



Published in final edited form as:

Schizophr Res. 2009 October ; 114(1-3): 91–97. doi:10.1016/j.schres.2009.07.006.

Correlation of Prepulse Inhibition and Wisconsin Card Sorting Test in Schizophrenia and Controls: Effects of Smoking Status

Rachel A. Rabin, B.Sc.¹, Kristi A. Sacco, Psy.D.³, and Tony P. George, M.D., FRCPC^{1,2,3}

¹ Schizophrenia Program, Centre for Addiction and Mental Health (CAMH)

² Division of Addiction Psychiatry, Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada M5T 1R8

³ Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut USA 06519

Abstract

Background—In schizophrenia, neurocognitive deficits associated with the illness are modulated by tobacco smoking. However, little is known about how smoking status modulates the relationships between neurocognitive measures in schizophrenia and healthy control subjects.

Objective—The goal of this study was to evaluate the relationship between sensorimotor gating assessed by prepulse inhibition (PPI) and executive cognitive function using the Wisconsin Card Sorting Test (WCST) in schizophrenia and controls as a function of smoking status.

Method—We studied PPI and neuropsychological function in four groups (N=50); smokers with schizophrenia (SS; n=15), control smokers (CS; n=13), non-smokers with schizophrenia (SNS; n=11) and control non-smokers (CNS; n=11).

Results—SNS demonstrated the poorest PPI, while SS showed comparably high levels of PPI to CNS. Non-psychiatric controls outperformed patients on WCST outcomes irrespective of smoking status. Several prefrontal outcome measures on the WCST (categories completed, percentage perseverative and non-perseverative errors) correlated significantly with PPI at the 60 and 120 msec prepulse intervals. In contrast, there were no significant correlations between PPI and any WCST outcomes in SNS, CS or CNS, and few significant correlations between PPI and other neuropsychological measures.

Discussion—Our preliminary data suggests that the correlation between sensorimotor gating (PPI) and prefrontal executive cognitive functioning (WCST) is enhanced by acute cigarette smoking in schizophrenia.

Address for Correspondence: Tony P. George, M.D., FRCPC, Professor of Psychiatry, Psychology and Medical Sciences, University Chair in Addiction Psychiatry, Head, Division of Addiction Psychiatry, University of Toronto, Faculty of Medicine, Clinical Director, Schizophrenia Program, Centre for Addiction and Mental Health (CAMH), 250 College Street, Room CS 734, Toronto, Ontario, Canada M5T 1R8, Tel: (416) 535-8501 ext.4544, Fax: (416) 979-4676, Email: tony.george@utoronto.ca.

Disclosures: Dr. George reports that he receives consulting income in the past 12 months from Janssen-Ortho International, Prempharm, and Bristol-Myers Squibb, and has received funding support from Pfizer, Inc. Ms. Rabin and Dr. Sacco have no disclosures to report.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

Smoking Status; Prepulse Inhibition; Wisconsin Card Sorting Test; Schizophrenia; Neurocognition; Cigarette Smoking; Non-smoker; Addiction; Vulnerability

INTRODUCTION

It is increasingly appreciated that among cigarette smokers, those with schizophrenia have elevated rates of smoking (58–88%) compared to the general population (~20%) (de Leon and Diaz 2005; Kalman et al., 2005). There is evidence that nicotine, the reinforcing agent in tobacco smoke, may ameliorate cognitive and information processing deficits associated with schizophrenia (Sacco et al., 2005; George, 2007), which may explain these high co-morbid rates tobacco smoking in this disorder. Many cognitive deficits are present in patients with schizophrenia, including deficits in attention (Park and Holzman 1992), executive function (Morice and Delahunty, 1996) verbal memory (Wexler et al. 1998) and spatial working memory (Keefe et al., 1995; Sacco et al., 2006). Prepulse inhibition (PPI), an operationalized measure of sensorimotor gating (Braff and Geyer, 1990), is also deficient in schizophrenia, and thought to be associated with dysfunction in the dopamine projections from the ventral tegmental area to the PFC (Knable and Weinberger, 1997).

Given that nicotine administration enhances dopamine release in cortical regions through nAChR modulation (George et al. 2000), cigarette smoking in schizophrenia may reflect an attempt to counteract cognitive performance and information processing deficits (George, 2007). Accordingly, nicotine's psychopharmacological effects have been most appreciably observed on measures of attention (Levin et al., 1996; Depatie et al., 2002; Sacco et al., 2005), working memory (George et al., 2002; Smith et al., 2002; Sacco et al., 2005; Smith et al., 2006) and executive function (George et al., 2002). Preliminary data suggests that cigarette smoking preferentially improves PPI deficits in patients with schizophrenia while acute nicotine abstinence impairs PPI in smokers with schizophrenia, but not in non-psychiatric controls (Kumari et al., 2001; George et al., 2006). Such pro-cognitive effects of nicotine may be indicative of a vulnerability factor predisposing these individuals to the initiation, maintenance and high cessation failure rates of cigarette smoking (Sacco et al., 2004; Kumari and Postma, 2005; George, 2007).

PPI and WCST performance deficits are core endophenotypic features of schizophrenia, and both have been implicated with prefrontal cortical dysfunction. While PPI is distinctly different from performance tasks measuring neurocognition, there is evidence to suggest that both are mediated by common brain pathways (Braff et al., 2001; George, 2007). Correlations between these measures might suggest whether these distinct tasks are influenced by common biological mechanisms. We sought to evaluate the relationship between PPI and neuropsychological functioning in smokers and non-smokers with schizophrenia and non-psychiatric controls. To date, these associations have received little empirical attention, and thus there is limited insight into how PPI deficits relate to cognitive impairment identified in schizophrenia.

Accordingly, we examined the correlations between PPI and executive function as assessed by the Wisconsin Card Sorting Test (WCST) and other neuropsychological measures known to be deficient in schizophrenia, by determining whether cigarette smoking modifies the strength of this relationship in patients with schizophrenia in comparison to non-psychiatric controls. This report extends our recent findings on the effects of smoking status on prepulse inhibition in schizophrenia (Woznica et al., 2009) to correlations of PPI with neuropsychological outcomes assessed concurrently in patients with schizophrenia and non-psychiatric controls as modified by smoking status, controlling for the time of last cigarette.

Specifically, we predicted that there would be a positive correlation between PPI [particularly at the 60 and 120 msec prepulse intervals where PPI is most robust; (Braff et al., 1992; George et al., 2006)] and prefrontal outcomes as assessed by the WCST.

METHODS

Subjects

The majority of the data from subjects with schizophrenia, and non-psychiatric controls were derived from a study of the effects cigarette smoking on cognitive function in schizophrenia, and the role of the nicotinic acetylcholine receptors (nAChRs) in smoking-related cognitive enhancement using the nAChR antagonist mecamylamine hydrochloride (Sacco et al., 2005; George et al., 2006; Woznica et al., 2009). Additional data was obtained from baseline neurocognitive assessments of smokers and non-smokers with schizophrenia and control smokers and non-smokers participating in other neurocognitive studies (Sacco et al., 2008; Sacco et al., 2009) in the Program for Research in Smokers with Mental Illness (PRISM) at the Connecticut Mental Health Center (CMHC) in New Haven, Connecticut.

Patients were recruited from CMHC, and controls were recruited from the Greater New Haven (Conn.) community using newspaper advertisements. Written informed consent was obtained from all subjects seeking participation as approved by the Human Investigation Committee at Yale University School of Medicine. All subjects were screened by trained clinicians using the Structured Clinical Interview for DSM-IV (SCID-V) for Axis I disorders (First et al., 1994). Subjects with schizophrenia or schizoaffective disorder were outpatients at the time of interview, judged to be psychiatrically stable, and on a stable dose of antipsychotic medication for at least three months prior to the study start date. Non-psychiatric control subjects did not meet criteria for any current Axis I disorder on the SCID. Subjects were divided into four groups (N=50); smokers with schizophrenia (SS; n=15), control smokers (CS; n=13), non-smokers with schizophrenia (SNS; n=11) and control non-smokers (CNS; n=11).

Smokers reported consumption of at least 10 cigarettes per day, had an expired breath carbon monoxide (CO level) ≥ 10 ppm, a plasma cotinine level of ≥ 150 ng/ml and a Fagerstrom nicotine dependence test (FTND) score of ≥ 5 to be eligible for the study. Non-smoking status was established by self-report, and verified biochemically with expired breath carbon monoxide readings of < 10 ppm, and plasma cotinine levels < 15 ng/ml (Benowitz et al., 2002).

Study Design

Data from psychiatric and control participants were derived from a single session. To minimize tobacco deprivation, all smoking subjects were studied on the neuropsychological testing battery while being given frequent smoking breaks, to ensure that deprivation from cigarette smoking did not exceed 30 minutes (Sacco et al., 2005).

Neuropsychological Battery

Details of the neuropsychological test battery have been previously detailed (Sacco et al., 2005). The VSWM was administered using PsyScope v 1.2 using a Macintosh G4 computer while WCST and CPT-X were administered on a Pentium IV chip PC computer using PAR software. The battery of neuropsychological tasks took approximately 2.5 hours to complete, and procedures were supervised by the study neuropsychologist (K.A.S.). All subjects received a brief training session in the Yale PRISM neurocognitive laboratory to ensure their familiarity with neuropsychological tasks. Intelligence quotient (IQ) was evaluated by the Shipley IQ Screening Test (Shipley and Burlington, 1941).

Wisconsin Card Sorting Test (WCST)—The WCST (Heaton et al., 1993) assesses executive functions including cognitive flexibility in response to feedback, and performance on this task is known to be impaired in schizophrenia and thought to relate to dorsolateral prefrontal cortex function (Goldberg et al., 1988). A total of 128 cards are presented and the test requires participants to sort the cards on the basis of color, shape, or number of figures. The only feedback provided to the subject is whether responses are correct or incorrect. Common outcomes are categories completed, % total errors, % perseverative errors and % non-perseverative errors.

Connors' Continuous Performance Test – Second Edition (CPT-II)—The CPT-II (Connors, 1995) is an assessment of sustained attention, concentration, response inhibition and impulsivity.

Visuospatial Working Memory (VSWM)—The VSWM task (George et al., 2002) is a delayed-response spatial working memory task, which assesses working memory for nonverbal (object) visuospatial stimuli.

PPI Procedures—The procedures for assessment of prepulse inhibition (PPI) of the acoustic startle response have been described previously (George et al., 2006), and are an adaptation of published procedures (Braff et al., 1992). PPI was recorded at the end of a series of cognitive testing procedures which included assessments of psychotic and affective symptoms and neuropsychological tests of working and verbal memory, attention, executive function, and intellectual function. In smokers, PPI was recorded under satiated conditions such that smokers received a 15 minute ad lib smoking break just prior to recording of PPI and acoustic startle during a 20 minute session. After this smoking break, the recording of PPI and startle responses occurred within 5 minutes of the last cigarette smoked.

All subjects screened for PPI procedures (N=75, across the four groups) underwent audiometry to ensure intact auditory thresholds to tones ≤ 35 dB at 250, 500, 750, 1000, 1500, 2000, 3000, 4000, and 6000 Hz. Subjects were classified as acoustic startlers if they had acoustic startle responses which displayed ≥ 20 machine unit (≥ 25 μ V, where 1 machine unit = 1.22 μ V) increases in the first block of startle stimuli over baseline amplitudes (Braff 1992). Of the total of 75 subjects screened for the PPI testing procedures (George et al., 2006), 15/23 (65.2%) SS, 11/19 (57.9%) CS, 13/19 (68.4%) SNS and 11/14 (78.6%) CNS were classified as acoustic startlers, and also contributed neuropsychological data from the WCST.

The eyeblink component of the acoustic startle reflex was measured using electromyography of the obicularis oculi muscle. Acoustic stimuli were produced on a computerized startle response system (Windows-based SR-LAB; San Diego Instruments) and presented binaurally through headphones. The system was programmed to record for 250 msec after the onset of the startle stimulus. EMG data were collected and stored for off-line analysis.

Test sessions began with a 1-minute acclimation period of 70-dB white noise that continued during the testing session. The test paradigm consisted of 9 blocks of 4 acoustic startle trials per block (36 trials per session). In each block the 0 msec (pulse alone) condition was presented first, followed by the three prepulse intervals (30, 60 and 120 msec) presented in a random order. Startle stimuli consisted of 40 msec, 115.5-dB bursts of white noise with near instantaneous rise time. Pre-pulse trials consisted of a 20-millisecond, 85-dB burst of white noise that was presented 30, 60 or 120msec before the startle pulse. Inter-trial intervals ranged from 14–17 seconds (Mean = 15.7 \pm 1.3). PPI sessions lasted 10 minutes, 40 seconds.

Criteria for inclusion of startle trials were described previously (Braff et al., 1992). Using these criteria, 11.3% of trials in schizophrenia and 14.7% of trials in controls were discarded using

these parameters (from 36 trials per session). PPI was defined as the percentage difference in startle magnitude with and without prepulse [$1 - (\text{pre-pulse to pulse interval startle magnitude} / \text{pulse alone startle magnitude}) \times 100\%$].

Determination of Plasma Cotinine Levels

Venous plasma for nicotine and its proximal metabolite cotinine was obtained at the time of neuropsychological testing. Nicotine and cotinine concentrations (ng/ml) were determined by reversed-phase HPLC based on established methods (Hariharan et al., 1988), as described in our previous studies (Sacco et al., 2005).

Statistical Analysis

Demographic and clinical characteristics were compared across the four groups using a one-way analysis of variance (ANOVA) for continuous measures and Chi square for categorical measures. Baseline differences in percentage PPI at the 30, 60 and 120 msec prepulse intervals and baseline differences on neuropsychological test performance were analyzed using one- and two-way ANOVAs across the four groups. ANOVAs were followed by Bonferroni post-hoc comparisons for multiple comparisons. Pearson product moment correlation coefficients were used to examine relationships between percentage PPI and neuropsychological test battery performance outcomes.

All calculations were done using Statistical Package for Social Sciences (SPSS) version 17.0 for PC. Statistical tests were considered significant when $p < 0.05$.

RESULTS

Demographic and Clinical Characteristics

The demographic and clinical characteristics of the four groups: smokers with schizophrenia ($n=15$), control smokers ($n=13$), non-smokers with schizophrenia ($n=11$) and control non-smokers ($n=11$) are presented in Table 1. The four groups were comparable on age, sex, and race. There were no differences in PANSS total or subscores between smokers and non-smokers with schizophrenia. Significant differences in education, IQ, and BDI scores were found across diagnostic groups. Smokers with schizophrenia and control smokers had no differences in the number of daily cigarettes smoked, their plasma cotinine levels or their level of dependence as measured by the FTND. However, expired carbon monoxide (CO) breath levels were higher in schizophrenia versus control smokers ($p=0.02$), consistent with previous studies (Williams et al., 2007). Amongst the non-smokers, the proportion of former versus never smokers was significantly different ($p < 0.05$) in the schizophrenia and control non-smoker groups (Table 1).

Using one-way ANOVAs, we found main effects of diagnosis on PPI at the 30 ms prepulse intervals, [$F=5.77$, $df=1,44$, $p < 0.02$]. A main effect of smoking status was observed at 120 msec [$F=7.04$, $df=1,44$, $p=0.01$]. Significant Diagnosis x Smoking Status interactions were observed at 30 msec [$F=3.75$, $df=3,42$, $p < 0.02$], and 120 msec [$F=8.78$, $df=3,42$, $p < 0.01$] prepulse intervals. Bonferroni-corrected post-hoc differences at 30 msec prepulse interval revealed differences between SNS and CNS ($p=0.01$). Significant differences were also found at the 120 ms prepulse interval between SNS and SS ($p < 0.01$), CS ($p < 0.03$) and CNS ($p < 0.01$).

Furthermore, significant Diagnosis x Smoking Status interactions were observed on WCST (trials completed [$F=4.70$, $df=3,46$, $p < 0.01$], percentage errors [$F=3.67$, $df=3,46$, $p < 0.02$] perseverative response [$F=2.88$, $df=3,46$, $p < 0.05$] and categories completed [$F=3.29$, $df=3,44$, $p < 0.03$]). Bonferroni post hoc tests demonstrated differences between CS and SNS on WCST trials completed ($p=0.01$) and percentage errors ($p < 0.05$). Post-hoc differences also existed

between SNS and CNS on WCST trials completed ($p=0.01$), percentage errors ($p<0.04$) and categories completed ($p=0.04$). In all cases non-psychiatric controls outperformed the non-smokers with schizophrenia.

The correlation between PPI at 30, 60 and 120 msec prepulse to pulse interval and WCST was examined in patients with schizophrenia and controls, collapsed across smoking status (Table 2). Correlation analyses in the psychiatric group revealed significant associations between PPI at 30, 60 and 120 msec prepulse to pulse interval and trials completed ($r=-0.45$, $p<0.05$; $r=-0.58$, $p<0.05$; $r=-0.50$, $p<0.05$) respectively; increased PPI was associated with fewer completed trials of the WCST. Furthermore, PPI at the 60 msec prepulse to pulse interval negatively correlated with non-perseverative responses ($r=-0.43$, $p<0.05$). No significant correlations for WCST and PPI were found at any of the intervals in the control group (Table 2).

Correlations were then examined in patient and control groups as a function of smoking status (Table 3) at 30, 60 and 120 msec prepulse intervals. At 30 msec, no significant relationships existed between PPI and any WCST performance measure in any of the four groups. Significant correlations emerged in smokers with the schizophrenia at 60 msec between PPI and categories completed ($r=0.58$, $p<0.05$), percentage errors ($r=-0.64$, $p<0.05$), trials completed ($r=-0.75$, $p<0.05$), and percentage of non-perseverative responses ($r=-0.68$, $p<0.05$), and at 120 msec for categories completed ($r=0.61$, $p=0.02$), percent errors ($r=-0.52$, $p=0.04$), and trends for trials completed ($r=-0.48$, $p=0.07$), perseverative responses ($r=-0.48$, $p=0.07$) and perseverative errors ($r=-0.50$, $p=0.06$). Patients who had greater PPI performed better on the WCST. No significant associations were present in control smokers or non-smokers, or non-smokers with schizophrenia (Table 3). Adjustment for gender differences between the four groups (Table 1) using partial correlations did not alter the pattern of results.

Only one significant correlation emerged between PPI and the other neuropsychological measures (e.g. CPT-II, VSWM-30 second delay) in patients with schizophrenia or controls as a function of smoking status. PPI at 120 msec prepulse interval was negatively associated with CPT Variability Index ($r=-0.39$, $p=0.02$) in non-smoking patients with schizophrenia (data not shown).

DISCUSSION

This is the first study to examine the effects of smoking status on the association between sensorimotor gating and executive cognitive functioning in patients with schizophrenia versus controls. Using a cross-sectional design, smokers with schizophrenia had comparable levels of PPI to control smokers and control nonsmokers, and significantly higher levels of PPI than non-smokers with schizophrenia (Woznica et al., 2009). Impairments in WCST performance were associated with a diagnosis of schizophrenia as non-psychiatric controls outperformed those with schizophrenia irrespective of their smoking status. Selected executive function outcomes such as categories completed, percentage errors, trials completed, perseverative responses, and perseverative errors on the WCST were significantly correlated with PPI in smokers with schizophrenia. Importantly, no significant associations were present in non-smoking patients, or in controls, suggest a specificity of these correlations to smokers with schizophrenia. Our results suggest that acute cigarette smoking enhances the relationship between sensorimotor gating and prefrontal executive functioning in schizophrenia. Smoking did not affect the correlations between sensorimotor gating and any of the other cognitive measures (e.g. CPT-II, VSWM) in patients with schizophrenia. This is not surprising, as the effects of nicotine in schizophrenia do not extend to all areas of cognition (Harris et al., 2004; Sacco et al., 2005; Smith et al., 2006).

The robust correlations between PPI and WCST outcomes in smokers with schizophrenia support observations from past studies that have identified overlapping areas of the brain that facilitate prefrontal executive functioning and sensorimotor gating. Kumari *et al.* suggested that PPI in schizophrenia is facilitated by the availability of neural resources in the frontal cortex (Kumari et al., 2001; Kumari and Postma, 2005). PPI levels predict gray matter availability in frontal cortical areas in patients with schizophrenia, which extends to the hippocampal, striatal, thalamic, and temporal regions in healthy subjects (Kumari et al. 2005). Cortico-striatal-pallido-thalamic neurocircuitry is thought to be primarily responsible for the genesis of PPI in rats (Swerdlow et al. 2001), and more recent neuroimaging studies support the role of this common neurocircuitry in the pathophysiology of schizophrenia (Kumari et al., 2003). Additionally, functional neuroimaging studies have found that the WCST activates the dorsolateral prefrontal cortex (DLPFC). Cortico-subcortical projections which connect the DLPFC, the basal ganglia and the cerebellum via the thalamus are believed to serve as the neuroanatomical substrates of executive processing (Heyder et al. 2004). It has been argued that disrupted interactions between the striatum and the PFC may underlie set shifting deficits (Rogers et al. 2000) commonly seen in patients with schizophrenia and their unaffected first-degree relatives (El Hamaoui et al., 2006).

PPI and WCST performance are also both sensitive to hypofrontality and excessive subcortical dopamine (DA) activity. Our data is consistent with the tenet that nicotine enhances DA release (Vezina et al. 1992) and improves dysregulation of the mesocortical dopamine projections from the ventral tegmental area (VTA) to the PFC (George et al. 2000). Smoking may selectively enhance PPI deficits and neurocognitive performance in schizophrenia through pre-synaptic nAChR activation on mesocortical dopamine neurons (George et al., 2000; George et al., 2006).

Elucidating the complex circuitry underlying prefrontal pathways and their neurobehavioral correlates (e.g. PPI and PFC-related cognition) may prove useful in investigating the effects of pharmacological agents in overcoming these cognitive and physiological impairments in schizophrenia. We suggest that interventions aimed at remedying PFC-related deficits such as nicotine receptor-stimulating drugs are a promising alternative to cigarettes, as they may target executive cognitive dysfunction and PPI deficits (George, 2007), without the adverse health consequences associated with tobacco use.

Limitations of the current study include relatively small sample sizes in the four study groups, and a small proportion of females in the control non-smoker group. Furthermore, several correlations between PPI and WCST outcomes were at a borderline level of statistical significance. Future studies with a larger number of participants in each of the four groups would provide more definitive data about the relationship between PPI and executive function.

Taken together, the present findings have implications for understanding the effects of cigarette smoking and nicotinic receptor activation on psychophysiological and neurocognitive functioning. Cigarette smoking may have strengthened the relationship between sensorimotor gating and executive functioning in smokers with schizophrenia, correlations which were not observed in non-smokers with schizophrenia or non-psychiatric controls. These preliminary findings may contribute to better understanding the vulnerability of patients with schizophrenia to nicotine dependence, and may lead to the development of targeted treatments for this comorbidity.

Acknowledgments

This work was supported by National Institute on Drug Abuse (NIDA) grants K02-DA-16611 and R01-DA-14039 to Dr. George, a NARSAD Independent Investigator Award to Dr. George, grants from the Canadian Institutes of Health Research (CIHR), the Canadian Tobacco Control Research Initiative (CTCRI) and the Canada Foundation for

Innovation (CFI) to Dr. George, a 2005 NARSAD Young Investigator Award to Dr. Sacco, and the Chair in Addiction Psychiatry from the University of Toronto to Dr. George.

References

- Benowitz NL, Jacob P III, Ahijevich K, Jarvis MJ, Hall S, LeHouzec J, Lichenstein E, Henningfield J, Tsoh J, Hurt RD, Velicer W. Biochemical verification of tobacco use and cessation. Report from the SRNT Subcommittee on Biochemical Verification. *Nicotine & Tobacco Res* 2002;4:149–159.
- Braff DL, Geyer MA. Sensorimotor gating and schizophrenia. Human and animal model studies. *Arch Gen Psychiatry* 1990;47(2):181–8. [PubMed: 2405807]
- Braff DL, Geyer MA, Swerdlow NR. Human studies of prepulse inhibition of startle: normal subjects, patient groups, and pharmacological studies. *Psychopharmacology* 2001;156:234–258. [PubMed: 11549226]
- Braff DL, Grillon C, Geyer MA. Gating and habituation of the startle reflex in schizophrenic patients. *Arch Gen Psychiatry* 1992;49:206–215. [PubMed: 1567275]
- Connors, CK. *The Continuous Performance Test (CPT)*. Odessa, FL: Psychological Assessment Resources, Inc; 1995.
- de Leon J, Diaz FJ. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophrenia Res* 2005;76:135–157.
- Depatie L, Driscoll GA, Holahan ALV, Atkinson V, Thavundayil JX, Ying Kin NN, Samarthji L. Nicotine and behavioral markers of risk for schizophrenia: a double-blind, placebo-controlled, cross-over study. *Neuropsychopharmacology* 2002;27:1056–1070. [PubMed: 12464463]
- El Hamaoui Y, Elyazaji M, Yaalaoui S, Rachidi L, Saoud M, d'Amato T, et al. Wisconsin card sorting task in patients with schizophrenia and their siblings. *Can J Psychiatry* 2006;51:48–54. [PubMed: 16491984]
- First, MB. *Diagnostic and Statistical Manual of Mental Disorders*. Vol. 4. Washington, D. C: American Psychiatric Association; 1994. (DSM-IV)
- George TP. Neurobiological links between nicotine addiction and schizophrenia. *J Dual Diagnosis* 2007;3(34):27–42.
- George TP, Termine A, Sacco KA, Seyal AA, Dudas MM, Allen TM, Vessicchio JC, Duncan EJ. Effects of cigarette smoking on prepulse inhibition in schizophrenia: Involvement of nicotinic receptor mechanisms. *Schizophr Res* 2006;87:307–315. [PubMed: 16854565]
- George TP, Verrico CD, et al. Nicotinic modulation of mesoprefrontal dopamine neurons: pharmacologic and neuroanatomic characterization. *J Pharmacol Exp Ther* 2000;295(1):58–66. [PubMed: 10991961]
- George TP, Verrico CD, et al. Nicotinic modulation of mesoprefrontal dopamine systems: pharmacological and neuroanatomic characterization. *The Journal of Pharmacology and Experimental Therapeutics* 2000;295:58–66. [PubMed: 10991961]
- George TP, Verrico CD, Picciotto MR, Roth RH. Nicotinic modulation of mesoprefrontal dopamine systems: Pharmacologic and neuroanatomic characterization. *J Pharmacol Exp Ther* 2000;295(1): 58–66. [PubMed: 10991961]
- George TP, Vessicchio JC, Termine A, Sahady DM, Head CA, Pepper WT, Kosten TR, Wexler BE. Effects of smoking abstinence on visuospatial working memory function in schizophrenia. *Neuropsychopharmacology* 2002;26:75–85. [PubMed: 11751034]
- George TP, VJC, Termine A, Sahady DM, Head CA, Pepper WT, Kosten TR, Wexler BE. Effects of smoking abstinence on visuospatial working memory function in schizophrenia. *Neuropsychopharmacology* 2002;26(1):75–85. [PubMed: 11751034]
- Goldberg TF, Weinberger DR. Probing prefrontal function in schizophrenia with neuropsychological paradigms. *Schizophrenia Research* 1988;14:179–183.
- Hariharan M, VanNoord TJ, Greden JF. A high performance liquid chromatographic method for routine simultaneous determination of nicotine and cotinine in plasma. *Clin Chem* 1988;34:724–729. [PubMed: 3359608]

- Harris JG, Kongs S, Allensworth D, Martin L, Tregellas J, Sullivan B, Zerbe G, Freedman R. Effects of nicotine on cognitive deficits in schizophrenia. *Neuropsychopharmacology* 2004;29:1378–1385. [PubMed: 15138435]
- Heaton, RK.; Chelune, GJ.; Talley, JL., et al. Manual. Odessa, FL: Psychological Assessment Resources; 1993. Wisconsin Card Sorting Test.
- Heyder K, Suchan B, et al. Cortico-subcortical contributions to executive control. *Acta Psychol (Amst)* 2004;115(2–3):271–89. [PubMed: 14962404]
- Kalman D, Morrisette SB, George TP. Co-morbidity of smoking with psychiatric and substance use disorders. *Am J Addict* 2005;14:106–123. [PubMed: 16019961]
- Keefe RSE, Lees Roitman SE, Harvey PD, Blum CS, DuPre RL, Prieto RM, Davidson M, Davis KL. A pen-and-paper human analogue of a monkey prefrontal cortex activation task: spatial working memory in patients with schizophrenia. *Schizophrenia Res* 1995;17:25–33.
- Knable MB, Weinberger DR. Dopamine, the prefrontal cortex and schizophrenia. *J Psychopharmacol* 1997;11(2):123–131. [PubMed: 9208376]
- Kumari V, Antonova E, et al. Structural brain correlates of prepulse inhibition of the acoustic startle response in healthy humans. *Neuroimage* 2005;26(4):1052–8. [PubMed: 15961045]
- Kumari V, Gray JA, Geyer MA, Effytche D, Soni W, Mitterschiffthaler MT, et al. Neural correlates of tactile prepulse inhibition: a functional MRI study in normal and schizophrenic subjects. *Psychiatr Res* 2003;122:99–113.
- Kumari V, Postma P. Nicotine use in schizophrenia: The self medication hypothesis. *Neurosci Biobehav Rev* 2005;29:1021–1034. [PubMed: 15964073]
- Kumari V, Soni W, Sharma T. Influence of cigarette smoking on prepulse inhibition of the acoustic startle response in schizophrenia. *Hum Psychopharmacol* 2001;16:321–326. [PubMed: 12404567]
- Levin ED, Wilson W, Rose J, McEvoy J. Nicotine-haloperidol interactions and cognitive performance in schizophrenics. *Neuropsychopharmacology* 1996;15:429–436. [PubMed: 8914115]
- Morice R, Delahunty A. Frontal/executive impairments in schizophrenia. *Schizophrenia Bulletin* 1996;22:125–137. [PubMed: 8685655]
- Park S, Holzman PS. Schizophrenics show spatial working memory deficits. *Arch Gen Psychiatry* 1992;49(12):975–82. [PubMed: 1449384]
- Rogers RD, Andrews TC, et al. Contrasting cortical and subcortical activations produced by attentional-set shifting and reversal learning in humans. *J Cogn Neurosci* 2000;12(1):142–62. [PubMed: 10769312]
- Sacco KA, Bannon KL, George TP. Nicotinic receptor mechanisms and cognition in normal states and neuropsychiatric disorders. *J Psychopharmacol* 2004;18(4):457–474. [PubMed: 15582913]
- Sacco KA, Creeden CL, Reutenauer EL, George TP. Effects of galantamine on neurocognitive deficits in smokers and non-smokers with schizophrenia. *Schizophr Res* 2008;103:326–327. [PubMed: 18571377]
- Sacco KA, Creeden CL, Reutenauer EL, Vessicchio JC, Weinberger AH, George TP. Effects of atomoxetine on cognitive function and cigarette smoking in schizophrenia. *Schizophr Res* 2009;107:332–333. [PubMed: 18995989]
- Sacco KA, Termine A, Dudas MM, Seyal AA, Allen TM, Vessicchio JC, Wexler BE, George TP. Neuropsychological Deficits in Non-Smokers with Schizophrenia: Effect of a Nicotinic Antagonist. *Schizophr Res* 2006;85:213–221. [PubMed: 16678390]
- Sacco KA, Termine A, Seyal AA, Dudas MM, Vessicchio JC, Krishnan-Sarin S, Jatlow PI, Wexler BE, George TP. Effects of cigarette smoking function on spatial working memory and attentional function in schizophrenia: Involvement of nicotinic receptor mechanisms. *Arch Gen Psychiatry* 2005;62:649–659. [PubMed: 15939842]
- Shipley WC, Burlington CC. A convenient self-administered scale for measuring intellectual impairment in psychotics. *Am J Psychiatry* 1941;97:1313–1325.
- Smith RC, Singh A, Infante M, Khandat A, Kloos A. Effects of cigarette smoking and nicotine nasal spray on psychiatric symptoms and cognition in schizophrenia. *Neuropsychopharmacology* 2002;27:479–497. [PubMed: 12225705]

- Smith RC, Warner-Cohen J, Matute M, Butler E, Kelly E, Vaidyanathaswamy S, Khan A. Effects of nicotine nasal spray on cognitive function in schizophrenia. *Neuropsychopharmacology* 2006;31:637–643. [PubMed: 16160711]
- Swerdlow NR, Geyer MA, et al. Neural circuit regulation of prepulse inhibition of startle in the rat: current knowledge and future challenges. *Psychopharmacology (Berl)* 2001;156(2–3):194–215. [PubMed: 11549223]
- Vezina P, Blanc G, et al. Nicotine and morphine differentially activate brain dopamine in prefrontocortical and subcortical terminal fields: effects of acute and repeated injections. *J Pharmacol Exp Ther* 1992;261(2):484–90. [PubMed: 1578364]
- Wexler BE, Stevens AA, et al. Word and tone working memory deficits in schizophrenia. *Arch Gen Psychiatry* 1998;55(12):1093–6. [PubMed: 9862552]
- Williams JM, Gandhi KK, Steinberg ML, Foulds J, Ziedonis DM, Benowitz NL. Higher nicotine and carbon monoxide levels in menthol cigarette smokers with and without schizophrenia. *Nicotine & Tobacco Res* 2007;9:873–881.
- Woznica AA, Sacco KA, George TP. Prepulse inhibition in patients with schizophrenia and controls: Effects of smoking status. *Schizophr Res* 2009;112:86–90. [PubMed: 19423298]

Table 1
Demographic and Clinical Characteristics of the Total Sample (N=50)

Variable	Schizophrenia (n= 26)		Control (n= 24)		P value
	Smoker (n=15)	Non-smoker (n= 11)	Smoker (n= 13)	Non-Smoker (n=11)	
Age	41.9 ±8.9	38.5 ± 8.6	38.8±11.7		0.30
Gender	44.2 ± 8.3	14M/12F	38.5 ± 9.9	39.1 ± 14.4	0.40
	9M/6F	5M/6F	15M/9F	10M/1F	0.77
Race	15W/11AA	6W/5AA	19W/5AA	9W/2AA	0.23
Education (years)	12.3±3.0	12.40±2.87	14.80±2.84		0.42
	12.3±3.0	12.5±2.7	13.8±3.1	16.3±1.9	<0.02
Intelligence Quotient (IQ)	89.4±13.5		103.5±15.1		<0.01
Non-Smoker Status (Former/Never)	87.20±14.95	90.00±12.76	99.46±13.29	111.73±11.80	<0.01
	--	8 Former/3 Never	--	1 Former/10 Never	P<0.05
Cigarettes per day	22.4±13.3	--	17.4±9.2	--	0.43
FTND	6.8±1.7	--	8.5±2.1	--	0.33
Plasma Cotinine (ng/ml)	41.3±14.7	0±0	336±153	10.8±21.5	0.00
Plasma Nicotine Level (ng/ml)	35.1±18.7	0±0	24.4±10.3	0±0	<0.01
CO Level (ppm)	28.9±8.6	1.0±0.6	21.5±7.6	1.3±0.5	<0.01
BDI	12.7±10.4	6.6±7.0	2.1±4.0	0.64±0.9	<0.01
PANSS: positive	14.0±2.3	15.4±2.7	--	--	0.21
PANSS: Negative	14.0±4.6	15.0±2.5	--	--	0.55
PANSS: General	28.4±7.5	32.5±4.0	--	--	0.14
PANSS: Total	56.4±12.8	62.7±8.4	--	--	0.20

Abbreviations: W, White; AA, African American; IQ, intelligence quotient; ppm, parts per million; FTND, Fagerstrom Test for Nicotine Dependence; PANSS, Positive and Negative Symptoms Scale for Schizophrenia; BDI, Beck Depression Inventory;

Table 2 Correlations between PPI and WCST: Schizophrenia versus Control Subjects at the 30, 60 and 120 msec Prepulse Interval Collapsed Across Smoking Status

30 msec Prepulse Interval									
r value	Categories Completed	% Errors	Trials Completed	% Perseverative Responses	Trials Correct	% Perseverative Errors	% Non-Perseverative Responses		
SZ (n=26)	0.27 p=0.20	-0.34 p=0.10	-0.45** p=0.03	-0.24 p=0.24	-0.13 p=0.54	-0.25 p=0.24	-0.34 p=0.10		
Control (n=24)	0.27 p=0.24	-0.16 p=0.49	-0.21 p=0.36	-0.05 p=0.83	-0.14 p=0.53	-0.05 p=0.82	-0.27 p=0.23		
60 msec Prepulse Interval									
r value	Categories Completed	% Errors	Trials Completed	% Perseverative Responses	Trials Correct	% Perseverative Errors	% Non-Perseverative Responses		
SZ (n=26)	0.34 p=0.11	-0.41** p=0.04	-0.58** p=0.00	-0.30 p=0.15	-0.19 p=0.36	-0.30 p=0.16	-0.43** p=0.03		
Control (n=24)	-0.05 p=0.84	0.09 p=0.70	0.01 p=0.97	0.10 p=0.66	-0.16 p=0.48	0.08 p=0.73	0.06 p=0.81		
120 msec Prepulse Interval									
r value	Categories Completed	% Errors	Trials Completed	% Perseverative Responses	Trials Correct	% Perseverative Errors	% Non-Perseverative Responses		
SZ (n=26)	0.35 p=0.09	-0.34 p=0.09	-0.50** p=0.01	-0.32 p=0.12	-0.19 p=0.36	-0.33 p=0.11	-0.24 p=0.25		
Control (n=24)	0.13 p=0.56	-0.02 p=0.93	0.01 p=0.98	-0.06 p=0.79	0.07 p=0.75	-0.03 p=0.88	0.05 p=0.84		

**
p < .05

Table 3 Correlations between PPI and WCST: Schizophrenia and Control Smokers and Non-smokers at 30, 60 and 120 msec Prepulse Intervals

30 msec Prepulse Interval										
r value	Categories Completed	% Errors	Trials Completed	% Perseverative Responses	Trials Correct	% Perseverative Errors	% Non-Perseverative Responses	Trials Correct	% Perseverative Errors	% Non-Perseverative Responses
	0.22 p=0.43	-0.29 p=0.30	-0.38 p=0.17	-0.14 p=0.62	-0.16 p=0.58	-0.15 p=0.61	-0.32 p=0.24	-0.16 p=0.58	-0.15 p=0.61	-0.32 p=0.24
	0.38 p=0.20	-0.26 p=0.39	-0.30 p=0.32	-0.21 p=0.49	-0.25 p=0.41	-0.19 p=0.53	-0.28 p=0.36	-0.25 p=0.41	-0.19 p=0.53	-0.28 p=0.36
	0.11 p=0.76	-0.08 p=0.83	-0.20 p=0.55	-0.05 p=0.89	-0.10 p=0.78	-0.01 p=0.97	-0.19 p=0.58	-0.10 p=0.78	-0.01 p=0.97	-0.19 p=0.58
	<i>a</i>	-0.08 p=0.87	-0.12 p=0.79	0.13 p=0.79	-0.24 p=0.60	0.12 p=0.80	-0.23 p=0.63	-0.24 p=0.60	0.12 p=0.80	-0.23 p=0.63
60 msec Prepulse Interval										
r value	Categories Completed	% Errors	Trials Completed	% Perseverative Responses	Trials Correct	Perseverative Errors (%)	Non-Perseverative Responses	Trials Correct	Perseverative Errors (%)	Non-Perseverative Responses
	0.58** p=0.02	-0.64** p=0.01	-0.75** p<0.01	-0.38 p=0.16	-0.03 p=0.92	-0.40 p=0.15	-0.68** p=0.01	-0.03 p=0.92	-0.40 p=0.15	-0.68** p=0.01
	0.14 p=0.64	0.02 p=0.96	-0.01 p=0.97	-0.02 p=0.95	0.04 p=0.90	-0.05 p=0.88	0.05 p=0.86	0.04 p=0.90	-0.05 p=0.88	0.05 p=0.86
	-0.31 p=0.38	0.32 p=0.34	0.07 p=0.83	0.23 p=0.49	-0.39 p=0.24	0.29 p=0.40	0.29 p=0.39	-0.39 p=0.24	0.29 p=0.40	0.29 p=0.39
	<i>a</i>	-0.29 p=0.53	-0.33 p=0.48	-0.57 p=0.19	-0.38 p=0.41	-0.53 p=0.22	-0.04 p=0.93	-0.38 p=0.41	-0.53 p=0.22	-0.04 p=0.93
120 msec Prepulse Interval										
r value	Categories Completed	% Errors	Trials Completed	Perseverative Responses (%)	Trial Correct	Perseverative Errors (%)	Non-Perseverative Responses	Trial Correct	Perseverative Errors (%)	Non-Perseverative Responses
	0.61** p=0.02	-0.52** p=0.04	-0.48* p=0.07	-0.48* p=0.07	0.30 p=0.27	-0.50* p=0.06	-0.31 p=0.27	0.30 p=0.27	-0.50* p=0.06	-0.31 p=0.27
	-0.03 p=0.92	0.18 p=0.55	0.17 p=0.59	0.27 p=0.38	0.17 p=0.57	0.29 p=0.35	0.09 p=0.78	0.17 p=0.57	0.29 p=0.35	0.09 p=0.78
	-0.07 p=0.86	0.10 p=0.77	-0.20 p=0.55	-0.02 p=0.96	-0.35 p=0.29	0.04 p=0.91	0.19 p=0.58	-0.35 p=0.29	0.04 p=0.91	0.19 p=0.58
	<i>a</i>	0.05 p=0.91	-0.06 p=0.89	0.05 p=0.92	-0.40 p=0.38	0.07 p=0.88	0.14 p=0.77	-0.40 p=0.38	0.07 p=0.88	0.14 p=0.77

^a All CNS subjects attained 6 categories completed, thus correlations could not be computed.