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Verbal working memory in schizophrenia from the Consortium on the Genetics of Schizophrenia (COGS) Study: The moderating role of smoking status and antipsychotic medications

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ABSTRACT

Objectives: Working memory impairment has been extensively studied in schizophrenia, but less is known about moderators of the impairment. Using the Consortium on the Genetics of Schizophrenia case-control study (COGS-2), we examined smoking status, types of antipsychotic medication, and history of substance as moderators for working memory impairment in schizophrenia.

Methods: From 5 sites, 1377 patients with schizophrenia or schizoaffective, depressed type and 1037 healthy controls completed the letter–number span (LNS) task. The LNS uses intermixed letter and digit stimuli that increase from 2 up to 8 stimuli. In the forward condition, participants repeated the letters and numbers in the order they were presented. In the reorder condition, participants repeated the digits in ascending order followed by letters in alphabetical order.

Results: Schizophrenia patients performed more poorly than controls, with a larger difference on reorder than forward conditions. Deficits were associated with symptoms, functional capacity, and functional outcome. Patients who smoked showed larger impairment than nonsmoking patients, primarily due to deficits on the reorder condition. The impairing association of smoking was more pronounced among patients taking first-generation than those taking second-generation antipsychotic medications. Correlations between working memory and community functioning were stronger for nonsmokers. History of substance use did not moderate working memory impairment.

Conclusions: Results confirm the working memory impairment in schizophrenia, and indicate smoking status as an important moderator for these deficits. The greater impairment in smokers may reflect added burden of smoking on general health or that patients with greater deficits are more likely to smoke.

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1. Introduction

Working memory is defined as an ability to maintain and manipulate the internal representation of a stimulus on-line (Baddeley, 1992). Working memory impairment is profound and enduring among schizophrenia patients (Lee and Park, 2005) and has been found in relatives of schizophrenia patients (Glahn et al., 2003) and individuals with schizotypal features (Mitropoulou et al., 2005; Smith et al., 2006). Thus, working memory impairment is suggested as a promising candidate for an endophenotype. Our previous phase of the Consortium on the Genetics of Schizophrenia (COGS) study showed the endophenotype validity of working memory in behavioral and heritability family studies (Horan et al., 2008; Greenwood et al., 2011, 2013). Using a large sample of participants from the COGS Phase 2 case-control study (COGS-2), this study examined potential moderators of verbal working memory impairment in schizophrenia.

The neurobiological mechanisms and components of working memory impairment (e.g., encoding as opposed to maintenance) are established, as well as its association with community functioning (Glahn et al., 2005; Green et al., 2008; Coleman et al., 2012; Mayer et al., 2012; Bittner et al., 2014). However, the effects of demographic and clinical features on working memory in schizophrenia are poorly understood. One consideration is the high rate of cigarette smoking in schizophrenia. Nicotine metabolites and other molecules in cigarette smoking interact with the dopaminergic system and increase release of dopamine in the mesolimbic system and prefrontal cortex (Marenco et al., 2004; Tsukada et al., 2005; Brody et al., 2009). Thus, schizophrenia patients might use nicotine as self-medication to ameliorate cognitive deficits or other clinical symptoms (e.g., Zammit et al., 2003).

Consistent with this hypothesis, several studies showed that nicotine administration reduced working memory impairment and other neurocognitive deficits in schizophrenia (George et al., 2002; Jacobsen et al., 2004; Sacco et al., 2005; Barr et al., 2008). However, most of these studies were conducted on smokers and examined effects before and after nicotine abstinence, raising a question as to whether the beneficial effects of nicotine were due to the reversal of smoking withdrawal-related working memory deficit. Indeed, acute nicotine administration worsened ketamine-induced working memory deficit in healthy individuals (D'Souza et al., 2012). Studies in non-clinical samples have shown either no effect or an impairing effect of chronic nicotine administration on working memory (Park et al., 2000; Wagner et al., 2013). A related consideration is that antipsychotic medications interact with nicotine receptors in the brain. Both first- and second-generation antipsychotic medications act as noncompetitive inhibitors (Grinevich et al., 2009), and it is possible that antipsychotic medication may negate any potential effect of nicotine on working memory (Addy and Levin, 2002). The interaction between antipsychotic medication and cigarette smoking on working memory in schizophrenia has yet to be examined.

Another factor to consider is comorbidity. Schizophrenia patients have higher rates of substance use than the general population (Regier et al., 1990; Hartz et al., 2014). In the general population, history of substance abuse is associated with poorer working memory (Wareing et al., 2000; Ersche et al., 2006). The studies on comorbid substance disorder and working memory in schizophrenia had relatively small samples and produced mixed findings: some studies found better performance of patients with a history of substance use (Schnell et al., 2009; Yucel et al., 2012), whereas others found no effect of past substance abuse (Thoma and Daum, 2008; Donoghue et al., 2012; Wojtalik and Barch, 2014). A recent meta-analysis (Donoghue et al., 2012) indicated that heterogeneity across studies makes it difficult to draw firm conclusions.

The aim of the current study is to investigate potential moderators of verbal working memory impairment in schizophrenia using the letter–number span task (LNS). With large samples of patients and controls from COGS-2, we asked two questions: 1) do the following moderators affect working memory impairment in schizophrenia: cigarette smoking, antipsychotic medication, the interaction between cigarette smoking and antipsychotic medication, and past substance abuse; and 2) do any of significant moderators identified modulate the relationship between working memory and community functioning in schizophrenia.

2. Method

More details about the recruitment, the selection criteria of participants and clinical assessment methods are available in the supplementary material and the introductory article for this theme (Swerdlow et al., submitted for publication). The local institutional review boards of each site approved the study. All participants provided informed consent and were compensated for their participation.

2.1. Procedures

The LNS (Gold et al., 1997; Wechsler, 1997) was administered as part of the COGS-2 research protocol. For the LNS task, the quality assurance (QA) site (University of California Los Angeles) performed QA checks periodically by verifying any score that was an outlier, defined as scores that were outside plus or minus 1.5 SD of the mean within each group. Every outlier score was then compared to the paper copy at the local site to confirm that it was accurate and valid (e.g., no data entry mistake, subjects understood the nature of the task, etc.).

The LNS task consisted of two conditions: the "forward" and "reorder" conditions. Both conditions employed a set of intermixed letters and digits that experimenters verbally presented at a rate of one per second. The number of characters (letters or digits) increased by one on each trial starting from the length of 2 stimuli, up to a maximum length of 8 stimuli. Each trial consisted of three sequences of the same length. In the forward condition, participants were asked to repeat the letters and numbers in the same order as they were presented. In the reorder condition, participants were asked to repeat the digits in ascending order first and then the letters in alphabetical order. Both conditions were discontinued if the participant failed all three sequences of the same length. The score for each condition was the total number of correctly recalled sequence (i.e., maximum score for each condition = 21).

Both patients and controls received the Global Assessment of Function Scale (GAF; Hall, 1995). Additional clinical assessment for patients included a modified versions of the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984a) and Positive Symptoms (SAPS; Andreasen, 1984b), the Brief University of California San Diego Performance-based Skills Assessment (UPSA; Mausbach et al., 2007) as a measure of functional capacity, and the Role Functioning Scale (RFS) (RFS; McPheeters, 1984) for community functioning. The UPSA assesses ability to perform everyday tasks necessary for independent community functioning (Twamley et al., 2002).

2.2. Statistical analysis

The main analytic tool for this study is the generalized linear model as it provides a unified statistical framework for univariate and repeated measures analysis of variance (ANOVA) and allows for covariate adjustment. To compare demographic and clinical characteristics, we conducted a series of univariate ANOVA with group and site as between-subject factors.

To examine the patient-group differences on LNS, we conducted a series of repeated measures ANOVA in a step-wise way: first, a 2 by 2 repeated measures ANVOA with condition as within-subject factor and group as between-subject factor was performed. Second, to examine whether significant effects from this analysis can be explained by key demographic differences, we conducted a 2 by 2 repeated measures ANOVA with key demographics as covariates. Finally, we include site as additional covariate to explore whether site could explain any

additional variance. To examine the potential moderators for working memory impairment in schizophrenia, we conducted a series of repeated measures ANOVA for each moderator variable, adjusted for covariates if needed. For any significant effect from ANOVA and repeated measures ANVOA, we also present Cohen's f^2 as a measure of effect size (Cohen, 1988). The Cohen's f^2 indicates the estimate of the amount of variances that can be explained by certain variables in multivariate models. f^2 of 0.02 represents a small; f^2 of 0.15 represents a moderate; and f^2 of 0.35 indicates a large effect size. Bivariate correlation was examined between performance of LNS and measures on functional and clinical symptoms to examine the association between verbal working memory and functional outcome as well as clinical symptoms. Correlations between patients who currently smoke and those who never smoked were compared using Fisher's r to z transformation.

3. Results

3.1. Demographic and clinical characteristics of participants across 5 sites

2414 participants (1377 patients with schizophrenia or schizoaffective disorder, depressed type and 1037 controls) had performance data on the LNS; see Table 1 for demographic and clinical characteristics across the 5 sites. There were significant site differences and group differences on key demographic characteristics. For age, there were significant effects of site ($F_{4,2405} = 40.54$, $p < .001$, $f^2 = 0.06$), group ($F_{4,2405} = 266.39$, $p < .001$, $f^2 = 0.10$) and a significant site by group interaction ($F_{4,2405} = 12.10$, $p < .001$, $f^2 = 0.01$). Overall patients were older than controls, with the differences significant within each site except site 2. Similarly, for personal education, there were significant effects of site ($F_{4,2405} = 5.33$, $p < .001$, $f^2 = 0.006$) and group ($F_{4,2405} = 795.22$, $p < .001$, $f^2 = 0.31$) and a significant site by group interaction ($F_{4,2405} = 12.33$, $p < .001$, $f^2 = 0.01$). Patients had lower personal education than controls. For parental education we also found significant effects of site ($F_{4,2205} = 3.53$, $p < .01$, $f^2 = 0.005$) and group ($F_{4,2205} = 144.76$, $p < .001$, $f^2 = 0.06$), as well as a significant site by group interaction ($F_{4,2205} = 4.67$, $p < .01$, $f^2 = 0.007$). For racial distribution, 3 major races (i.e., Asian, African-American, Caucasian) were compared, and there was a significant site effect when examining patients and controls separately ($X^2 = 172.16$, $p < .001$, and $X^2 = 72.08$, $p < .001$, respectively). For clinical characteristics of patients across sites, we found significant site effects for clinical symptoms on the SANS ($F_{4,1175} = 278.87$, $p < .001$, $f^2 = 0.95$) and SAPS ($F_{4,1173} = 17.48$, $p < .001$, $f^2 = 0.05$), as well the UPSA ($F_{4,1145} = 10.84$, $p < .001$, $f^2 = 0.03$), SOF ($F_{4,1168} = 27.48$, $p < .0001$, $f^2 = 0.09$), and RFS Total ($F_{4,820} = 12.06$, $p < .001$, $f^2 = 0.05$). Across sites, patients also differed on smoking status (i.e., nonsmokers who never smoked and current smokers based on self-report) ($X^2 = 33.52$, $p < .001$), past-mood disorders ($X^2 = 128.77$, $p < .001$) and past substance disorders ($X^2 = 93.51$, $p < .001$).

3.2. Patient-control differences on LNS

A 2 by 2 repeated measures ANOVA with condition as within-subject factor and group as between-subject factor showed a significant effects of condition ($F_{1,2408} = 3595.73$, $p < .001$, $f^2 = 1.49$), group ($F_{1,2408} = 731.21$, $p < .001$, $f^2 = 0.30$) and a significant condition by group interaction ($F_{1,2408} = 14.11$, $p < .001$, $f^2 = 0.005$). Patients performed worse than controls, and the group difference was more pronounced on reorder condition (see Fig. 1). The impairment of these patients on the reorder condition ($f^2 = 0.29$) was similar to the impairment seen previously in the COGS-1 samples ($f^2 = 0.22$) (Horan et al., 2008).

Table 1
Demographic and clinical characteristics of schizophrenia patients and healthy controls.

	Site 1		Site 2		Site 3		Site 4		Site 5	
	Control	Patients	Control	Patients	Control	Patients	Control	Patients	Control	Patients
N	222	351	209	259	195	269	195	256	216	242
Age	40.1 (12.7)	46.6 (11.0)	46.5 (8.2)	48.4 (10.5)	35.6 (12.3)	45.8 (10.1)	32.6 (12.5)	43.8 (11.2)	37.3 (14.6)	46.3 (11.8)
% Female	57.2	32.7	38.8	26.3	54.4	33.1	52.8	36.7	49.5	23.1
Personal Edu.	14.8 (2.1)	12.3 (1.9)	14.7 (1.6)	12.8 (1.8)	15.5 (2.3)	11.9 (2.1)	14.8 (2.3)	12.5 (2.3)	15.1 (2.4)	13.1 (1.8)
Parental Edu.	13.4 (3.1)	12.5 (2.9)	13.4 (2.6)	12.3 (3.3)	14.3 (3.2)	11.8 (2.9)	14.2 (2.8)	12.5 (3.1)	14.2 (3.0)	12.8 (2.9)
% Hispanic	19.4	18.5	15.3	15.8	10.3	22.7	6.7	4.7	6.5	5.4
Race										
Native American	2	5	0	1	0	1	0	1	1	2
Asia	26	7	11	14	26	3	12	7	13	14
Pacific Islander	3	4	2	4	1	1	0	0	7	5
African American	38	64	55	100	67	149	68	172	17	52
Caucasian	112	192	129	118	92	99	100	63	155	128
More than one	41	79	11	22	8	10	15	13	23	41
Not reported	0	0	1	0	1	6	0	0	0	0
% Right handed	84.7	88.4	83.7	89.2	89.2	85.5	89.2	84.8	83.8	82.2
Smoking										
Never:Past:Now	177:23:22	107:41:203	174:8:27	102:16:141	171:1:23	106:11:152	178:0:17	122:1:133	190:0:26	140:1:101
# cigarettes/day	9.3	15.0	10.2	16.3	8.1	11.1	7.2	13.5	6.8	11.1
% Past mood dis	2.7	32.4	4.3	23.2	1.0	12.6	12.8	32.8	15.3	28.5
% Past sub dis	7.7	52.6	17.2	44.4	0.5	17.5	13.8	51.2	19.9	47.1
GAF	89.7 (7.6)	40.6 (4.9)	81.7 (8.3)	45.6 (9.3)	91.9 (5.4)	48.9 (8.5)	87.1 (6.1)	43.8 (9.5)	82.3 (7.1)	40.5 (4.2)
Age of onset		22.5 (7.4)		21.8 (7.7)		22.1 (5.3)		21.5 (6.2)		23.1 (7.1)
Global_SANS		16.2 (4.0)		9.2 (4.4)		4.6 (3.7)		10.4 (4.0)		12.8 (3.7)
Global_SAPS		8.1 (4.1)		6.1 (4.2)		5.5 (3.1)		7.5 (4.2)		6.9 (3.6)
UPSA Total		71.8 (15.5)		73.1 (14.1)		65.7 (17.2)		70.1 (15.3)		73.2 (13.4)
SOF Total		45.8 (5.7)		48.3 (5.9)		46.1 (6.0)		47.5 (6.0)		42.9 (5.1)
RFS Total		14.3 (4.2)		15.4 (4.6)		15.0 (3.5)		17.4 (4.5)		15.4 (3.0)
RFS Work		1.6 (1.4)		2.2 (1.5)		3.5 (1.1)		3.7 (1.6)		3.2 (1.2)
RFS INDEP		5.0 (1.4)		4.4 (1.3)		3.7 (.9)		5.0 (1.2)		5.3 (1.2)
RFS FAMILY		4.3 (2.0)		4.6 (1.8)		3.9 (1.1)		4.9 (1.5)		4.2 (1.4)
RFS SOCIALNET		3.3 (1.9)		4.1 (1.7)		3.7 (1.0)		3.7 (1.7)		2.7 (1.3)

RFS Total: Site 1, N = 242; site 2, N = 176; site 3, N = 220; site 4, N = 166; site 5, N = 161.
GAF: GAF of the last month.

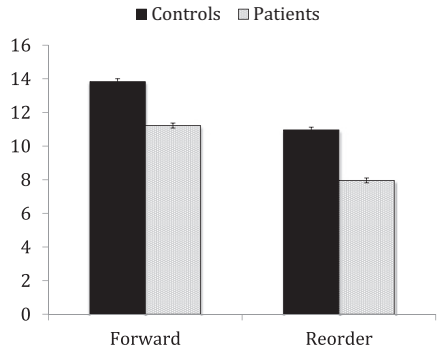

Fig. 1. Performance of schizophrenia patients and controls on LNS.

Next, we examined whether demographics or sites could explain group differences on LNS by conducting a 2 by 2 repeated measures ANOVA with covariates. First, we included age and parental education as covariates, and both were significant (age, $F_{1,2207} = 55.89$, $p < .001$, $f^2 = 0.02$; parental education, $F_{1,2207} = 100.81$, $p < .001$, $f^2 = 0.04$). Even with these covariates main effects and the interaction remained significant. Second, we included site as an additional covariate. The site effect was significant ($F_{1,2206} = 27.51$, $p < .001$, $f^2 = 0.01$), but site did not interact with other factors. Thus, the patient-control difference and group by condition interaction on LNS were not explained by demographic differences between groups or across sites.

Table 2
Demographic and clinical characteristics of nonsmoker schizophrenia patients and smoker schizophrenia patients across sites.

	Nonsmoker	Smokers	Statistics
N	577	730	
Age	45.6 (11.8)	46.8 (10.1)	$F_{1,1306} = 4.03$, $p < .05$, $f^2 = 0.003$
% Female	34.3	28.5	$X^2 = 5.10$, $p < .02$
Personal Edu.	13.1 (2.1)	12.1 (1.9)	$F_{1,1306} = 44.57$, $p < .001$, $f^2 = 0.05$
Parental Edu.	12.6 (3.3)	12.3 (2.8)	$F_{1,1135} = 2.38$, NS
% Hispanic	14.2	13.6	
Race			$X^2 = 15.14$, $p < .01$
Native American	5	4	
Asia	27	16	
Pacific Islander	5	9	
African American	197	319	
Caucasian	266	301	
More than one	73	79	
Not reported	4	2	
% Right handed	86.0	86.2	$X^2 = .14$, NS
% Past mood dis	26.9	24.9	$X^2 = 2.25$, NS
% Past sub dis	27.4	53.4	$X^2 = 89.76$, $p < .001$
GAF	45.0 (8.5)	42.8 (7.7)	$F_{1,1289} = 23.02$, $p < .001$, $f^2 = 0.017$
Age of onset	22.5 (7.0)	22.0 (6.7)	$F_{1,1292} = 1.92$, NS
Global_SANS	10.4 (5.3)	11.2 (5.8)	$F_{1,1299} = 6.19$, $p < .05$, $f^2 = 0.004$
Global_SAPS	6.3 (3.9)	7.3 (4.1)	$F_{1,1291} = 17.53$, $p < .001$, $f^2 = 0.013$
UPSA Total	71.8 (15.3)	70.1 (15.5)	$F_{1,1266} = 4.03 = 8$, $p < .05$, $f^2 = 0.003$
SOF Total	47.1 (6.2)	45.3 (5.7)	$F_{1,1293} = 23.39$, $p < .001$, $f^2 = 0.021$
RFS Total	16.5 (4.2)	14.6 (3.9)	$F_{1,906} = 50.34$, $p < .001$, $f^2 = 0.055$
RFS Work	3.2 (1.7)	2.5 (1.5)	$F_{1,906} = 32.72$, $p < .001$, $f^2 = 0.036$
RFS INDEP	4.9 (1.3)	4.4 (1.3)	$F_{1,906} = 37.87$, $p < .001$, $f^2 = 0.041$
RFS FAMILY	4.7 (1.5)	4.1 (1.7)	$F_{1,906} = 24.40$, $p < .001$, $f^2 = 0.026$
RFS SOCIALNET	3.6 (1.6)	3.4 (1.5)	$F_{1,906} = 4.16$, $p < .05$, $f^2 = 0.004$

RFS Total: Nonsmokers (N = 393) and current (N = 514).
GAF: GAF of the last month.

3.3. Moderator variables for verbal working memory within the schizophrenia sample

We examined whether smoking status moderates impaired performance of schizophrenia patients on LNS. Table 2 presents demographic and clinical characteristics of 577 nonsmokers (never smoked) and 730 smokers (currently smoking). A 2 by 2 repeated measures ANOVA with condition as within-subject factor and smoking status as between-subject factor (see Fig. 2) showed a significant effect of condition ($F_{1,1301} = 2375.27$, $p < .001$, $f^2 = 1.825$) and a significant condition by smoking status interaction ($F_{1,1306} = 7.84$, $p < .01$, $f^2 = 0.006$). Post-hoc analyses showed that although the groups were comparable on forward ($F_{1,1301} = .03$, NS), nonsmokers performed better on the reorder condition than smokers ($F_{1,1301} = 7.20$, $p < .01$, $f^2 = 0.005$). To explore whether demographic differences (i.e., age) between groups explained the interaction, we conducted a 2 by 2 repeated measures ANOVA with age as a covariate. The main effect of age was significant ($F_{1,1300} = 32.04$, $p < .001$, $f^2 = 0.024$), but no other effects were altered. We also examined the effect of age using age-matched subgroups of smokers and nonsmokers (577 nonsmokers and 715 smokers) and found that no effect was altered. Finally, when site was added as an additional covariate, no other effect was significant. Thus, the modulation of LNS performance by the smoking status was not explained by demographic differences between the two smoking groups or across site.

To examine antipsychotic medication as a potential moderator we compared performance of 4 subgroups of patients based on type of antipsychotic medication (105 patients taking first-generation antipsychotics, 993 patients taking second-generation antipsychotics, 130 patients taking both first- and second-generation antipsychotics, and 149 patients taking no antipsychotic medication). The supplementary table shows demographic and clinical characteristics. A 2 by 2 repeated measures ANOVA with condition as within-subject factor and medication subgroup as between-subject factor found a significant effect of condition ($F_{1,1369} = 1253.01$, $p < .001$, $f^2 = 0.98$) and a significant condition by medication interaction ($F_{1,1369} = 4.61$, $p < .01$, $f^2 = 0.010$) (see Fig. 3). All patients performed better on the forward than reorder conditions; 4 medication groups did not differ on the forward, but patients taking no antipsychotic medication performed better on the reorder than other medication groups.

To examine the interaction of antipsychotic medication and smoking status, we examined the effect of smoking status separately for patients who take first- and second-generation antipsychotic medications (Ns = 103 and 946 respectively). For this analysis we excluded patients who were taking both types of medication. The patients taking first-generation antipsychotic medication included 41 nonsmokers and 62 smokers (see Fig. 4a). The ANOVA showed a significant effect of condition ($F_{1,101} = 155.33$, $p < .001$, $f^2 = 1.537$) and a significant condition by smoking status interaction ($F_{1,101} = 6.15$, $p < .05$, $f^2 = 0.060$). Post-hoc analyses showed that, although both groups performed better on

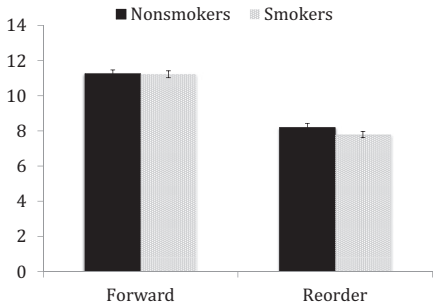

Fig. 2. The modulation of LNS performance by smoking status.

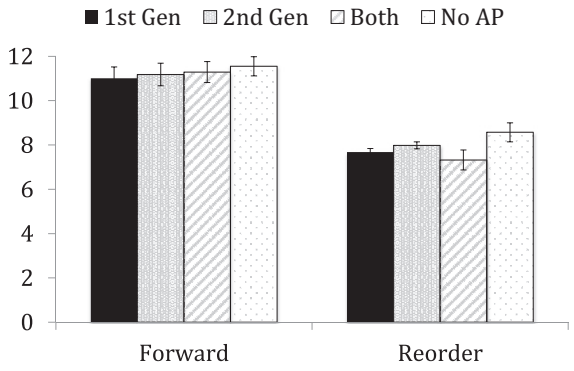

Fig. 3. The modulation of LNS performance by antipsychotic medications.

the forward than reorder conditions, the condition effect was more pronounced for smokers than nonsmokers. The second-generation antipsychotic group included 423 nonsmokers and 523 smokers (see Fig. 4b). A 2 by 2 repeated measures ANOVA with condition as within-subject factor and smoking status as between-subject factor showed a significant effect of condition ($F_{1,944} = 1762.61$, $p < .001$, $f^2 = 1.867$), but no other effect was significant. Both smokers and nonsmokers taking second-generation antipsychotic medications showed better performance on the forward than reorder conditions.

As another potential moderator, we examined the effect of history of substance use on LNS performance. There were 589 patients with a history of substance use and 784 without such a history. A 2 by 2 repeated measures ANOVA showed a significant effect of condition ($F_{1,1372} = 2468.44$, $p < .001$, $f^2 = 1.80$), but no other effect.

3.4. Correlates of verbal working memory within the schizophrenia group

Table 3 shows association between LNS performance and clinical symptoms and functioning in the schizophrenia sample. Performance on the forward condition was negatively correlated with SANS global score and positively correlated with UPSA total, and RFS work, RFS Independent Living and RFS Total. Similarly, performance on the reorder condition was negatively correlated with SANS global score and SAPS global score and positively related to UPSA total and all scales of RFS except social. Smoking status further moderated these associations. Performance on both conditions was more strongly associated with clinical symptoms and functioning in nonsmokers than smokers. For the forward condition, these differences reach significance for the RFS Total ($p < .05$). For the reorder condition, there were significant differences in association with SANS global, RFS Work, RFS Family and RFS Total between nonsmokers and smokers (ps < .05).

Table 3
Association between performance on LNS and clinical symptoms and functional outcome.

	Total sample of schizophrenia patients		Nonsmoker		Smoker	
	Forward	Reorder	Forward	Reorder	Forward	Reorder
SANS Global	−.10**	−.09**	−.13**	−.15**	−.07*	−.04
SAPS Global	−.03	−.06*	−.02	−.08*	−.06	−.05
UPSA	.29**	.39**	.32**	.44**	.28**	.35**
RFS						
Work	.13**	.14**	.18**	.21**	.11*	.05
Independent	.06*	.15**	.13**	.14**	.01	.11*
Family	.04	.08**	.12*	.15**	−.01	.01
Social	−.01	.03	.04	.05	−.02	.01
Total	.09**	.15**	.17**	.21**	.03	.07

* <.05.
** <.01.

4. Discussion

With a large sample of schizophrenia patients and controls, this study examined the role of smoking status, type of antipsychotic medication, and history of substance use as moderators for verbal working memory impairment in schizophrenia. COGS-2 included 5 sites, and we observed significant variation on demographic and clinical characteristics across sites. However, these site differences did not explain our main findings. Overall, schizophrenia patients showed poorer performance than controls on LNS, and the group difference was larger on reorder than forward conditions, consistent with previous findings (Gold et al., 1997; Pukrop et al., 2003; Horan et al., 2008). Smoking status, but not history of substance use, moderated working memory performance. Patients who were currently smoking performed worse than nonsmoking patients, and this effect was more pronounced on the reorder condition. Patients who take no antipsychotic medication showed better performance on the reorder conditions compared to other medication groups. Smoking status also interacted with antipsychotic medication, such that the adverse effect of smoking on LNS reorder performance was more pronounced among patients taking first-generation antipsychotic medications. Finally, better performance on LNS was associated with lower clinical symptoms and better indices of functioning in schizophrenia, but several of these associations were significantly weaker among patients who were smoking.

Previous studies on smoking and working memory in schizophrenia showed beneficial effects of smoking by assessing performance before and after smoking abstinence. Our study examined the effect of smoking status on performance rather than the acute effects of cigarette smoking. The impairing association of smoking status we found is consistent with findings in non-psychiatric samples (Jacobsen et al., 2005;

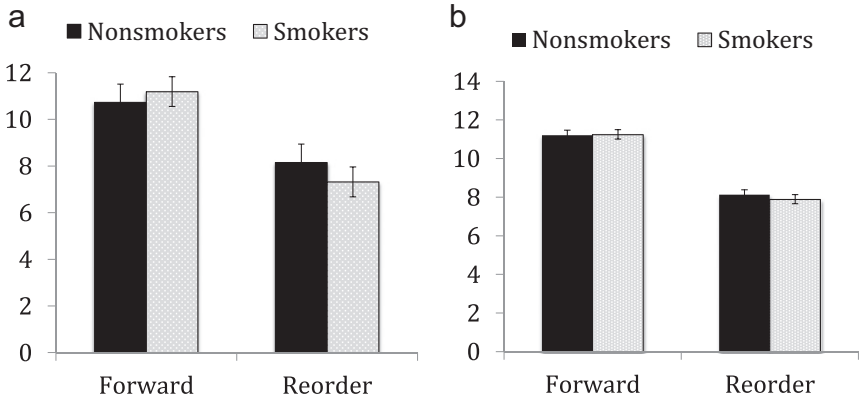

Fig. 4. The modulation of LNS performance by smoking status and antipsychotic medications. a) LNS performance by smoking status among patients taking first-generation antipsychotic medications; and b) LNS performance by smoking status among patients taking second-generation antipsychotic medication.

Sabia et al., 2008; Chamberlain et al., 2012), which showed detrimental effects of chronic smoking on cognitive function, including working memory. Our finding is also in line with recent studies using diffusion tensor imaging that showed lower white matter integrity in smoking compared to nonsmoking schizophrenia patients in several brain regions, including areas linked to working memory such as the frontal lobe (Zhang et al., 2010; Cullen et al., 2012). Thus, the beneficial effect of acute nicotine intake on cognition in schizophrenia seen in previous studies might be due to the reversal of withdrawal (Sacco et al., 2005; Falcone et al., in press). Indeed, smoking cessation impairs working memory (Jacobsen et al., 2004). The effect of abstinence is modulated by catechol-O-methyltransferase (Loughead et al., 2009), and variability in this gene has been shown to be associated with working memory in both healthy and clinical samples (Tunbridge et al., 2006; Tan et al., 2007).

This study also found that patients who did not take any antipsychotic medication performed better on the reorder condition compared to patients who were taking antipsychotic medication. Although our finding is consistent with previous studies on the negative effect of antipsychotic medications on working memory (Castner et al., 2000; Reilly et al., 2006, 2007), it should be noted that the COGS-2 cross-sectional design did not allow us to draw any firm conclusion about the casual relationship between antipsychotic medication and verbal working memory in schizophrenia. In other words, it is possible that better performance in non-medicated patients could be due to certain personal characteristics (e.g., not requiring medication) rather than the direct effect of antipsychotic medication per se (see Swerdlow et al., submitted for publication about further discussion on antipsychotic medications and COGS endophenotypes). This study further showed that the negative effect of smoking on working memory was more pronounced among patients taking first-generation antipsychotic medications. There were no major demographic or clinical differences between patients taking first- and second-generation antipsychotic medications. Thus, the poorer performance of smoking patients with first-generation antipsychotic medication cannot be explained by these features. Chronic cigarette smoking appears to decrease in D1-like receptors in the brain (Bruijnzeel and Markou, 2005). Both first- and second-generation antipsychotic medications may affect working memory, possibly due to down-regulation of D1 receptors and D2 receptor blockade (Castner et al., 2000; Reilly et al., 2006, 2007) or an interaction of nicotine stimulation with dopamine hypofunction. Thus, chronic smoking along with antipsychotic treatments could contribute to impaired working memory performance of schizophrenia patients. Further studies will be needed to determine the mechanism for this effect and why it appears to be more pronounced in patients taking first-generation antipsychotic medication.

We also observed that better working memory performance was associated with higher indices of community functioning, which is consistent with previous findings on working memory as an important cognitive determinant of poor functioning in schizophrenia (Green et al., 2000; Harvey et al., 2011; Vesterager et al., 2012). Further, several of these associations were significantly weaker among smokers versus nonsmokers. Partly due to the association of cognition to daily functioning through functional capacity, there are considerable efforts to develop psychosocial and pharmacological interventions for cognitive deficits, including working memory impairment, in schizophrenia (Green et al., 2004; Nuechterlein et al., 2004). The pathway from working memory to functional outcome in schizophrenia may be moderated by smoking status.

In summary, in these large samples of patients and controls across 5 sites, verbal working memory impairment was clearly present and larger for patients who currently smoke. The effect of smoking status also interacted with types of antipsychotic medications: the impairing effect of smoking on reorder was more pronounced among patients taking first-generation antipsychotics. History of substance use did not moderate LNS performance. Studies with more specific subtypes of working memory tasks instead of a relatively global measure such as the LNS will be able to investigate the underlying mechanisms through which these moderators affect working memory impairment and their clinically important associations to real world functioning. Future COGS studies will examine the genomic substrates of working memory and the relationship with other COGS-2 endophenotypes, similar to what we have done in COGS 1 (Seidman et al., 2015).

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Contributors

Dr. Lee completed all statistical analyses and wrote the first draft of this manuscript. Dr. Green conducted quality assurance for the LN measures across sites. Dr. Sprock conducted quality assurance for all data entered on the COGS2 website. All other authors participated in aspects of study design, including subjects recruitment, phenotyping, and validation of the clinical and endophenotype data. All authors were responsible for reviewing and approving the final version of the manuscript.

Conflict of interest

Dr. Green has been a consultant to AbbVie, Biogen, DSP, EnVivo/Forum and Roche, and he is on the scientific advisory board of Mnemosyne. He has received research funds from Amgen. Dr. Lazzeroni is an inventor on a patent application filed by Stanford University on genetic polymorphisms associated with depression. Dr. Light has served as a consultant for Astellas, Forum, and Neuroverse. Dr. Nuechterlein has received unrelated research support from Janssen Scientific Affairs, Genentech, and Brain Plasticity, Inc., and has consulted to Genentech, Otsuka, Janssen, and Brain Plasticity, Inc. Dr. Swerdlow has been a consultant for Genco Sciences, Ltd. All other authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2014.08.014.

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