



Nicotine in action: cigarette smoking modulated homotopic functional connectivity in schizophrenia

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Abstract

Cigarette smoking is intimately associated with both early onset and increased severity of schizophrenia. The self-medication hypothesis suggests that nicotine can relieve or restore neurocognitive deficits and symptoms associated with schizophrenia. Schizophrenia patients and healthy subjects who smoked showed deficits in communication between their hemispheres. These homotopic connectivity mechanisms associated with both schizophrenia and smoking comorbidity were largely unknown until now. A mixed sample including patients with schizophrenia (22 smokers and 27 non-smokers) and healthy controls (22 smokers and 21 non-smokers) based on clinical diagnoses and cigarette dependence were recruited for the current study. All subjects underwent resting-state functional magnetic resonance imaging to determine possible interactions between schizophrenia and smoking, and to determine the main effects of schizophrenia and smoking on homotopic functional connectivity. Decreased homotopic functional connectivity of the subgenual anterior cingulate cortex suggested a main effect of schizophrenia and smoking—an additive effect. Furthermore, we found an antagonistic interaction effect between schizophrenia and smoking located in the ventrolateral prefrontal cortex (VLPFC). In addition, the connectivity strength of the bilateral VLPFC was negatively correlated with the Positive and Negative Syndrome Scale Negative scores and positively correlated with lifetime smoking. These results suggest that smoking has multiple effects on the modulation of interhemispheric connectivity in schizophrenia. Our findings provide valuable information underlying the pathophysiological mechanisms of schizophrenia and offer a potential target for future clinical treatment of schizophrenia and smoking comorbidity.

Keywords Cigarette smoking · Homotopic functional connectivity · Schizophrenia · Self-medication · Ventrolateral prefrontal cortex · Subgenual anterior cingulate cortex

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Introduction

The schizophrenia population, relative to the general population, has an exceptionally high prevalence (70% ~ 80%) of cigarette smoking (de Leon and Diaz 2005). The addiction vulnerability hypothesis infers that schizophrenia patients with smoking undervalue the potential negative consequences of substance abuse (Krystal et al. 2006) and that smoking increases severity of disease in schizophrenia patients with smoking (Schwartz 2007). Alternatively, the self-medication hypothesis infers that smoking alleviates the negative symptoms of schizophrenia and reduces side effects associated with the use of antipsychotics (Winterer 2010). Although both epidemiological and symptomatic links between schizophrenia and smoking are well established, a neurophysiological mechanism remains unclear.

A promising way to understand the biological basis of schizophrenia and smoking comorbidity may be through mapping brain dynamics. Recently, task-free functional magnetic resonance imaging (fMRI) was shown to circumvent several interpretative ambiguities of endogenous or spontaneous neural responses to smoking-related cues or cravings in schizophrenia patients (Potvin et al. 2016; Jacobsen et al. 2004; Moran et al. 2017; Khan et al. 2018). Another study on schizophrenia and smoking comorbidity revealed that inherent disease-related circuits, including the insular and dorsal anterior cingulate circuits, were weakened in smokers with schizophrenia (Moran et al. 2012). Notably, nicotine was shown to normalize, and even reverse, pathological states in the parietofrontal network, giving support to the self-medication hypothesis (Smucny et al. 2016; Adler et al. 1998). However, these studies did not examine possible direct interactions between schizophrenia and smoking.

Interhemispheric connections play a key role in the etiology of schizophrenia and disease related to smoking. A growing body of evidence has revealed that both structural and functional asymmetry are altered in schizophrenia (Baker et al. 2014; Zhang et al. 2015; Ribolsi et al. 2009; Jalili et al. 2010). Converging evidence from brain morphological and structural studies demonstrated decreased callosal thickness in schizophrenia patients and lower callosal axonal integrity in dependent smokers (Lin et al. 2013; Savjani et al. 2014; Walterfang et al. 2008, 2009; Bersani et al. 2010). Recently, a study demonstrated that callosal as well as extracallosal anatomical connections play a role in the maintenance of interhemispheric functional connectivity (Roland et al. 2017). It would be logical that brain asymmetry and the callosal deficits may lead to functional abnormalities between the two hemispheres. Furthermore, intrinsic functional connectivity between the hemispheres was shown to be aberrant in the default mode network, sensorimotor network, and prefrontal cortex (PFC) of schizophrenia patients (Camchong et al. 2009; Hoptman et al. 2012; Guo et al. 2014; Chang et al. 2015). Moreover, nicotine increased homotopic functional connectivity in the PFC, which was involved in the accumulative effects of smoking (Yu et al. 2017). Finally, both schizophrenia patients and smokers showed abnormal homotopic functional connectivity in the PFC (Chang et al. 2015; Yu et al. 2017). Yet, to date, there is no study on smoking and schizophrenia comorbidity regarding functional connectivity changes between the brain hemispheres.

We explored whether there was a homotopic functional connectivity interaction between schizophrenia and smoking. Specifically, we subdivided schizophrenia patients and healthy controls into smoking and non-smoking groups, and measured homotopic functional connectivity using voxel-mirrored homotopic connectivity (Kelly et al. 2011; Zuo

et al. 2010). We hypothesized that i) both the effect of schizophrenia and smoking would show abnormal homotopic connectivity in the PFC (Chang et al. 2015; Yu et al. 2017), and we aimed to test whether main effects of these two variables additively affected common brain regions; and ii) the effects of schizophrenia diagnosis on homotopic connectivity would interact with the effects of smoking, and we aimed to determine the nature of such an interaction.

Methods and materials

Subjects

Fifty-six schizophrenia patients and 43 age-matched healthy controls were recruited for the current study. Controls had no history of neurological disorders or psychiatric illnesses and no gross abnormalities were evident on brain MR images. Diagnosis of schizophrenia was confirmed using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (SCID-I/P, Chinese version) by trained physicians or clinical psychologists. Subjects were excluded if: i) they were < 16 of age; ii) they had no current (last 12 months) comorbid substance use disorder (other than cigarette); or iii) if they had concomitant neurologic disorders. Three patients were excluded due to incomplete scanning, and four patients were excluded from further analyses, due to excessive head motions. Finally, 49 patients were confirmed for further analysis. Five patients were first-episode and 44 were chronic schizophrenia patients. Thirty-nine patients who took antipsychotic medication were clinically medication stable (> 3 months with no change in medication). Besides antipsychotic drugs, no other drug was continuously used more than 1 week within the last month. Symptom severity was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987).

Written informed consent was obtained from all patients and healthy controls according to the study protocol. All examinations were carried out under the guidance of the Declaration of Helsinki 1975. The protocol was reviewed and approved by the Local Medical Ethics Committee of the First Affiliated Hospital of Chongqing Medical University.

Healthy controls were divided into two groups: a smoking group (HCsm, $n = 22$, all right handed, 19 males, mean age \pm SEM = 34.55 ± 2.14 years, mean education \pm SEM = 14.59 ± 0.63 years) and a non-smoking group (HCnos, $n = 21$, all right handed, 14 males, mean age \pm SEM = 31.43 ± 1.94 years, mean education \pm SEM = 12.71 ± 0.76 years). Schizophrenia patients were also divided into a smoking group (SCHsm, $n = 22$, all right handed, 19 males, mean age \pm SEM = 29.45 ± 2.12 years, mean education \pm SEM = 11.05 ± 0.54 years) and

a non-smoking group (SCHnos, $n = 27$, all right handed, 12 males, mean age \pm SEM = 30.85 ± 1.68 years, mean education \pm SEM = 11.78 ± 0.64 years). Subjects were considered to be smokers if they smoked daily any numbers of cigarettes for ≥ 1 year. Subjects were considered non-smokers if they never smoked or were completely abstinent in the use of all nicotine products. Nicotine addiction severity was assessed using the 6-item Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al. 1991). Smokers were encouraged to smoke a cigarette prior to scanning to avoid withdrawal-related imaging after-effects. All subjects refrained from smoking 30 min before scanning to avoid an immediate nicotine peak (Addicott et al. 2015; Galvan et al. 2011). In addition, we collected data on current use of tobacco products, number of cigarettes smoked per day, and onset of smoking age.

Imaging protocol

Functional images were acquired on a 3.0-Tesla MRI system (GE Medical Systems, Waukesha, WI, USA) at the First Affiliated Hospital of Chongqing Medical University. All subjects were instructed to lie in the scanner, keep their eyes closed but stay awake. Foam padding was used to minimize head motion for all subjects. Functional images were acquired using an echo-planar imaging sequence (TR = 2000 ms, TE = 30 ms and flip angle = 90°). Thirty-three transverse slices (field of view = 220×240 mm², matrix = 64×64 , slice thickness = 4 mm, and 240 volumes) that aligned along the anterior commissure–posterior commissure line were acquired with a total scan time of 480 s. At the end, subjects were asked if they had fallen asleep during the scanning.

Data preprocessing

Data preprocessing was performed using the DPABI (Yan et al. 2016) (DPABI2.3 revision 170,105, <http://rfmri.org/dpabi>), which is based on statistical parametric mapping (SPM8, <http://www.fil.ion.ucl.ac.uk/spm>). The first ten images were discarded, after which the remaining images were corrected for temporal differences and head motion (cut off < 3 mm or 3°). To account for differences in the geometric configuration of the cerebral hemispheres, we further transformed the preprocessed functional images to a symmetric space using the following procedure. In line with our previous works (Ji et al. 2014; Liao et al. 2017): i) The functional images were normalized to the Montreal Neurological Institute space using the echo-planar imaging template in the SPM8 toolkit and resampled to $3 \times 3 \times 3$ mm³; ii) these normalized images were averaged for all subjects to create a mean normalized image; iii) this mean normalized image was then averaged with its left-right

mirrored version to generate a group-specific symmetrical template in all subjects; and iv) normalized images were registered to the symmetric template. Next, using linear regression, we removed nuisance variables, including motion parameters (Friston 24-parameter model) (Friston et al. 1996), global signal, ventricular signal and white matter signal. Frame-wise displacement (FD) was calculated for each time point (Power et al. 2012); four participants with mean FD value exceeding the 0.5 mm were excluded for further analyses. Functional images were then spatially smoothed with an 8-mm full-width at half-maximum isotropic Gaussian kernel. Finally, we: i) corrected for linear trends; ii) passed images through a band-pass filter (0.01–0.08 Hz); and iii) scrubbed bad time points identified as image frames with FD (> 0.5 mm). Along with the bad time points, the preceding point, as well as the two following points, were used for Piecewise cubic Hermite interpolation (Ji et al. 2015).

Homotopic functional connectivity

Homotopic functional connectivity quantifies the intrinsic functional connectivity between each voxel in one hemisphere and its mirrored counterpart in the opposite hemisphere (Kelly et al. 2011; Zuo et al. 2010). We therefore removed three voxels from the middle of each image, to eliminate the impact of similar signals from neighboring voxels in the middle of the brain. We computed the Pearson's correlation coefficients between the time series of every pair of symmetrical interhemispheric voxels. The resulting correlations for each paired voxel constituted a homotopic functional connectivity map (Fisher *r*-to-*z* transformation) and were used for subsequent second-level group analyses.

Demographic and clinical data statistical analysis

All data were analyzed using GraphPad Prism 6 (GraphPad Software, Inc.). The Chi-square test (χ^2) was used for sex and handedness. Two-sample *t*-tests or the Mann-Whitney *U*-test (the data is not normally distributed) were used for the other demographic characteristics and/or clinical scores. Differences were considered significant at $P < 0.05$.

Statistical analyses

Using the full factorial model in SPM8, we conducted two-way analysis of variance (ANOVA) to analyze the two factors—diagnosis group (schizophrenia and healthy controls) and smoking status (smoking and non-smoking)—of interest on homotopic functional connectivity maps. As small amounts of the temporal derivative of movement can influence homotopic functional connectivity (Power et al. 2012),

we calculated the mean FD for our data. Based on previous studies, education level was associated with brain structural abnormalities (DeMyer et al. 1988; Rossi et al. 1991) in schizophrenia, and it was a confounding variable in the experimental design (Resnick 1992). Therefore, education, sex, age, and the mean FD were entered into two-way ANOVA as nuisance covariates. However, liberalizing the statistical threshold can dramatically increase the family-wise error rate (FWER), as recently demonstrated systematically for widely used statistical methods (Eklund et al. 2016). Considering the trade-off between reproducibility and FWER (Chen et al. 2017), we set the statistical significance level at $P_{\text{FWER}} < 0.05$ under Monte Carlo Simulation based corrections (a combination of cluster size inference and height threshold with $P < 0.005$ as the cluster-forming threshold and the cluster extent threshold at $k > 20$ voxels) using the DPABI (Yan et al. 2016) for interaction effect and the two main effects.

Correlation analyses

Brain regions showing altered homotopic functional connectivity were set as the regions of interest (ROIs). The average strength of homotopic functional connectivity was extracted within each ROI. Pearson's correlation coefficients were calculated between the specific values of each ROI and clinical scores including PANSS positive scores, PANSS negative scores and lifetime smoking (pack-years). Spearman's correlation coefficients were calculated between the ROIs and FTND, as the FTND scores were non-normal distributed. Pack-years of smoking were defined as the number of years of smoking multiplied by the average number of packs of cigarettes smoked daily (Sturmer et al. 2000). To improve the standards correlation analysis, we excluded all points with an average D_s of 6 or greater through identifying outliers by bootstrapping the Mahalanobis distance D_s for each observation (Schwarzkopf et al. 2012).

Validation analysis

To validate our findings, we carried out auxiliary analyses performed as whole-brain voxel-wise analyses of connectivity values as follows:

Because demographic and clinical characteristics showed that smokers differed from non-smokers in % male, we repeated the main analysis only using male subjects.

Furthermore, we added several factors as covariates in our statistical analysis. In particular, we added that severity of general symptoms differed in patients with/without smoking and that the number of cigarettes smoked per day differed in smokers with/without schizophrenia and medication dose (Chlorpromazine dose-years) (Horn et al. 2003; Andreasen et al. 2010). In addition, we also performed analysis between the homotopic connectivity of ROIs and patient medication

dose (Chlorpromazine dose-years) using Spearman's correlation. Moreover, when performing the correlation analysis between homotopic functional connectivity strength and behavior. We conducted the partial correlation analysis to regress out the nuisance covariates, including age, sex, education and the mean FD.

As global signal regression (GSR) is still a controversial issue in the resting-state fMRI field and with recent data suggesting that cortical power and neural information flow in the brain of schizophrenia patients may be affected by global signals (Yang et al. 2014, 2017), we reevaluated results without GSR.

Results

Demographics and clinical characteristics

Demographic and clinical characteristics were shown in Table 1. Schizophrenia patients did not differ from controls in age (Mann-Whitney $U = -880.5$, $P = 0.18$), sex ($\chi^2 = 1.965$, $P = 0.65$), and handedness (Fisher's $P = 1$). Schizophrenia patients who smoked did not differ from healthy controls who smoked in FTND, onset of smoking, cigarettes per day, and lifetime smoking (pack-years). Schizophrenia patients who smoked differed from non-smoker schizophrenia patients in PANSS general scores ($t_{(47)} = 2.29$, $P = 0.03$), which was consistent with findings that smoking is associated with increased disease severity (Schwartz 2007); but not disease onset. The mean FD for schizophrenia patients was greater than healthy controls (Mann-Whitney $U = 772$, $P = 0.03$), but no difference between smoker and non-smokers (Mann-Whitney $U = 991$, $P = 0.61$).

The main effects

The main effect of schizophrenia was found in the bilateral dorsal anterior cingulate cortex (dACC), the bilateral thalamus (THA), the bilateral rolandic operculum, the bilateral subgenual cingulate cortex (sgACC), the bilateral inferior frontal gyrus, the postcentral gyrus and the bilateral paracentral lobule. All brain regions showed lower connectivity in schizophrenia patients than in healthy controls (Fig. 1a and Table 2). The main effect of smoking was found in the sgACC (Fig. 1b and Table 2), with smoking groups exhibiting lower homotopic functional connectivity than non-smoking groups.

Compared to healthy controls, schizophrenia patients exhibited lower homotopic functional connectivity in the sgACC; to non-smoking counterparts, smokers exhibited even lower homotopic functional connectivity, suggesting that the main effects of these 2 variables additively affect common

Table 1 Demographic and clinical characteristics of subjects

Demographics	Patients (<i>n</i> = 49)		Controls (<i>n</i> = 43)		Comparison	
	SZnos (<i>n</i> = 27)	SZsm (<i>n</i> = 22)	HCnos (<i>n</i> = 21)	HCsm (<i>n</i> = 22)	patients vs. controls	smoking vs. nonsmoking
Gender (male/female)	12/15	19/3	14/7	19/3	$\chi^2 = 1.965$ ($P = 0.16$)	$\chi^2 = 11.24$ ($P = 0.001$)
Handedness (left/right)	0/27	0/22	0/21	0/22	–	–
Age (years)						
Current	30.85 ± 1.68	29.45 ± 2.12	31.43 ± 1.94	34.55 ± 2.14	U = -880.5 ($P = 0.18$)	U = 1047.0 ($P = 0.95$)
At onset of SZ	25.85 ± 1.58	23.36 ± 1.55	–	–	–	U = -240.0 ($P = 0.256$)
At onset of smoking	–	17.68 ± 0.58	–	19.64 ± 0.98	$t_{(42)} = -1.721$ ($P = 0.093$)	–
Education (years)	11.78 ± 0.64	11.05 ± 0.54	12.71 ± 0.76	14.59 ± 0.63	$t_{(90)} = -3.39$ ($P = 0.001$)	$t_{(90)} = 0.91$ ($P = 0.37$)
Type (first-episode/chronic)	4/18	1/26	–	–	–	$\chi^2 = 2.77$ ($P = 0.10$)
Duration of illness (years)	5.02 ± 0.641	7.23 ± 1.827	–	–	–	U = 283 ($P = 0.78$)
Anti-psychotic medication (yes/no)	17/5	22/5	–	–	–	$\chi^2 = 0.13$ ($P = 0.72$)
Anti-psychotic medication dose (Chlorpromazine dose-years)	20.27 ± 5.04	21.29 ± 8.07	–	–	–	U = 147 ($P = 0.2635$)
Cigarettes per day	–	17.18 ± 1.86	–	23.09 ± 2.61	$t_{(42)} = -1.84$ ($P = 0.073$)	–
Lifetime cigarette use (pack years)	–	12.06 ± 3.3	–	20.01 ± 4.3	U = -174 ($P = 0.114$)	–
FTND	–	5.41 ± 0.55	–	5.86 ± 0.61	$t_{(42)} = -0.55$ ($P = 0.58$)	–
RTQ	–	28.32 ± 1.51	–	29.55 ± 1.55	$t_{(42)} = -0.57$ ($P = 0.57$)	–
PANSS						
Total scores	59.19 ± 3.52	67.14 ± 5.53	–	–	–	$t_{(47)} = 1.26$ ($P = 0.22$)
General scores	26.48 ± 1.75	34.05 ± 2.97	–	–	–	$t_{(47)} = 2.29$ ($P = 0.03$)
Positive scores	11.89 ± 1.23	13.77 ± 1.59	–	–	–	U = 244 ($P = 0.28$)
Negative scores	20.81 ± 1.61	19.32 ± 1.67	–	–	–	$t_{(47)} = -0.64$ ($P = 0.53$)

Values are mean ± SEM

Abbreviations: PANSS Positive and Negative Symptom Scale, FTND Fagerstrom Test for Nicotine Dependence, RTQ Revised Tolerance Questionnaire, SZ schizophrenia, SZnos non-smoking schizophrenia, SZsm smoking schizophrenia, HCnos non-smoking controls, HCsm smoking controls

^a The χ^2 value for gender distribution was obtained by chi-square test

^b The U values were obtained by Mann-Whitney tests

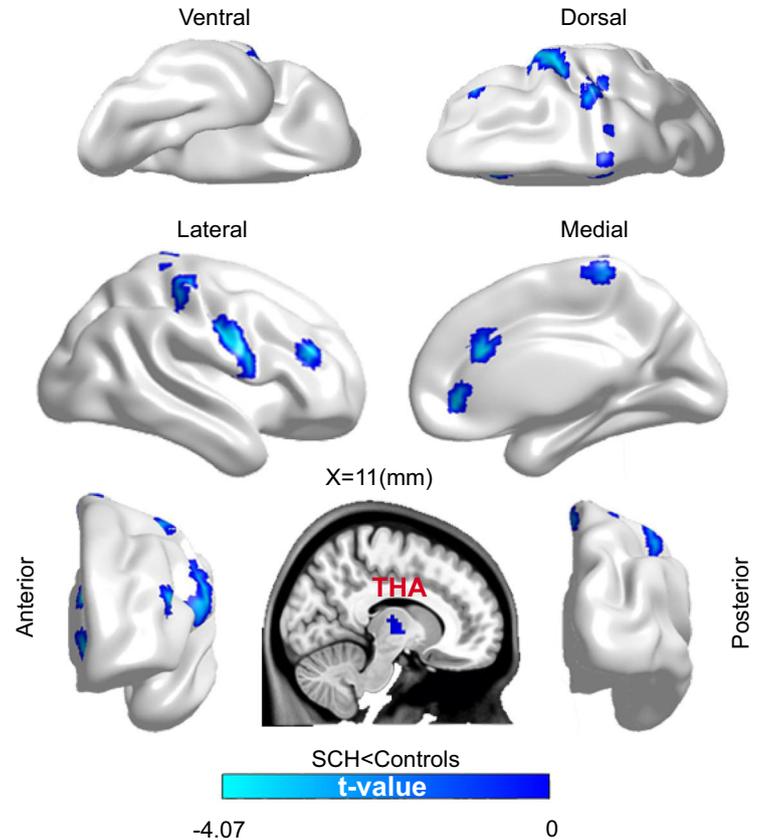
^c The $T_{(df)}$ values were obtained by two-sample *t*-test

^d Chlorpromazine dose-year = 100 mg of Chlorpromazine per day for 1 year

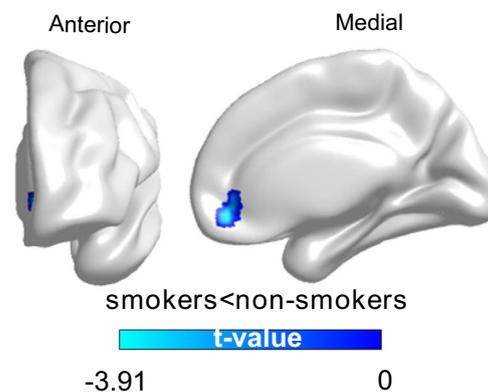
Fig. 1 The main effect of schizophrenia and smoking.

Homotopic functional connectivity between brain regions shows the significant main effect of disease (a) and smoking (b) using two-way ANOVA. The statistical significance level was set $P_{FWER} < 0.05$ under Monte Carlo Simulation based corrections. The brain regions colored in cool denote decreased homotopic functional connectivity in schizophrenia patients, compared with healthy controls (a), and the decreased connectivity in smokers, compared with non-smoker (b)

a disease effect



b smoking effect



brain region sgACC (Fig. 2a). Post-hoc analysis show Dice overlap 0.41 between the sgACC regions identified as displaying a main effects of diagnosis group ($F_{(1,88)} = 10.18$, $P = 0.002$) and a main effect of smoking status ($F_{(1,88)} = 16.08$, $P = 0.0001$) (Fig. 2b).

The interaction effect

The interaction effect of schizophrenia and smoking in the bilateral ventrolateral prefrontal cortex (VLPFC) is shown in

Fig. 3a. Planned post-hoc analysis of the VLPFC showed higher homotopic functional connectivity in smoking schizophrenia patients compared to non-smoking patients ($t_{(47)} = 4.12$, $P = 0.0002$, Bonferroni corrected for four times planned comparisons); while lower homotopic functional connectivity was found in smoking healthy controls compared to non-smoking healthy controls ($t_{(41)} = 3.1$, $P = 0.0034$, corrected for planned comparisons) (Fig. 3b). The strength of homotopic functional connectivity of the VLPFC was negatively correlated with the PANSS negative scores ($r_{(21)} =$

Table 2 Significant Group Differences in Homotopic Functional Connectivity

Cluster Location	Peak(MNI) (X, Y, Z)	Brodman area	Cluster Size	Peak <i>t</i> /F value
Interaction effect				
VLPFC	±51, 45, -12	47	35	F = 5.27
Main effect (schizophrenia vs. HC)				
dACC	±6, 30, 27	32	32	<i>t</i> = -4.07
THA	±15, -12, 0	–	40	<i>t</i> = -3.89
ROL	±48, 3, 15	6	138	<i>t</i> = -3.97
sgACC	±9, 39, -3	11	23	<i>t</i> = -3.61
IFGtriang	±48, 36, 24	45	29	<i>t</i> = -3.42
PoCG	±39, -27, 54	4	36	<i>t</i> = -3.80
PCL	12, -33, 66	3	45	<i>t</i> = -3.66
Main effect (smoking vs. non-smoking)				
sgACC	±6, 45, -9	10	21	<i>t</i> = -3.92

Abbreviation: VLPFC ventrolateral prefrontal cortex, dACC dorsal anterior cingulate cortex, THA thalamus, ROL rolandic operculum, sgACC subgenual anterior cingulate cortex, IFGtriang inferior frontal gyrus, triangular part, PoCG, postcentral gyrus, PCL paracentral lobule

-0.46, $P = 0.03$) and positively correlated with lifetime smoking ($r_{(20)} = 0.49$, $P = 0.03$) in schizophrenia smokers (Fig. 3c and d). One outlier and two outliers were identified in these two correlation analyses, respectively. The connectivity did not correlate with PANSS positive scores ($r_{(22)} = -0.0056$, $P = 0.98$) and FTND ($\rho_{(22)} = -0.2$, $P = 0.36$). Our results suggest that smoking among schizophrenia patients increased homotopic connectivity in the VLPFC; furthermore, this increase is directly related to the number of years the patients smoked and is associated with lower negative PANSS scores. To explore the nature of the diagnosis group * smoking status interaction on connectivity, correlations were additionally calculated between the PANSS-N scores and VLPFC of schizophrenia non-smokers ($\rho_{(22)} = 0.16$, $P = 0.44$) and the lifetime smoking and VLPFC of normal smokers ($\rho_{(22)} = 0.19$, $P = 0.44$).

In our validation analysis, we repeated the ANOVA using only male subjects (Fig. S1). The interaction effect of diagnosis and smoking status also found in the VLPFC, and post-hoc analysis showed overlap (Dice coefficient = 0.61) between male subjects' results with main interaction results. We also re-examined how general symptom scores, education, medication and cigarettes per day related to the interaction finding (Fig. S2). When we added these factors as covariates in the two-way ANOVA, the interaction effect of schizophrenia and smoking also found in VLPFC. Post-hoc analysis show overlap (Dice coefficient = 0.88) for this validation analysis. These results proved that the interaction effect was not affected by these factors. In addition, there was no correlation between the medication dosage of schizophrenia and the strength of connectivity in VLPFC (Fig. S3) ($r_{(34)} = -0.046$, $P = 0.79$). When we regressed out the nuisance covariates above mentioned,

there were significant correlations between the PANSS-N scores with the adjusted connectivity strength in the VLPFC ($r_{(21)} = -0.49$, $P = 0.024$), and the lifetime smoking with the adjusted connectivity strength in the VLPFC of schizophrenia smokers ($r_{(20)} = 0.46$, $P = 0.04$).

After performing two-way ANOVA on homotopic functional connectivity maps with GSR, we performed the exact analysis again without GSR. Post-hoc analysis show Dice overlap 0.92 for this validation analysis. Results indicated the interaction effect was evident following both analyses (Fig. S4), suggesting that the interaction effect is not significantly affected by GSR.

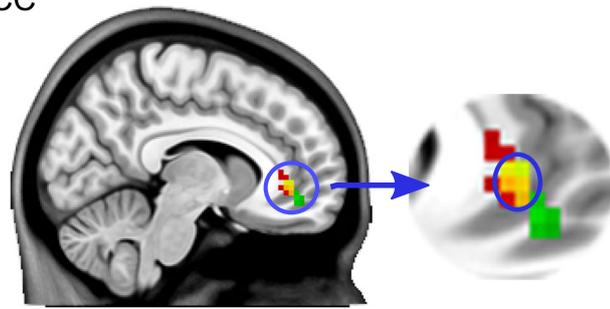
Discussion

The novel findings of this study demonstrate that additive negative effects of schizophrenia diagnosis and smoking were found on homotopic connectivity of the sgACC. Moreover, this is the first study to elucidate an antagonistic interaction between schizophrenia and smoking in relation to homotopic functional connectivity. We found that higher connectivity between the bilateral VLPFC was directly related to lifetime smoking and inversely related to the schizophrenia negative PANSS scores.

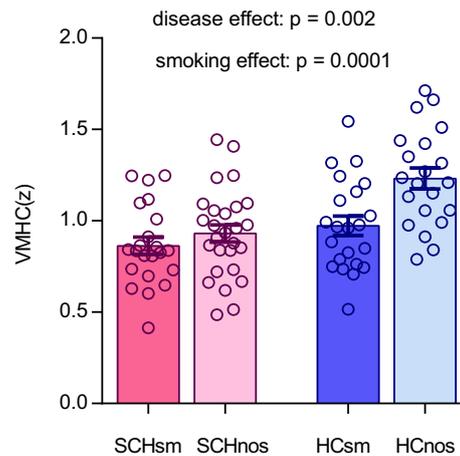
Our findings regarding a role of the THA, the somatosensory cortex, and the sgACC in the disease main effect was consistent with previous studies (Hoptman et al. 2012; Li et al. 2015; Chang et al. 2015). The smoking main effect also reflecting decreased homotopic functional connectivity in the sgACC, was inconsistent with previous studies (Yu et al. 2017; Viswanath et al. 2015). They found increased

Fig. 2 The intersection effect. a

The brain regions colored in yellow shows the additive effect of schizophrenia and smoking in the subgenual anterior cingulate cortex (sgACC). Brain regions colored in red and green show the main effect of schizophrenia and smoking, respectively. **b** Using histogram and circles distribution to show the homotopic functional connectivity of the overlapping sgACC among the four groups. The vertical bar indicates the standard deviation across subjects

a sgACC

■ schizophrenia effect
 ■ smoking effect
 ■ intersection effect

b main effect

connectivity in PFC; we believe this inconsistency may be related to the influence of age and sex (only young males used in one of the previous studies) (Yu et al. 2017), and the abstinent conditions (tobacco-deprived smokers and tobacco-sated smokers) (Viswanath et al. 2015).

Notably, the sgACC is a coincident region in both the effect of schizophrenia and smoking. Both schizophrenia and smoking reduced homotopic functional connections in the sgACC, indicating a negative additive effect. A previous study found reduced gray matter volume in left sgACC, which also was directly and additively associated with schizophrenia and smoking (Yokoyama et al. 2017). However, the authors did not find an interaction between these two factors, and suggested there were no neuroprotective benefits from smoking on gross brain structure (Yokoyama et al. 2017). This finding, as well as the reduced homotopic functional connectivity in sgACC, indicates a structural and functional disorder of smoking in schizophrenia patients. It has been suggested that the sgACC may be used as a target for intervention treatment (Fox et al. 2014) and our finding reinforce this suggestion. Furthermore, we provide a potential physiological target for future clinical intervention treatment for smoking and schizophrenia comorbidity.

To explore whether there was a homotopic functional connectivity interaction between schizophrenia and smoking, we

recruited a mixed sample using four groups (smoking and non-smoking schizophrenia patients, and smoking and non-smoking healthy controls). Compared with previous four group experimental designs that yielded no interactions either in relation to white matter integrity, gray matter volume, or dACC functional connectivity circuits (Moran et al. 2013; Zhang et al. 2010; Yokoyama et al. 2017), we found an antagonistic interaction between schizophrenia and smoking. We believe these inconsistencies may be the result of substantial differences from functional and structural modalities. In general, brain function is thought to be highly plastic; while brain morphology and/or structure is relatively stable (Bullmore and Sporns 2009). We therefore reasoned that homotopic connectivity based on brain function would be highly responsive to the perturbation of schizophrenia and/or smoking addiction (Camchong et al. 2009; Hoptman et al. 2012; Guo et al. 2014; Chang et al. 2015; Yu et al. 2017). Furthermore, the self-medication theory supports the idea that nicotine can regulate the mood of schizophrenia patients who smoke and enhance their cognitive competence (Leonard et al. 2007). Another alternative explanation is that smoking activates nicotine receptors resulting in a compensatory mechanism in schizophrenia, which transiently corrects or ameliorates certain abnormalities in interneuron subtypes in the prefrontal cortex (Koukoulis et al. 2017). Our results indicate a

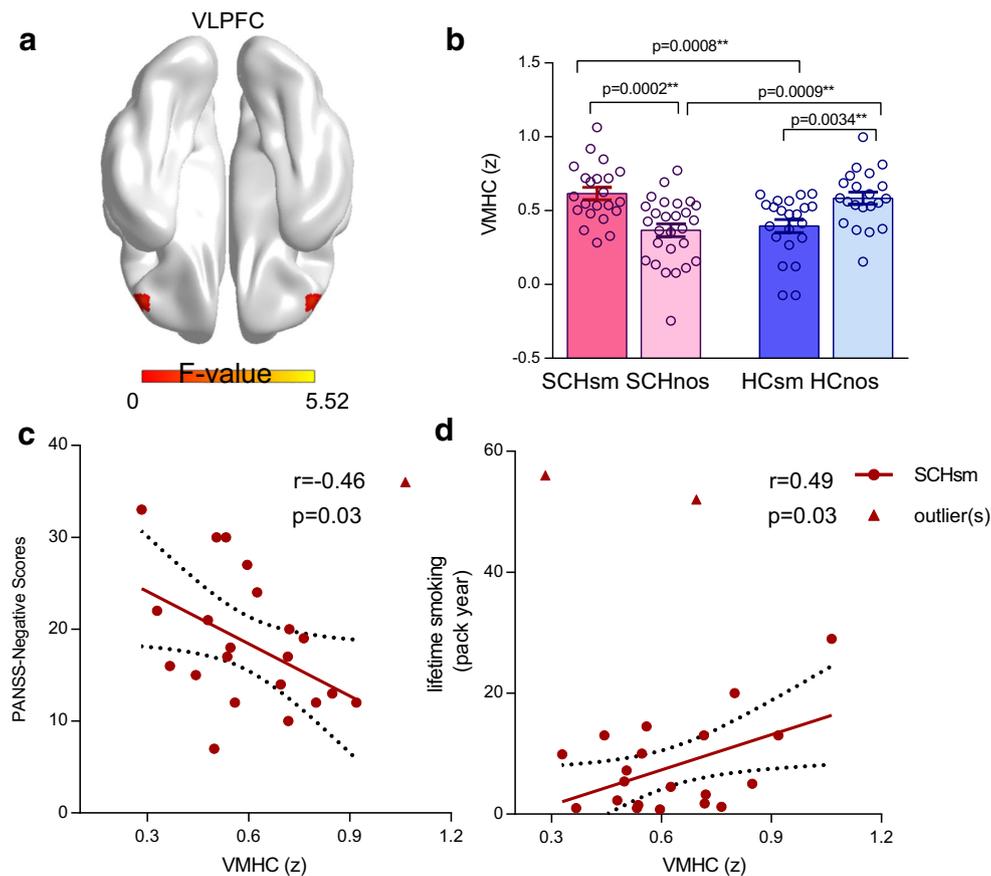


Fig. 3 The interaction effect of schizophrenia and smoking. **a** Homotopic functional connectivity between the bilateral ventrolateral prefrontal cortex (VLPFC) shows a significant interaction effect using two-way ANOVA. The statistical significance level was set $P_{FWER} < 0.05$ under Monte Carlo Simulation based corrections. **b** Planned post-hoc analysis of the VLPFC among the four groups. The vertical bar indicates the standard deviation across subjects. The statistical significance level was set at $P < 0.05$, using Bonferroni correction with four

times planned comparisons. **c** The strength of homotopic functional connectivity of the VLPFC was negatively correlated with PANSS negative scores ($r = -0.46$, $P = 0.03$) and **(d)** positively correlated with lifetime smoking ($r = 0.49$, $P = 0.03$) in smoking schizophrenia patients using Pearson's correlation. The statistical significance level was set at $P < 0.05$. * and ** denote $P < 0.05$, uncorrected and Bonferroni correction, respectively. Of note, the correlation was significant after one outlier **(c)** and two outliers **(d)** were removed by Shepherd's π correlation

conservative restoration of brain interhemispheric connectivity in schizophrenia patients who smoke.

This interaction was further reinforced by our correlation analysis results. Specifically, higher connectivity between the bilateral VLPFC, was associated with lower PANSS negative scores. The VLPFC plays a key role in cognitive control (Badre and Wagner 2007). In addition, cognitive improvement in schizophrenia is more typically associated with negative symptoms rather than positive symptoms (Schuepbach et al. 2002). Thus, antagonistic interaction effects are consistent with the idea that smoking impacts negative symptoms (Saliba et al. 2017; Patkar et al. 2002). In addition, the VLPFC is involved in automatic response tendencies, impulsivity (Goldstein and Volkow 2011), and monetary loss (de Ruiter et al. 2009) that initiates brain hypoactivation. With the increase of lifetime smoking, the interhemispheric connectivity

of VLPFC is also increased, which enhances the interaction results from smoking factor perspective. Both correlations from the interaction results support the self-medication hypothesis, and smoking has a reversal effect on VLPFC in schizophrenia.

There were several limitations to this study. First, the study cannot dissociate acute effects of nicotine from chronic effects of being a smoker. All smokers smoked 30 min before the scan to avoid withdrawal, and peak nicotine blood concentrations during the scan. However, it is not known if the remaining nicotine levels had any effects on brain dynamics. Future work would better to have a non-smoking control group on nicotine. Second, the proportions of females in this study may have been an issue; although this imbalance is partly a result of the unbalanced ratio of male to female smokers in China. The secondary analysis using only male subjects avoided this

imbalance, but in general, men with schizophrenia tend to have more chronic illness courses and more negative symptoms than women. The relationship between these factors and smoking should be further studied. Finally, the findings may have been minimally confounded by antipsychotic medication, as the interaction effects were maintained when medication was considered as a covariate. In the future, first episode drug-naïve schizophrenia patients should be recruited as a sample population to reduce the possible confounding effects of medication.

Conclusion

Using homotopic functional connectivity, both disease and smoking affected the sgACC, suggesting the existence of an additive negative effect between smoking and disease diagnosis. Furthermore, we also found a novel antagonistic interaction effect of disease and smoking in the bilateral VLPFC of schizophrenia patients who smoke, which support the self-medication scenario in schizophrenia. Our findings provide valuable information underlying the pathophysiological mechanisms of smoking and its effects on schizophrenia severity, and also offer a potential target for future clinical treatment of smoking and schizophrenia comorbidity.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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