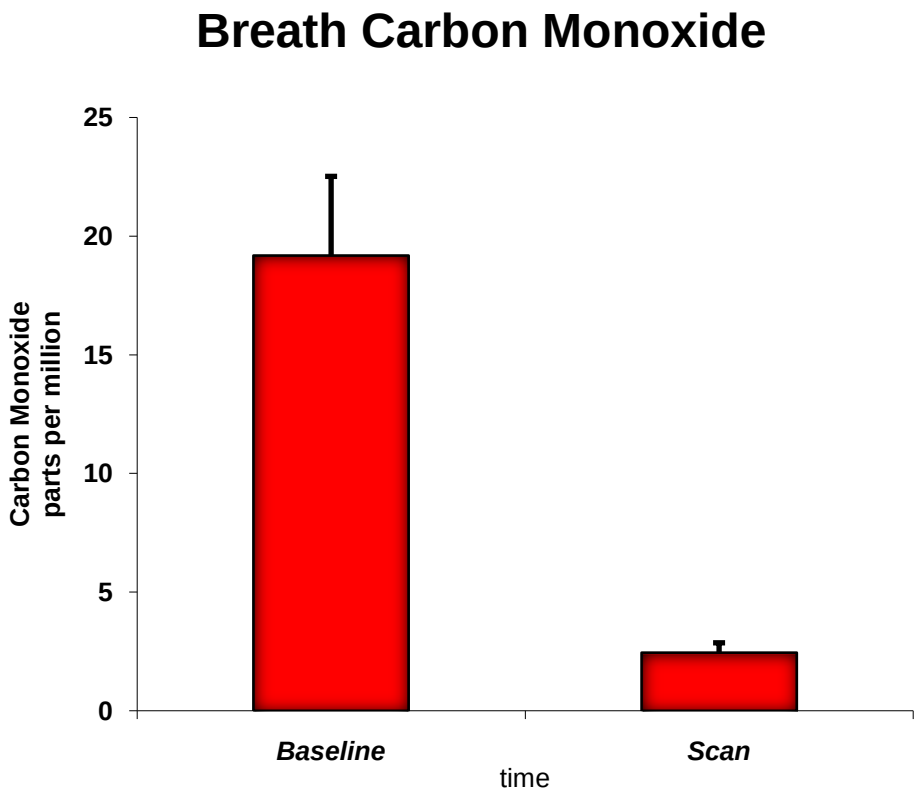
($300). They were also told that if they were unable to abstain, they would be discharged from the study.

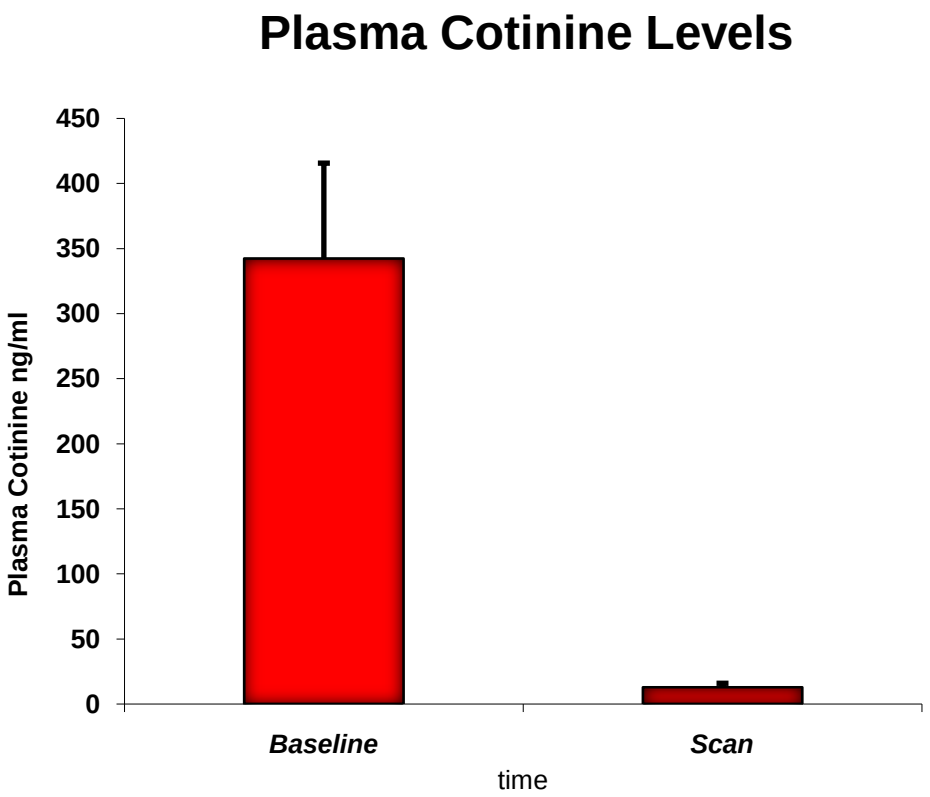
Contingency Management For Smokers with Schizophrenia			
Time	Smoking Status	Patient Status	Payment (dollars)
Day 1	Abstinent	Inpatient	25
Day 2	Abstinent	Inpatient	50
Day 3	Abstinent	Inpatient	75
Day 4	Abstinent	Inpatient	100
Day 5	Abstinent	Inpatient	125
Day 6	Abstinent	Inpatient	150
7 (scan)	Abstinent	Inpatient	300
Total			825
In rare instances the abstinence period could be extended because of technical difficulties with the camera, delays in shipping of the tracer, availability of scan slots, or availability of inpatient beds days. In such instances, subjects were paid more, according to the $25/day escalation schedule.			

REFERENCES

1. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO: The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. Br J Addiction 1991; 86:1119-1127
2. Tidey JW, Higgins ST, Bickel WK, Steingard S: Effects of response requirement and the availability of an alternative reinforcer on cigarette smoking by schizophrenics. Psychopharmacology (Berl) 1999; 145(1):52-60
3. Roll JM, Higgins ST, Steingard S, McGinley M: Use of monetary reinforcement to reduce the cigarette smoking of persons with schizophrenia: a feasibility study. Exp Clin Psychopharmacol 1998; 6(2):157-61
4. Tidey JW, Rohsenow DJ, Kaplan GB, Swift RM, Reid N: Effects of contingency management and bupropion on cigarette smoking in smokers with schizophrenia. Psychopharmacology (Berl) 2011
5. SRNT Subcommittee on Biochemical Verification: Biochemical verification of tobacco use and cessation. Nicotine Tob Res 2002; 4:149-159
6. Higgins ST, Heil SH, Badger GJ, Mongeon JA, Solomon LJ, McHale L, Bernstein IM: Biochemical verification of smoking status in pregnant and recently postpartum women. Exp Clin Psychopharmacol 2007; 15(1):58-66

Supplemental Fig. 1: Measures of Smoking Abstinence in Smokers with Schizophrenia

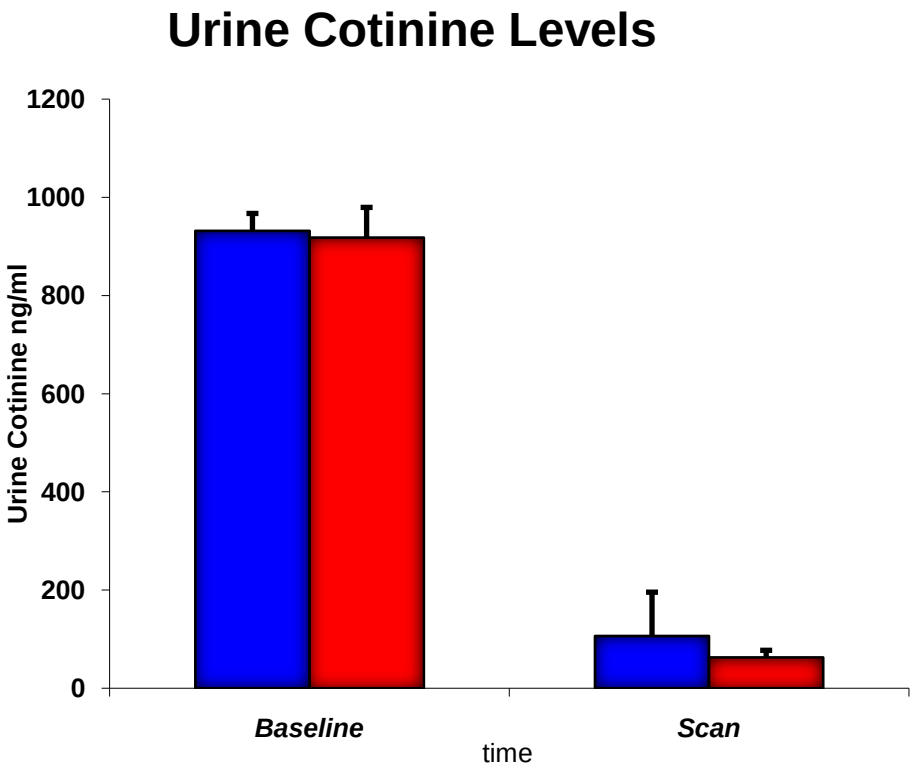


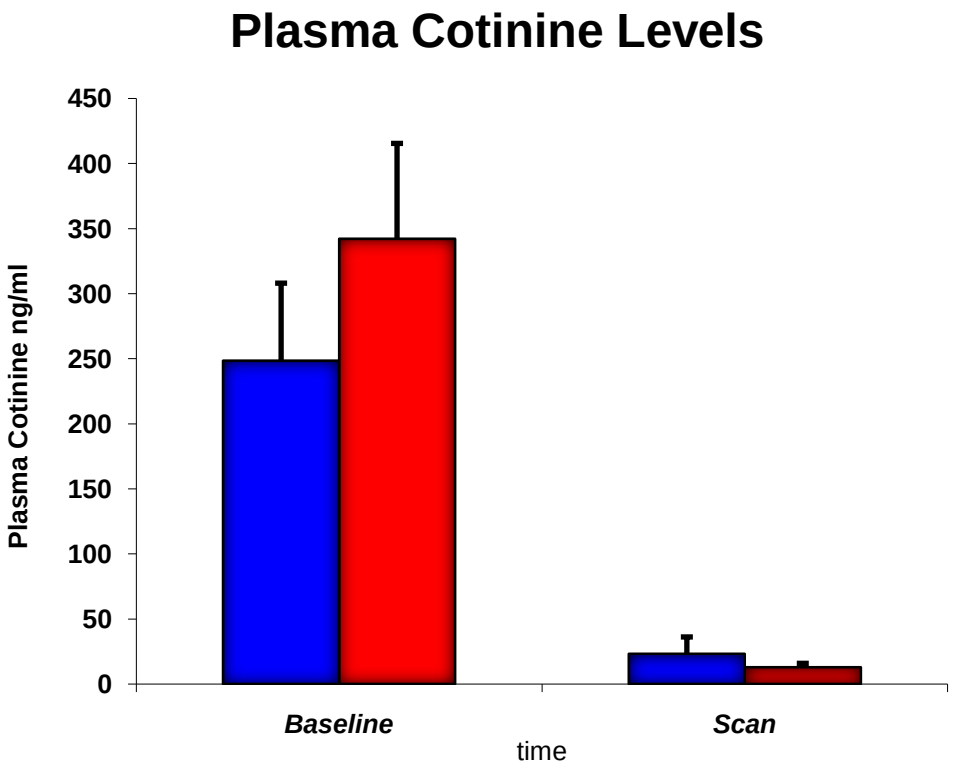


Left panel shows breath carbon monoxide levels (in parts per million) at baseline (smoking as usual) and on the day of the scan (~7 days abstinence) in smokers with schizophrenia. There was a significant reduction in breath carbon monoxide levels with abstinence (F (1, 10)= 26.35, p=0.0004).

Right panel shows plasma cotinine levels (ng/ml) at baseline (smoking as usual) and on the day of the scan (~7 days abstinence) in smokers with schizophrenia. There was a significant reduction in plasma cotinine levels with abstinence (F (1, 10)= 87.91, p<0.0001).

Supplemental Fig. 2: Plasma & Urine Cotinine in Schizophrenia and Comparison Smokers



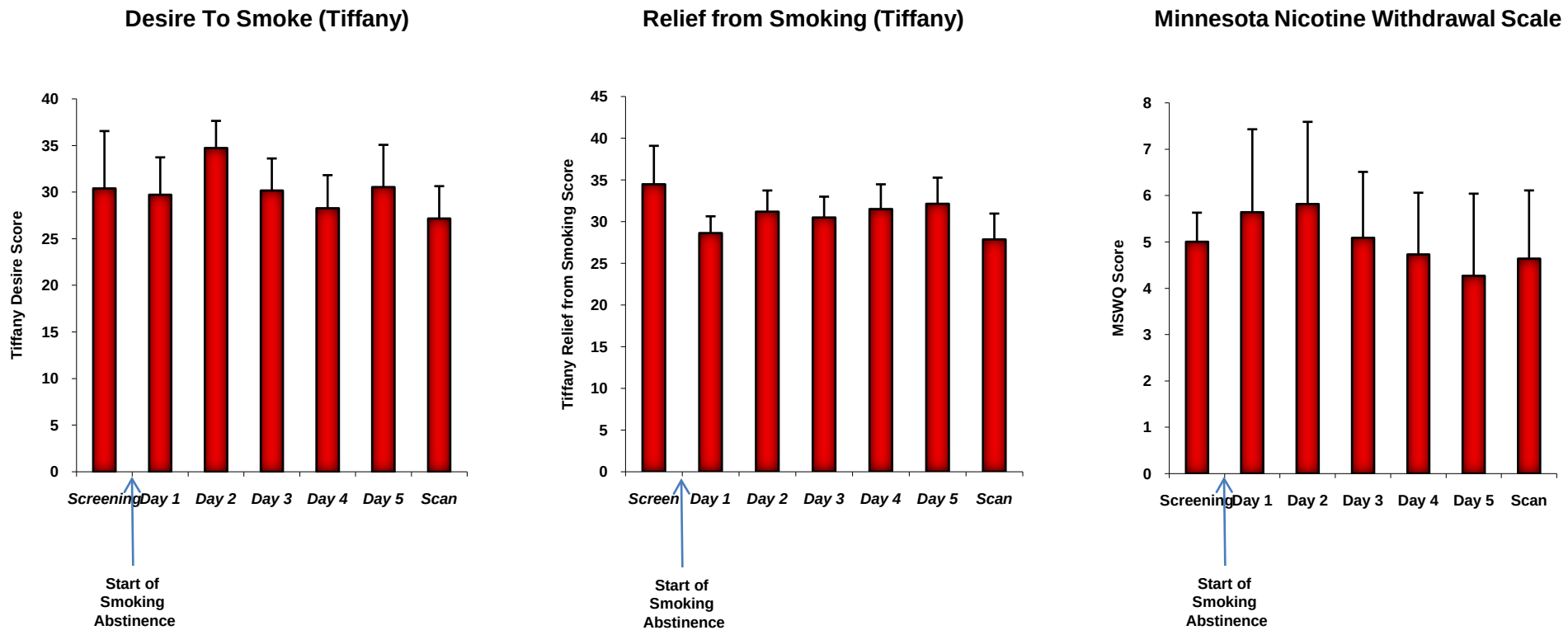


Comparison Smokers Schizophrenia Smokers

Left panel shows urine cotinine levels (ng/ml) at baseline (smoking as usual) and on the day of the scan (~7 days abstinence) in smokers with schizophrenia and comparison smokers. There was no significant group effect (F=0.22, df=1, 20, p=0.65) or group-by-time interaction (F=0.08, df=1, 20, p=0.78).

Right panel shows plasma cotinine levels (ng/ml) at baseline (smoking as usual) and on the day of the scan (~7 days abstinence) in smokers with schizophrenia and comparison smokers. There was no significant group effect (F=0.71, df=1, 17, p=0.41) or group-by-time interaction (F=1.25, df=1, 17, p=0.28).

Supplemental Fig. 3: Smoking Behaviors in Smokers with Schizophrenia

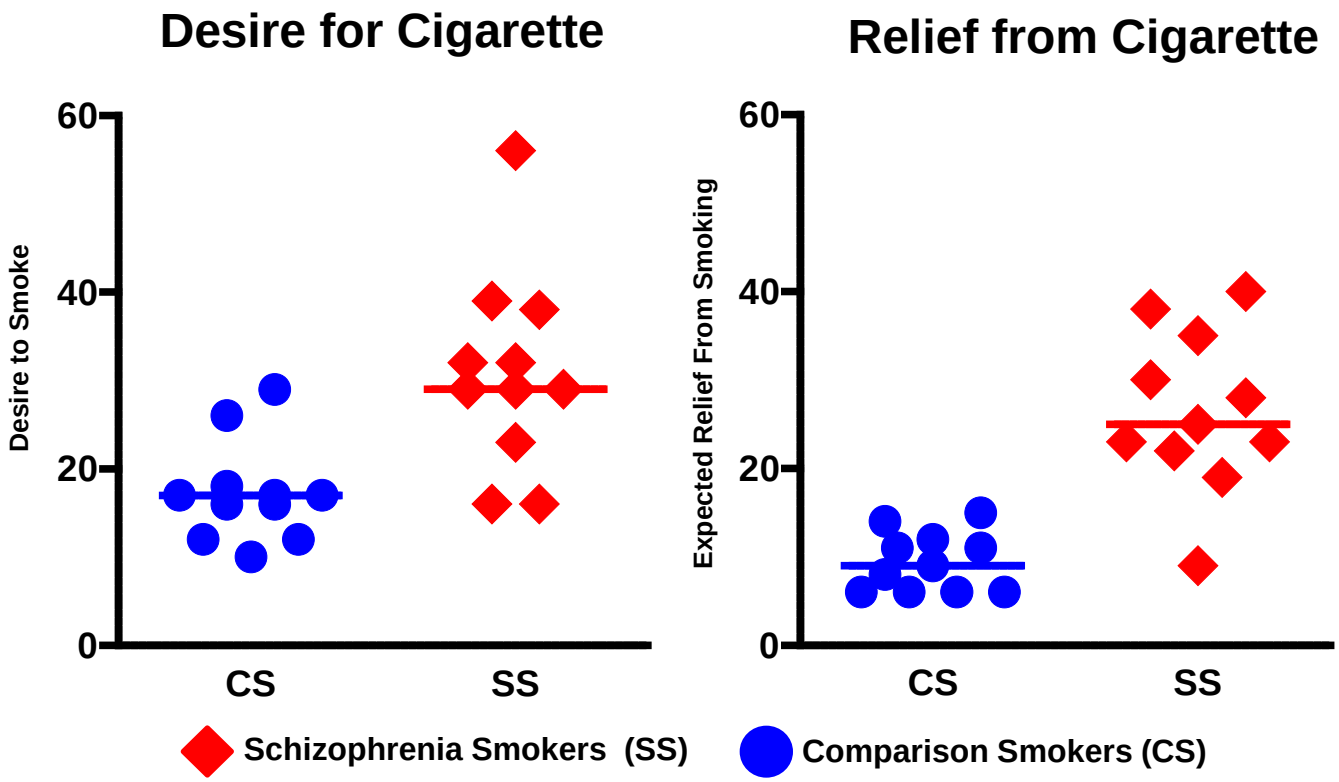


Left panel shows change in the desire to smoke over time measured by the Tiffany Urge to Smoke Questionnaire desire for smoking subscale. There was no significant change over time.

Middle panel shows the change in the expected relief from smoking a cigarette over time measured by the Tiffany relief from smoking subscale. There was no significant change over time.

Right panel shows change in smoking withdrawal over time measured by the Minnesota Nicotine Withdrawal Scale. There was no significant change over time.

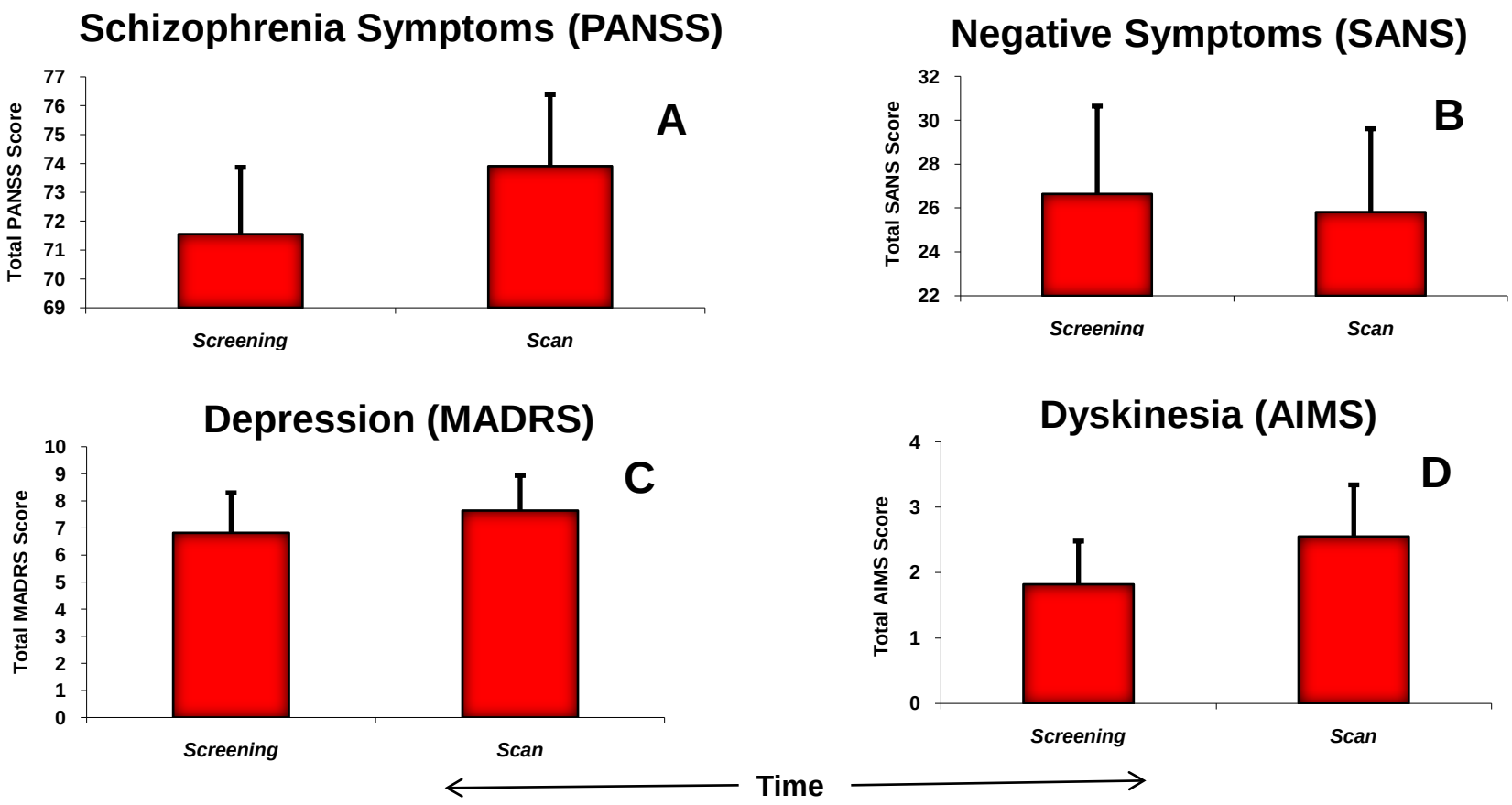
Supplemental Fig. 4:
Group Differences in Smoking Behaviors



Left panel shows significant differences (t = –3.56, p=0.002) in desire for a cigarette measured by the Tiffany Urge to Smoke Questionnaire between smokers with schizophrenia (red filled diamonds) and comparison controls (blue filled circles).

Right panel shows significant differences (t = –5.90, p=0.000) in expected relief from smoking a cigarette measured by the Tiffany Urge to Smoke Questionnaire between smokers with schizophrenia (red filled diamonds) and comparison controls (blue filled circles).

Supplemental Fig. 5:
Symptoms In Smokers with Schizophrenia



A: Symptoms of schizophrenia measured by the Positive and Negative Syndrome Scale (PANSS) at screening (smoking as usual) and on the day of the scan (~7 day abstinence); no statistically significant differences.
B: Negative symptoms of schizophrenia measured by the Scale for the Assessment of Negative Symptoms (SANS) at screening (smoking as usual) and on the day of the scan (~7 day abstinence); no statistically significant differences.
C: Depression symptoms measured by the Montgomery-Åsberg Depression Scale (MADRS) at screening (smoking as usual) and on the day of the scan (~7 day abstinence); no statistically significant differences.
D: Significant increase (F (1, 10)= 5.71, p=0.038) in dyskinesia measured by the Abnormal Involuntary Movements Scale (AIMS) at screening (smoking as usual) and on the day of the scan (~7 day abstinence).

Supplemental Table 1. Symptoms in Smokers with Schizophrenia

		Score			Effect of Time (df=1, 10)	
Time	**N**	**Mean**	**SD**	**SE**	**F**	**p**
Schizophrenia symptoms (PANSS)						
Baseline day	11	71.55	7.69	2.32		
Scan day	11	73.91	8.23	2.48		
Effect of time					2.14	0.17
Negative symptoms (SANS)						
Baseline day	11	26.64	13.25	4		
Scan day	11	25.82	12.56	3.79		
Effect of time					0.14	0.72
Depression (MADRS)						
Baseline day	11	6.82	4.9	1.48		
Scan day	11	7.64	4.3	1.3		
Effect of time					0.58	0.46
Dyskinesia (AIMS)						
Baseline day	11	1.82	2.18	0.66		
Scan day	11	2.55	2.62	0.79		
Effect of time					5.71	0.038