Schizophrenia Bulletin vol. 45 no. 6 pp. 1242–1250, 2019
doi:10.1093/schbul/sby184
Advance Access publication 17 December 2018

Preservation Effect: Cigarette Smoking Acts on the Dynamic of Influences Among Unifying Neuropsychiatric Triple Networks in Schizophrenia

Wei Liao[1,2], Yun-Shuang Fan[1,2], Siqi Yang[1,2], Jiao Li[1,2], Xujun Duan[1,2], Qian Cui[1,2], and Huafu Chen*[,1,2]

[1]The Clinical Hospital of Chengdu Brain Science Institute, MOE Key Laboratory for NeuroInformation, University of Electronic Science and Technology of China, Chengdu, P.R. China; [2]School of Life Science and Technology, Center for Information in BioMedicine, University of Electronic Science and Technology of China, Chengdu, P.R. China

*To whom correspondence should be addressed; tel: +86-28-61831273, fax: +86-28-61831273, e-mail: chenhf@uestc.edu.cn

Objective: **The high prevalence of cigarette smoking in schizophrenia (SZ) is generally explained by the self-medication theory. However, its neurobiological mechanism remains unclear. The impaired dynamic of influences among unifying neuropsychiatric triple networks in SZ, including the central executive network (CEN), the default mode network (DMN), and the salience network (SN), might explain the nature of their syndromes, whereas smoking could regulate the dynamics within networks. Therefore, this study examined whether cigarette smoking could elicit a distinct improvement in the dynamics of triple networks in SZ and associated with the alleviation of symptoms.** ***Methods:*** **Four groups were recruited, namely, SZ smoking (n = 22)/nonsmoking (n = 25), and healthy controls smoking (n = 22)/nonsmoking (n = 21). All participants underwent a resting-state functional magnetic resonance imaging (fMRI). The dynamics among unifying neuropsychiatric triple networks were measured using Granger causality analysis on the resting-sate fMRI signal. Interaction effects between SZ and smoking on dynamics were detected using 2-way analysis of covariance, correcting for sex, age, and education level.** ***Results:*** **Whereas smoking reduced SN→DMN dynamic in healthy controls, it preserved the dynamic in SZ, thus suggesting a preservation effect. Moreover, smoking additionally increased DMN→CEN dynamic in SZ.** ***Conclusions:*** **This finding from neural pathways shed new insights into the prevailing self-medication hypothesis in SZ. More broadly, this study elaborates on the neurobiological dynamics that may assist in the treatment of the symptomatology of SZ.**

Key words: cigarette smoking/dynamic of influences/neuropsychiatric triple networks/preservation effect/schizophrenia

Introduction

According to a meta-analysis, the rate of cigarette smoking in schizophrenia (SZ) (62%) is more than 5 times higher than that observed in the general population.[1] The high prevalence of smoking in SZ is largely attributed to the self-medication hypothesis.[2] More specifically, smoking is viewed to ameliorate the symptomatology of SZ.[3] Recent neuroimaging studies on the comorbidity of smoking and SZ have posited 2 types of effects that may be attributed to the self-medication hypothesis.[4–6] One such effect is preservation. Smoking can preserve decreased gray matter volume in SZ, but cannot restore it to normal levels.[7] Another effect is recovery. Smoking can normalize aberrant activity within specific brain regions in SZ and is associated with improvement in symptomatology.[8–10] However, all these studies were not 2 × 2 factorial designs controlling for the diagnostic group (SZ and healthy controls [HCs]) and smoking status (smoking and nonsmoking). They did not directly compare the impact of smoking between SZ and HCs. Thus, these studies cannot clarify the specific self-medicated effect of smoking that attributed to the high smoking prevalence in SZ. Only 3 studies had used 4 groups, while they failed to found any interaction effect on brain structures including white matter (WM) integrity[11] and gray matter volume,[12] and brain functional connectivity circuits,[13] respectively. Therefore, the neurobiological mechanism underlying the self-medication hypothesis remains unclear.

One possible explanation for no interaction effect in previous studies may be due to the local region-scale they used. As a recent review suggested, the impact of smoking on the brain is complex and spatially broad.[5] Thus, the interaction effect should be examined at the systematic network-scale to effectively explore the differential smoking effect between SZ and HCs. The unifying neuropsychiatric triple network

model, consisting of the central executive network (CEN), the default mode network (DMN), and the salience network (SN), plays a fundamental role in psychopathological and higher cognitive processes.[14–16] As a hierarchical causal model, the triple networks model is associated with the brain function.[17–19] The disengagement of these networks underlies the neural substrates of pathological states in various psychiatric disorders including SZ.[20] Moreover, the impaired dynamic of influences in SZ among triple networks might explain the nature of their symptomatology.[21–23] However, cigarette smoking could regulate the dynamic of influences within triple networks by promoting functional integration.[24] Therefore, this study attributed the specific effect of cigarette smoking on the psychiatric symptomatology of SZ to the way in which smoking may regulate the dynamics within triple networks.

To this end, this study used a mixed sample consisting of 4 groups (ie, SZ smoking/nonsmoking, and HCs smoking/nonsmoking). To examine an interaction effect between the diagnosis of SZ and smoking status on the dynamics of triple networks, Granger causality (GC) analysis was used on the resting-state functional magnetic resonance imaging (fMRI) data sets. Residual GC analysis, as one of GC analysis, can yield information concerning about causal relationships and directionality among large-scale brain networks.[15,18,25,26] Moreover, coefficient GC analysis can additionally examine an excitatory or inhibitory effect on directionality among networks,[27] which may underlie the neural primacy of various pathological states, such as SZ,[21] major depressive disorder,[28] and epilepsy.[29] In line with the self-medication hypothesis, this study hypothesized that cigarette smoking can normalize or at least preserve impaired dynamic of influences within triple networks in SZ. It was assumed that the amelioration of the dynamic of influences observed in patients as a result of smoking would be associated with an improvement in symptomatology.

Methods and Materials

Subjects

Fifty-six patients with SZ participated in this study. The diagnosis of SZ was in accordance with the Structured Clinical Interview for *DSM-IV* Patient Edition and was confirmed by trained physicians or clinical psychologists by a structured clinical interview after at least 1-year follow-up. Patients were excluded if they (1) were less than 16 years old, (2) had current (within the last 12 months) comorbid substance use disorder (other than cigarettes), (3) had any other current or past psychotic disorders and serious physical diseases, (4) had gross morphological anomalies as evidence by brain MRI scans, and (5) had any electronic or metal implants. Three patients were excluded from further analyses due to incomplete scanning. Six patients were excluded due to excessive head motion (see details in the "Data Preprocessing" section). Ultimately, 47 patients took part in further analysis. Of them, 5 patients were classed as first-episode SZ. The remaining patients were diagnosed with chronic SZ. Of 47 patients, 37 patients who took atypical antipsychotic medication were clinically medication stable (ie, more than 3 months with no change in medication). With the exception of antipsychotic drugs, no other drug was continuously used for more than 1 week during the last month.

Sex- and age-matched HC participants were recruited (N = 43). Both HC participants and their first-degree relatives had no prior history of SZ and were confirmed by the Structured Clinical Interview for *DSM-IV* Non-Patient Edition. The additional exclusion criteria were the same for both HC participants and patients with SZ.

Written informed consent was obtained from all patients and HCs. All examinations were carried out under the guidance of the Declaration of Helsinki 1975.[30] This study was reviewed and approved by the local medical ethics committee of the First Affiliated Hospital of Chongqing Medical University.

Smokers within both the patients and HCs were current daily smokers for at least 1 year, smoked any number of cigarettes, and had not abstained from smoking for longer than 3 months in the past year. All nonsmokers neither smoked regularly nor daily and completely used of any nicotine products.[31] Patients and HCs were separately divided into smoking groups (SZ smokers [SZ-smokers], n = 22; healthy smokers [HC-smokers], n = 22) and non-smoking groups (SZ-nonsmokers, n = 25; HC-nonsmokers, n = 21).

Clinical Assessments

Clinical symptoms in patients with SZ were measured using the Positive and Negative Syndrome Scale (PANSS).[32] For both HC-smokers and SZ-smokers, the severity of nicotine addiction was assessed using the Fagerström Test for Nicotine Dependence (FTND).[33] In addition, the number of cigarettes smoked per day, age of onset of smoking, and lifetime cigarette use (LTU) were obtained (see supplementary materials for details).

Data Acquisition

Imaging data were acquired using a 3.0 Tesla MRI scanner (GE Medical Systems) at the First Affiliated Hospital of Chongqing Medical University. Participants were requested to relax without falling asleep, to keep eyes closed and not think of anything in particular, and to refrain from moving their heads during the MRI scan. Resting-state functional images were acquired using an echo-planar imaging sequence (repetition time, 2000 ms; echo time, 30 ms; flip angle, 90°; field of view, 240 × 240 mm^2; matrix, 64 × 64; slice thickness, 4 mm; 33 axial slices). A total of 240 volumes were collected within a total scan time of 480 seconds.

Data Preprocessing

fMRI data were preprocessed using DPARSF software (v4.3, advanced edition; www.restfmri.net) and SPM12 toolkits (www.fil.ion.ucl.ac.uk/spm). Spatially preprocessing included slice-timing, realign, and spatially normalization. Following normalization, nuisance covariates, including 24 head motion parameters, WM signals, cerebrospinal fluid signals, and global signals, were regressed out using linear regression. Smoothing was not performed to avert blurring between several predefined adjacent brain regions.[22] Next, the functional images were detrended and a 0.01–0.1 Hz temporal band-pass filter was applied to remove low-frequency drifts and physiological high-frequency noise (see supplementary materials for details).

Triple-Network Nodes Selection

The nodes were selected from previous literatures examining SZ and cigarette smoking. Each node was defined as a 6 mm radius sphere. Twenty-one nodes were selected (supplementary table S1).

Coefficient GC Analysis

To measure the dynamic of influences between the nodes, multivariate coefficient GC analysis was performed.[34] For each node, the blood oxygenation level-dependent functional MRI time series was extracted by averaging the time series of all voxels within it. The GC strength was evaluated among nodes using a vector auto-regression model in REST (v1.8; www.restfmri.net). The GC strength characterizes the signed strength and direction of the relationship between each pair of nodes. It may be noted that the sign of the GC strength was not involved in further between-group comparisons. Finally, a 21 × 21 asymmetric adjacency matrix (GC pattern) was obtained for each participant.

Within-Group Comparison

First, node-level within-group GC patterns were evaluated for each directed edge across participants in each group using 1-sample *t* test. A statistical significance level was set at *P* value of less than .05 and false discovery rate (FDR) adjusted for multiple testing correction. Second, network contingency analyses were used to evaluate significant network-level GC patterns (see supplementary materials for details).

Between-Groups Comparison

First, to examine the interaction effect on network-level GC patterns among the 4 groups, a 2-way ANCOVA was carried out for each directed edge. Sex, age, and education level were included as covariates. Two factors included diagnosis (SZ and HCs) and smoking status (smoking and nonsmoking). Network contingency analysis based on permutation test was then performed to determine whether 2 networks exhibited different GC strengths in the 4 groups. This analysis was restricted to node-level GC group mask images where only the same-sign directed edges for the 4 groups were shown. A statistical significance level was set at *P* value of less than .05 with FDR adjustment for multiple testing correction. A 95% confidence intervals (CIs)[35] and binomial effect size display (BESD)[36] for permutation test were calculated to reveal among-4-groups differences in GC patterns.

To further clarify the effects of SZ and smoking on GC patterns among networks, 2-sample *t* tests were used at each directed edge between the groups (see supplementary materials for details).

Clinical Correlation

To explore the relationship between the interaction of GC patterns and symptom severity, as well as nicotine addiction severity, clinical correlation analyses were used for the 2 SZ groups, separately (see supplementary materials for details).

Validation Analyses

Head motion could potentially affect brain information dynamics.[37] Furthermore, antipsychotic medication has been shown to modulate functional connectivity in patients with SZ.[38] Thus, 2 validation analyses were performed (see supplementary materials for details).

Results

Demographic and Clinical Variables

The demographic and clinical characteristics of the 4 groups are presented in table 1. An effect size (Cohen's *w*) was calculated to reveal group differences in the ratio of clinical variables. We did not report the CI for group differences in the ratio of clinical variables due to no more than 5 subjects in each cell of the contingency table. SZ-smokers and HC-smokers showed no difference in FTND scores or LTU scores. SZ-smokers and SZ-nonsmokers did not significantly differ with respect to PANSS-N or PANSS-P scores. These SZ groups also showed no difference in the ratio of first-episode type (χ^2 = 2.48, *P* = .12, Cohen's *w* = 0.23) or antipsychotic medication use (χ^2 = 0.05, *P* = .82, Cohen's *w* = 0.03). Significant differences were found in gender composition between SZ-smokers and SZ-nonsmokers (χ^2 = 10.64, *P* = .001, Cohen's *w* = 0.48). However, the fact that male smokers consume more cigarettes than female smokers is a common phenomenon in China.[39] Nonetheless, the researchers attempted to control for this sex difference when recruiting participants.

Within-Group GC Patterns

Node-level GC patterns were obtained for the 4 groups by using GC analysis (figure 1). From a visual perspective, the GC strength flow from or out of SN appeared to be

Table 1. Demographic and Clinical Characteristics

Characteristic	Healthy controls (HC, $N = 43$)		Schizophrenia patients (SZ, $N = 47$)		Comparison	
	Nonsmokers ($n = 21$)	Smokers ($n = 22$)	Nonsmokers ($n = 25$)	Smokers ($n = 22$)	HC-nonsmokers vs SZ-nonsmokers	SZ-nonsmokers vs SZ-smokers
Sex (male/female)	14/7	19/3	10/15	19/3	$\chi^2 = 3.253$[a] $P = 0.07$	$\chi^2 = 10.64$[a] $P = .001$
Age (years)						
Current	31.43 ± 1.94	34.55 ± 2.14	31.16 ± 1.8	29.45 ± 2.12	$U = 254$[b] $P = .86$	$U = 229$[b] $P = .33$
At onset of SZ	—	—	26.04 ± 1.7	23.36 ± 1.55	—	$T_{(45)} = 1.15$[c] $P = .26$
At onset of smoking	—	19.64 ± 0.98	—	17.68 ± 0.58	—	—
Education (years)	12.71 ± 0.76	14.59 ± 0.63	11.64 ± 0.68	11.05 ± 0.54	$T_{(44)} = 1.06$[c] $P = .3$	$T_{(45)} = 0.67$[c] $P = .5$
Duration of illness (years)	—	—	5.14 ± 0.69	7.23 ± 1.83	—	$U = 268$[b] $P = .89$
Medication use (dose years)	—	—	16.04 ± 1.72	21.19 ± 8.07	—	$U = 237$[b] $P = .42$
Cigarettes per day	—	23.09 ± 2.61	—	17.18 ± 1.86	—	—
Lifetime cigarette use (pack years)	—	20.01 ± 4.3	—	12.06 ± 3.3	—	—
FTND	—	5.86 ± 0.61	—	5.41 ± 0.55	—	—
PANSS						
Total scores	—	—	60.36 ± 3.69	67.14 ± 5.53	—	$U = 241$[b] $P = .47$
General scores	—	—	26.92 ± 1.86	34.05 ± 2.97	—	$U = 195$[b] $P = .09$
Positive scores	—	—	12.28 ± 1.29	13.77 ± 1.59	—	$U = 240$[b] $P = .46$
Negative scores	—	—	21.16 ± 1.72	19.32 ± 1.67	—	$U = 246$[b] $P = .54$

Note: Mean ± SEM. PANSS: Positive and Negative Symptom Scale; FTND: Fagerstrom Test for Nicotine Dependence.
[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 values were obtained by 2-sample t test.

substantially greater compared with the GC patterns of other networks in the HC-nonsmokers group. Furthermore, the effect of smoking on GC patterns appeared to differ between the patients and healthy controls.

Between-Groups GC Patterns

The GC patterns for among-4-groups and between-2-groups were obtained using a 2-way ANCOVA and 2-sample t tests, separately. Network-level GC patterns were determined using network contingency analyses based on node-level GC patterns.

First, an antagonistic interaction effect (Permutation test, $P_{FDR} = .0004$, 95% CI = –0.004 to 0.005, BESD = 2.00) was found between smoking status and the SZ diagnosis for the GC result related to SN→DMN (figure 2A). An antagonistic interaction effect means that, in comparison to controls, patients showed an active or at least a less inactive effect as a result of smoking. With respect to HCs, cigarette smoking significantly reduced the negative SN→DMN GC strength (Permutation test, $P_{FDR} = .02$, 95% CI = –0.009 to 0.049, BESD = 2.08). However, the SN→DMN GC strength in SZ-smokers and SZ-nonsmokers showed no significant difference. Thus, smoking may preserve a deficit in the SN→DMN GC strength of patients, which suggests a less inactive effect of smoking in patients compared to healthy controls. However, the absence of such a decreasing effect as a result of smoking might imply a floor effect, reflecting the lowest SN→DMN GC strength caused by SZ. Although this study cannot exclude the possibility of a floor effect, further longitudinal studies are needed to explore the SN→DMN GC strength changes in SZ-smokers. In addition, the SN→DMN strength was negatively correlated with N scores in the SZ-nonsmokers group (Rho = −0.46, $P = .02$), and it was positively correlated with LTU scores in the SZ-smokers groups (Rho = 0.47, $P = .04$) (figure 2B).

Second, with regard to the further exploration of cigarette smoking effects, this study found an additional effect of smoking on the DMN→CEN GC strength in SZ. Consistent with the result of interaction effect, SZ exhibited decreased negative GC strength from SN to

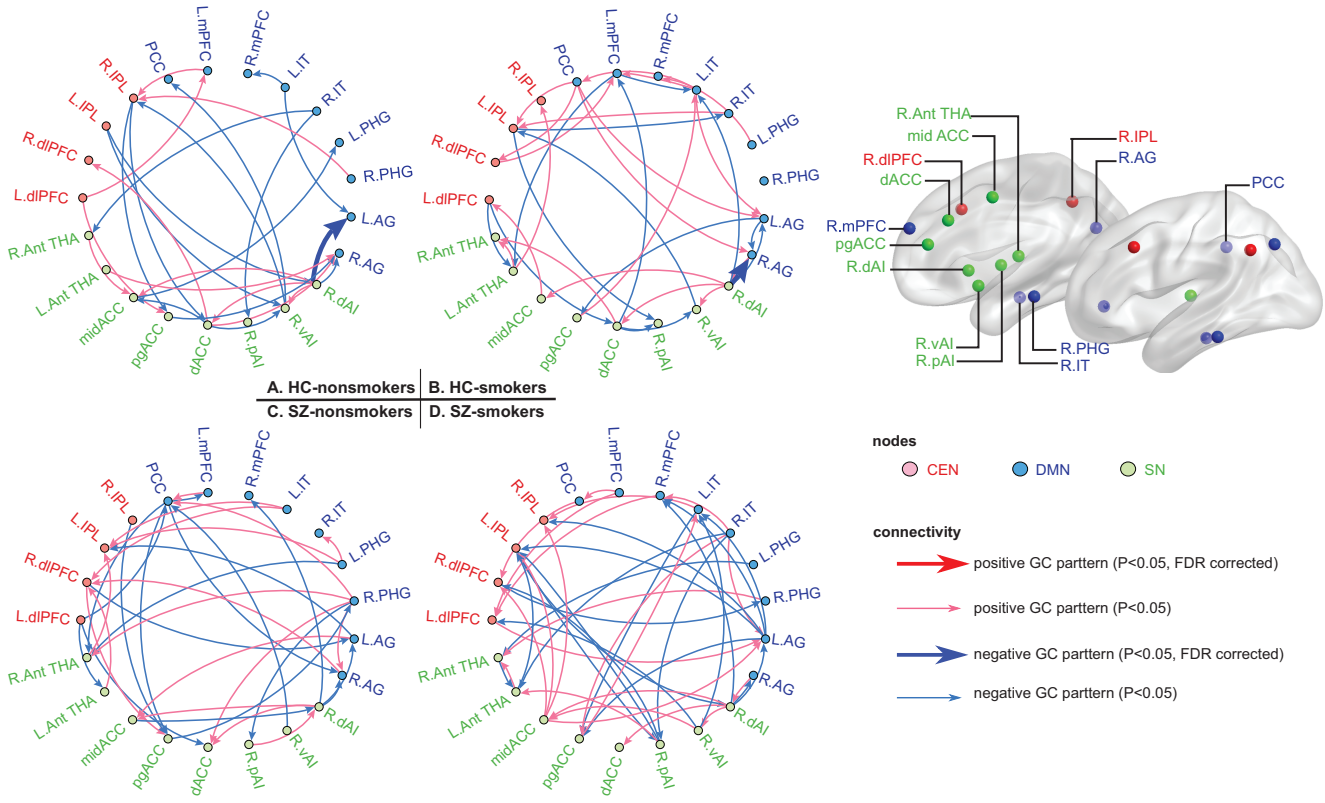

Fig. 1. Within-group Granger causality (GC) patterns at node-level. Arrow lines represent GC strength. Bold arrow lines indicate that those GC strength survived multiple testing correction ($P < .05$, false discovery rate [FDR] corrected). Nodes are form the central executive network (CEN), the default mode network (DMN), and the salience network (SN). HC, healthy controls; SZ, schizophrenia.

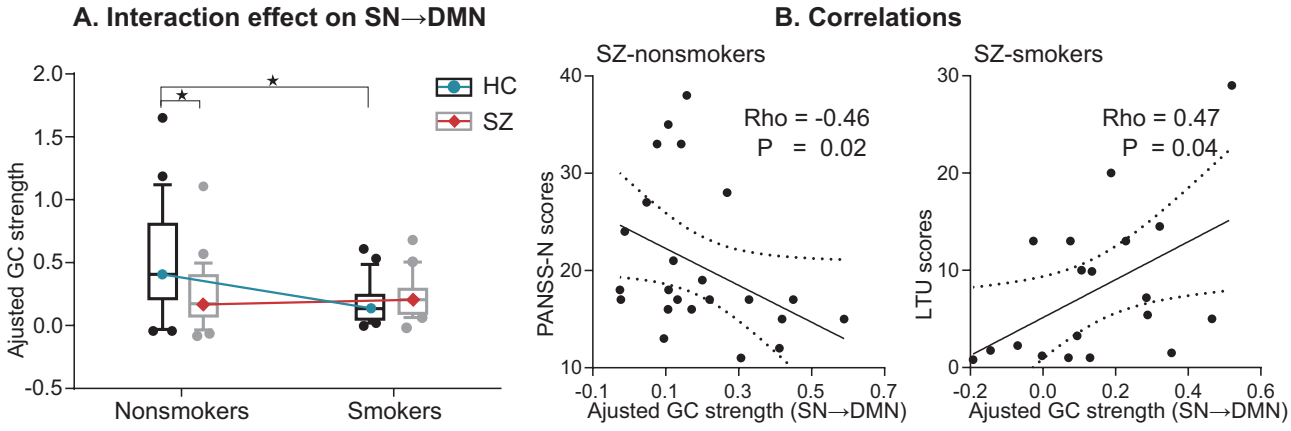

Fig. 2. Schizophrenia (SZ) × smoking interaction effect and corresponding correlations. (A) Significant SZ × smoking interaction effect (Permutation test, $P_{FDR} = .0004$) existed in the Granger causality (GC) strength from the salience network (SN) to the default mode network (DMN). The lower to upper horizontal lines in the box represent the lower extreme of the 90th percentile, lower quartile, median, upper quartile and upper extreme of the 90th percentile for *F* scores of GC strength in each group. (B) The SN→DMN GC strength was negatively correlated with N scores in SZ-nonsmokers (the left scatterplot), whereas it was positively correlated with lifetime cigarette use (LTU) scores in SZ-smokers (the right scatterplot). Solid line represents the best-fit line, whereas dashed lines represent a 95% confidence interval. ★ denotes $P < .05$ (Permutation test, false discover rate [FDR] corrected). PANSS, the Positive and Negative Syndrome Scale.

DMN (Permutation test, $P_{FDR} = .04$, 95% CI = –0.018 to 0.098, BESD = 2.17) (figure 3A). However, smoking increased the positive DMN→CEN GC strength in SZ (Permutation test, $P_{FDR} = .01$, 95% CI = –0.011 to 0.031, BESD = 2.04) (figure 3B).

Validation Results

First, no correlation was found between the main result of SN→DMN GC strength and head motion (Rho = –0.08, $P = .44$) or antipsychotic medication use (Rho = –0.13, $P = .22$). Furthermore, when head motion

parameters were identified as covariates in the ANCOVA, the group difference showed in the SN→DMN GC (Permutation test, P_{FDR} = .0002, 95% CI = –0.003 to 0.003, BESD = 2.00), which was consistent with the main result. In addition, when the impact of antipsychotic medication use was regressed out in the ANCOVA, the result (Permutation test, P_{FDR} = .0006, 95% CI = –0.004 to 0.006, BESD = 2.01) was also consistent with the main result. All in all, these validation results suggested that head motion and antipsychotic medication use exerted no influence on the SN→DMN GC strength.

Discussion

For the first time, this study sought elaborate on the self-medication theory by investigating the dynamic of influences within the unifying neuropsychiatric triple network model with respect to the comorbidity of smoking and SZ. The results revealed an antagonistic interaction on dynamic from SN to DMN with respect to smoking in SZ, thereby suggesting a preservation effect of the self-medication hypothesis. Moreover, an additional effect of cigarette smoking in SZ was observed on the DMN→CEN dynamic. This finding from neural pathway shed new insights into the prevailing self-medication hypothesis in SZ.

The antagonistic interaction between smoking and SZ on the dynamic of influences from SN to DMN suggested a preservation effect of the self-medication hypothesis. Consistent with the results of patients' GC patterns outlined in the current research, a previous study found that the SN→DMN GC strength was disrupted in SZ.[22] Considering the consistency in results that suggested a correlation between the disrupted SN→DMN GC strength and negative symptoms, this study proposes that such disruption may be the underlying reason for the dysfunctional integration observed in patients with respect to cognition, emotion, and behavior. Critically, this study revealed, for the first time, a preservation effect of smoking with regard to the disruption of SN→DMN GC strength. A research demonstrated that the nicotine agonist could alter DMN activity in SZ and improve symptomatology.[8] However, abnormal activity in regions of DMN, which could contribute to negative symptoms in SZ,[40,41] may be caused by a loss in the regulation of SN.[20] Thus, smoking may actually act on regulation from SN to DMN, potentially altering the activity of DMN, thereby alleviating patients' negative symptoms. However, consistent with the previous study,[24] an inactive effect was observed in healthy participants, such that smoking reduced the GC strength from SN to DMN. Therefore, it was inferred that cigarette smoking may, in particular, preserve the deficit of diminishment of the SN→DMN GC strength in SZ, this leading to an alleviation in negative symptoms. Considering the high rates of smoking-related morbidity and mortality,[42,43] alternative target-therapy schemes without side effects should be developed. It is widely accepted that transcranial magnetic stimulation (TMS) represents a safe and reliable method

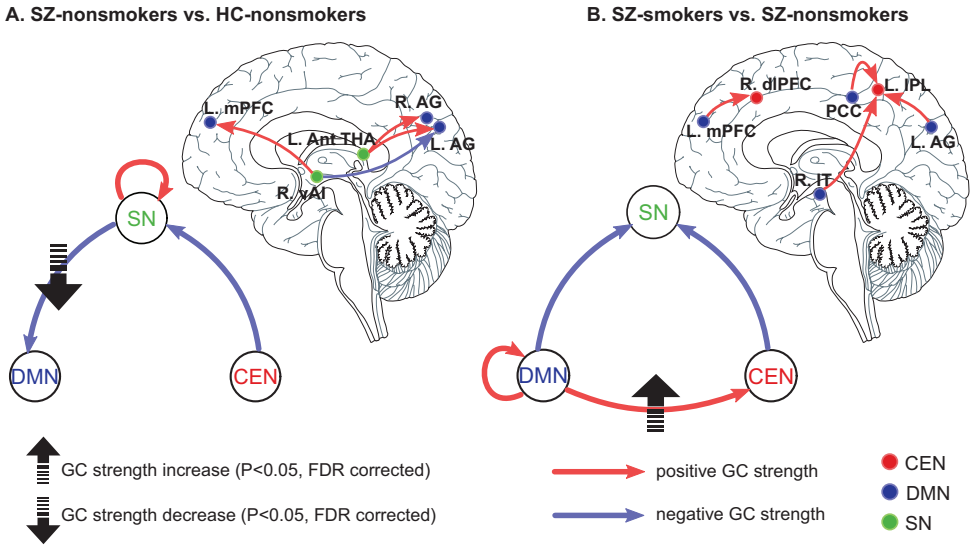

Fig. 3. Impacts of schizophrenia (SZ) and smoking on Granger causality (GC) patterns. (A) Effects of SZ showed on the negative SN→DMN GC strength (Permutation test, P_{FDR} = .04). The baseplate on the left graph represents within-group GC patterns for healthy controls (HC)-nonsmokers. Corresponding node-level GC strengths from the salience network (SN) to the default mode network (DMN) are exhibited in the right brain map. (B) Effects of smoking in SZ showed on the positive DMN→CEN GC strength (Permutation test, P_{FDR} = .01). The baseplate on the left graph represents within-group GC patterns for SZ-nonsmokers. The right map illustrates the GC strength from DMN to central executive network (CEN) for nodes. vAI, ventral anterior insular; Ant THA, anterior thalamus; mPFC, medial prefrontal cortex; AG, angular gyrus; IT, inferior temporal; PCC, posterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; IPL, inferior parietal lobe.

of target therapy[44] and can stimulate specific brain areas to alter the activity of related system-level neural circuits[45] and improve symptoms in SZ.[46] Thus, from a clinical perspective, it is important to develop TMS as a treatment method that targets the regulation of neurobiological networks to treat the symptomatology of SZ and in particular, its associated negative symptoms.

An additional effect of cigarette smoking in SZ was observed on the DMN→CEN dynamic. Although no study has reported that smoking could increase the DMN→CEN GC strength in SZ, a previous study has demonstrated the association between nicotine use and the DMN-CEN coupling.[47] The interaction between DMN and CEN is crucial for neurocognitive process.[48,49] Thus, smoking may increase the dynamic from DMN to CEN to improve the cognitive function in SZ. This extra finding offers novel insight into the impact of smoking on the brain network regulation in SZ.

The researchers acknowledge 2 methodological considerations in this study. First, both the main effects of SZ and smoking were not analyzed. According to the self-medication hypothesis, smoking exerts a heterogeneous impact on GC patterns in patients with SZ and HCs, as confirmed by interaction result found in this study. Thus, the main effects of pooled groups are mixed and less physiologically meaningful. Second, this study used coefficient GC analysis, rather than residual GC analysis, because coefficient GC analysis can determine whether in-source activity would predict a subsequent increase or decrease in target activity.[27]

This study had several limitations. First, the sample size was relatively small, which may render the findings likely unreliable. The small sample size also resulted in the impact of gender nonnegligible. Thus, future studies are necessary to recruit additional participants and balance the ratio of gender to validate current findings. Second, the lack of cognitive function measures was underpowered to support the association between the DMN→CEN GC strength increased by smoking and cognitive function improvement in SZ. Third, 37 of 47 patients took antipsychotic medication. Therefore, medication use was added as a covariate of no interest in the ANCOVA and correlation analysis to regress out its influence. Although the retested interaction result was consistent with the original result, additional studies are still necessary to eliminate the influence of medication use. Forth, cigarette consumption and oral nicotine dosage were not accessed by using measurements such as expired breath carbon monoxide determination or plasma and urine cotinine levels. Therefore, the impact of the cigarette consumption cannot be eliminated in this study. Finally, this study investigated the dynamic of influences restricted on gray matter. However, the neurobiological significance of spontaneous brain activity in WM cannot be neglected.[50] Therefore, dynamic of influence should be explored in the WM to understand the functional dynamics of WM and its relationship with changes in gray matter.

Conclusion

This is the first study that has found an interaction effect between cigarette smoking and SZ, thus supporting the self-medication hypothesis in terms of brain functional dynamic of influences. Furthermore, the current findings offer a system-level neurobiological theory for the treatment of SZ's seemingly untreatable negative symptoms. Future efforts are being undertaken to further develop neural intervention methods that target these system-level neurobiological mechanism to advance the treatment of SZ.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

Funding

This work was supported by the National Natural Science Foundation of China (61533006, 81471653, 81771919, and 61673089), China Postdoctoral Science Foundation (2013M532229), Sichuan Science and Technology Program (2018TJPT0016), and the "111" project (B12027).

Acknowledgments

We are grateful to all the participants in this study. The current data have published in https://openneuro.org/datasets/ds001461. The authors declare that they have no conflict of interest.

References

1. de Leon J, Diaz FJ. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophr Res.* 2005;76(2-3):135–157.
2. Kumari V, Postma P. Nicotine use in schizophrenia: the self medication hypotheses. *Neurosci Biobehav Rev.* 2005;29(6):1021–1034.
3. Winterer G. Why do patients with schizophrenia smoke? *Curr Opin Psychiatry.* 2010;23(2):112–119.
4. Smucny J, Tregellas J. Nicotinic modulation of intrinsic brain networks in schizophrenia. *Biochem Pharmacol.* 2013;86(8):1163–1172.
5. Smucny J, Tregellas JR. Targeting neuronal dysfunction in schizophrenia with nicotine: evidence from neurophysiology to neuroimaging. *J Psychopharmacol.* 2017;31(7):801–811.
6. McClernon FJ. Neuroimaging of nicotine dependence: key findings and application to the study of smoking-mental illness comorbidity. *J Dual Diagn.* 2009;5(2):168–178.
7. Tregellas JR, Shatti S, Tanabe JL, et al. Gray matter volume differences and the effects of smoking on gray matter in schizophrenia. *Schizophr Res.* 2007;97(1-3):242–249.
8. Tregellas JR, Tanabe J, Rojas DC, et al. Effects of an alpha 7-nicotinic agonist on default network activity in schizophrenia. *Biol Psychiatry.* 2011;69(1):7–11.
9. Jacobsen LK, D'Souza DC, Mencl WE, Pugh KR, Skudlarski P, Krystal JH. Nicotine effects on brain function

and functional connectivity in schizophrenia. *Biol Psychiatry.* 2004;55(8):850–858.

10. Hong LE, Schroeder M, Ross TJ, et al. Nicotine enhances but does not normalize visual sustained attention and the associated brain network in schizophrenia. *Schizophr Bull.* 2011;37(2):416–425.
11. Zhang X, Stein EA, Hong LE. Smoking and schizophrenia independently and additively reduce white matter integrity between striatum and frontal cortex. *Biol Psychiatry.* 2010;68(7):674–677.
12. Yokoyama N, Sasaki H, Mori Y, et al. Additive effect of cigarette smoking on gray matter abnormalities in schizophrenia. *Schizophr Bull.* 2018;44:535–541.
13. Moran LV, Sampath H, Kochunov P, Hong LE. Brain circuits that link schizophrenia to high risk of cigarette smoking. *Schizophr Bull.* 2013;39(6):1373–1381.
14. Bressler SL, Menon V. Large-scale brain networks in cognition: emerging methods and principles. *Trends Cogn Sci.* 2010;14(6):277–290.
15. Sridharan D, Levitin DJ, Menon V. A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proc Natl Acad Sci U S A.* 2008;105(34):12569–12574.
16. Barrett LF, Satpute AB. Large-scale brain networks in affective and social neuroscience: towards an integrative functional architecture of the brain. *Curr Opin Neurobiol.* 2013;23(3):361–372.
17. Zhou Y, Friston KJ, Zeidman P, Chen J, Li S, Razi A. The hierarchical organization of the default, dorsal attention and salience networks in adolescents and young adults. *Cereb Cortex.* 2018;28(2):726–737.
18. Liao W, Mantini D, Zhang Z, et al. Evaluating the effective connectivity of resting state networks using conditional Granger causality. *Biol Cybern.* 2010;102(1):57–69.
19. Chen AC, Oathes DJ, Chang C, et al. Causal interactions between fronto-parietal central executive and default-mode networks in humans. *Proc Natl Acad Sci U S A.* 2013;110(49):19944–19949.
20. Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. *Trends Cogn Sci.* 2011;15(10):483–506.
21. Palaniyappan L, Simmonite M, White TP, Liddle EB, Liddle PF. Neural primacy of the salience processing system in schizophrenia. *Neuron.* 2013;79(4):814–828.
22. Moran LV, Tagamets MA, Sampath H, et al. Disruption of anterior insula modulation of large-scale brain networks in schizophrenia. *Biol Psychiatry.* 2013;74(6):467–474.
23. Manoliu A, Riedl V, Doll A, et al. Insular dysfunction reflects altered between-network connectivity and severity of negative symptoms in schizophrenia during psychotic remission. *Front Hum Neurosci.* 2013;7:216.
24. Sutherland MT, McHugh MJ, Pariyadath V, Stein EA. Resting state functional connectivity in addiction: lessons learned and a road ahead. *Neuroimage.* 2012;62(4):2281–2295.
25. Liao W, Ding J, Marinazzo D, et al. Small-world directed networks in the human brain: multivariate Granger causality analysis of resting-state fMRI. *Neuroimage.* 2011;54(4):2683–2694.
26. Jiao Q, Lu G, Zhang Z, et al. Granger causal influence predicts BOLD activity levels in the default mode network. *Hum Brain Mapp.* 2011;32(1):154–161.
27. Chen G, Hamilton JP, Thomason ME, Gotlib IH, Saad ZS, Cox RW. Granger causality via vector auto-regression tuned for fMRI data analysis. *Proc Intl Soc Mag Reson Med.* 2009;17:1718.
28. Hamilton JP, Chen G, Thomason ME, Schwartz ME, Gotlib IH. Investigating neural primacy in major depressive disorder: multivariate granger causality analysis of resting-state fMRI time-series data. *Mol Psychiatry.* 2011;16(7):763–772.
29. Ji GJ, Zhang Z, Zhang H, et al. Disrupted causal connectivity in mesial temporal lobe epilepsy. *PLoS One.* 2013;8(5):e63183.
30. Shephard DA. The 1975 declaration of Helsinki and consent. *Can Med Assoc J.* 1976;115(12):1191–1192.
31. Liu H, Luo Q, Du W, et al. Cigarette smoking and schizophrenia independently and reversibly altered intrinsic brain activity. *Brain Imaging Behav.* 2018. doi:10.1007/s11682-017-9806-8
32. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull.* 1987;13(2):261–276.
33. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström test for nicotine dependence: a revision of the Fagerström tolerance questionnaire. *Br J Addict.* 1991;86(9):1119–1127.
34. Zang ZX, Yan CG, Dong ZY, Huang J, Zang YF. Granger causality analysis implementation on MATLAB: a graphic user interface toolkit for fMRI data processing. *J Neurosci Methods.* 2012;203(2):418–426.
35. Brown LD, Cai TT, DasGupta A. Interval estimation for a binomial proportion. *Statistical science.* 2001;16(2):101–117.
36. Hentschke H, Stüttgen MC. Computation of measures of effect size for neuroscience data sets. *Eur J Neurosci.* 2011;34(12):1887–1894.
37. Webb JT, Ferguson MA, Nielsen JA, Anderson JS. BOLD Granger causality reflects vascular anatomy. *PLoS One.* 2013;8(12):e84279.
38. Sambataro F, Blasi G, Fazio L, et al. Treatment with olanzapine is associated with modulation of the default mode network in patients with Schizophrenia. *Neuropsychopharmacology.* 2010;35(4):904–912.
39. Zhang XY, Zhang RL, Pan M, Chen DC, Xiu MH, Kosten TR. Sex difference in the prevalence of smoking in Chinese schizophrenia. *J Psychiatr Res.* 2010;44(14):986–988.
40. Camchong J, MacDonald AW III, Bell C, Mueller BA, Lim KO. Altered functional and anatomical connectivity in schizophrenia. *Schizophr Bull.* 2011;37(3):640–650.
41. Orliac F, Naveau M, Joliot M, et al. Links among resting-state default-mode network, salience network, and symptomatology in schizophrenia. *Schizophr Res.* 2013;148(1-3):74–80.
42. Brown S, Inskip H, Barraclough B. Causes of the excess mortality of schizophrenia. *Br J Psychiatry.* 2000;177:212–217.
43. Hennekens CH, Hennekens AR, Hollar D, Casey DE. Schizophrenia and increased risks of cardiovascular disease. *Am Heart J.* 2005;150(6):1115–1121.
44. Rossi S, Hallett M, Rossini PM, Pascual-Leone A; Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol.* 2009;120(12):2008–2039.
45. Hallett M. Transcranial magnetic stimulation and the human brain. *Nature.* 2000;406(6792):147–150.
46. Chen X, Ji GJ, Zhu C, et al. Neural correlates of auditory verbal hallucinations in schizophrenia and the therapeutic response to theta-burst transcranial magnetic stimulation. *Schizophr Bull.* 2019;45(2):474–483.

47. Cole DM, Beckmann CF, Long CJ, Matthews PM, Durcan MJ, Beaver JD. Nicotine replacement in abstinent smokers improves cognitive withdrawal symptoms with modulation of resting brain network dynamics. *Neuroimage.* 2010;52(2):590–599.
48. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci U S A.* 2005;102(27):9673–9678.
49. Spreng RN, Stevens WD, Chamberlain JP, Gilmore AW, Schacter DL. Default network activity, coupled with the frontoparietal control network, supports goal-directed cognition. *Neuroimage.* 2010;53(1):303–317.
50. Ji G-J, Liao W, Chen F-F, Zhang L, Wang K. Low-frequency blood oxygen level-dependent fluctuations in the brain white matter: more than just noise. *Sci Bull.* 2017;62:656–657.