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Temporal dynamic changes of intrinsic brain activity in schizophrenia with cigarette smoking

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ABSTRACT

Mounting evidence from multimodal neuroimaging studies has supported a neurobiological basis for schizophrenia-nicotine dependence comorbidity. However, this evidence comes exclusively from studies measuring static intrinsic activity/connectivity of the brain, while the dynamic effects of this comorbidity remain poorly understood. The current study therefore sought to examine whether temporal dynamic intrinsic brain activity interacted with diagnosis (schizophrenics vs. healthy controls) and smoking status (smokers vs. non-smokers). We used a mixed sample design and included the following four groups: i) schizophrenic smokers (n = 22), ii) schizophrenic non-smokers (n = 27), iii) healthy control smokers (n = 22), and iv) healthy control non-smokers (n = 21). All subjects underwent functional magnetic resonance imaging during the resting state. The temporal variability in intrinsic brain activity among the four groups was compared using a novel dynamic amplitude of low-frequency fluctuation (dALFF) method. A significant main effect of diagnosis was found in the left superior parietal gyrus (SPG; $F_{(1, 88)} = 142.1$, $P < 0.0001$). Moreover, the dALFF strength in the SPG was positively correlated with disease duration in patients with schizophrenia ($Rho_{(46)} = 0.43$, $P = 0.002$). In addition, a significant interaction between diagnosis and smoking status was observed in the left dorsolateral prefrontal cortex (DLPFC; $F_{(1, 88)} = 7.39$, $P = 0.008$), which was consistent with the self-medication hypothesis. Together, this study has demonstrated for the first time that nicotine restores dynamic intrinsic brain activity in the left DLPFC in patients with schizophrenia. This interaction may be a clinical neuromarker for increased comorbid smoking in schizophrenia.

1. Introduction

Individuals with schizophrenia have a higher prevalence (70–80%) of cigarette smoking than the general population (de Leon and Diaz, 2005), termed schizophrenia-nicotine dependence comorbidity, which is an association that is complicated and multifactorial (Krishnadas et al., 2012; Liao et al., 2018a; Liao et al., 2018c). Currently, the schizophrenia–nicotine dependence comorbidity is attributed to two plausible hypotheses (Potvin et al., 2016). The self-medication hypothesis supposes that smoking can alleviate the negative symptoms and cognitive symptoms of schizophrenia, as well as reduce the side-effect of antipsychotics (Winterer, 2010). Alternatively, the addiction vulnerability hypothesis maintains that patients with schizophrenia overvalue drug-like rewards, and devalue the potential negative consequences of substance abuse, which makes patients with schizophrenia more vulnerable to the rewarding effect of nicotine (Krystal et al., 2006). However, the neurobiological basis underlying these hypotheses of schizophrenia-nicotine dependence comorbidity remains unclear.

Mounting evidence from human multimodal neuroimaging studies has supported a neurobiological basis for the schizophrenia-nicotine dependence comorbidity. Brain morphometry study has found reduced gray matter volume in the prefrontal cortex in both main effect of disease (schizophrenia vs. health) and main effect of smoking (smokers vs. non-smokers), demonstrating an additive effect of schizophrenia and smoking (Yokoyama et al., 2018). Moreover, diffusion study has found reduced white matter integrity in the striatal and frontal cortices in both simple effect of disease (schizophrenic non-smokers vs. healthy non-smokers) and simple effect of smoking (healthy smokers vs. healthy non-smokers), indicating an independent effect of schizophrenia and smoking (Zhang et al., 2010). In addition, recent task-free (resting-state) functional magnetic resonance imaging (fMRI) studies have evaluated intrinsic brain activity and connectivity in individuals with schizophrenia-nicotine dependence comorbidity, and found that cigarette smoking restores intrinsic brain activity in the right striatal and prefrontal cortices in patients with schizophrenia (Liu et al., 2018). An

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earlier study reported that schizophrenia and smoking status shared functional connectivity circuits between the dorsal anterior cingulate cortex and limbic system. Findings from resting-state studies have largely supported or complemented the prevailing self-medication hypothesis. However, these resting-state fMRI studies have focused on static intrinsic brain activity and connectivity, and have not assessed the dynamic effects of the schizophrenia-smoking comorbidity.

Brain activity is inherently dynamic (Bassett and Sporns, 2017; Calhoun et al., 2014). A map of the brain's dynome reflects its temporal variability, which relates to the functional ability of neural networks (Kim et al., 2017). The study of the brain's dynome can assess the variability of network interactions as well as compare stability across populations, whereas a static analysis cannot (Cai et al., 2018). Several studies have reported aberrant dynamic connectivity in schizophrenia, such as abnormalities in the temporal variability of functional connectivity (Rashid et al., 2016) and weakened dynamic connectivity states (Du et al., 2016). In addition to functional connectivity, which mainly targets the spatial dimension, the amplitude of low-frequency fluctuations (ALFF) of fMRI signals measures information in the temporal dimension (Liao et al., 2019). Furthermore, using simultaneous electroencephalography (EEG)-fMRI, Liao et al. have demonstrated that dynamic ALFF changes are linked to changes in EEG band power, and that there was a positive association between the activation of EEG alpha rhythms and dynamic ALFF in the default mode network (DMN). Higher ALFF dynamics (i.e. temporal variabilities) would generally be beneficial to the adaptability and efficiency of neural systems (Liao et al., 2019). Thus, time-variant brain activity characterized by dynamic ALFF might underscore the disrupted brain activity in various mental disorders (Fu et al., 2018; Li et al., 2019). The dynamics of brain activity in patients with schizophrenia-smoking comorbidity have not yet been quantified.

In this study, we assessed dynamic ALFF (dALFF) (J. Guo et al., 2019; Li et al., 2019) in order to measure the temporal variability of intrinsic brain activity. To test whether, and how, an interaction exists between schizophrenia and nicotine addiction, four groups of subjects (smoking/non-smoking patients with schizophrenia and smoking/non-smoking healthy controls) were recruited. We hypothesized that the interaction between schizophrenia and smoking would show altered dynamic patterns of intrinsic brain activity, and that analysis of these patterns would support either the self-medication hypothesis or the vulnerability hypothesis. Furthermore, we assessed whether schizophrenia diagnosis and smoking status affected certain brain regions.

2. Materials and methods

2.1. Participants

Four groups of subjects were included: i) schizophrenia patients with no history of smoking (n = 29); ii) schizophrenia patients who were current daily smokers (n = 27); iii) healthy controls with no history of smoking (n = 21), and iv) healthy controls with a history of smoking (n = 22). Patients were evaluated using schizophrenia criteria based on the Structured Clinical Interview of the DSM-IV, Patient Edition, by trained physicians. Subjects were excluded if they i) had current (within the last 12 months) comorbid substance use disorder other than cigarettes; ii) had concomitant neurological disorders; or iii) had gross abnormalities detected by brain MRI. Three patients were excluded due to incomplete scanning, and four patients were excluded from further analyses due to excessive head motion. In total, 27 non-smokers and 22 smokers with schizophrenia were included for further analysis. They provided information on medication and duration of illness. Five patients were classed as first-episode patients, and the remaining 44 were diagnosed as chronic schizophrenia patients. Thirty-nine patients who took antipsychotic medication were considered clinically medication stable, as they had no change in medication over the past 3 months. With the exception of antipsychotic drugs, no other drugs were reported to be continuously used for >1 week during the month prior to testing. The duration of disease was calculated using age at onset and age at the time of assessment. The Positive and Negative Syndrome Scale (PANSS) was used to assess symptom severity in all patients.

Participants who had never smoked and reported complete abstinence from all nicotine products were classified as non-smokers. Participants who smoked any number of cigarettes daily for at least 1 year, and had not abstained from smoking for longer than 3 months in the past year, were classified as smokers. Smokers were encouraged to smoke prior to scanning to avoid withdrawal after effects. However, participants were required to refrain from smoking 30 min before scanning to avoid the effects of an immediate nicotine peak (Addicott et al., 2015). The severity of nicotine addiction was assessed using pack-years for chronic effects, and the Fagerstrom Test for Nicotine Dependence [FTND] for current effects.

All patients and healthy controls provided informed consent to the study protocol. Examinations were carried out in accordance with the Declaration of Helsinki, 1975. The study was reviewed and approved by the Local Medical Ethics Committee of the First Affiliated Hospital of Chongqing Medical University.

2.2. MRI data acquisition

Functional images were acquired on a 3.0 Tesla MRI scanner (GE Medical Systems) at the First Affiliated Hospital of Chongqing Medical University. All subjects were requested to keep their eyes closed, and foam padding was used to minimize head movements. After each scanning session, the responsiveness of the subjects was tested by vocal communication to determine if they had fallen asleep during the scan. At the end of each session, subjects were also asked if they had fallen asleep during scanning. Resting-state functional images were acquired using an echo-planar imaging sequence (repetition time = 2000 ms, echo time = 30 ms, flip angle = 90°). Thirty-three transverse slices (field of view = 220 × 240 mm^2, matrix = 64 × 64, slice thickness = 4 mm, 240 volumes) that aligned along the AC-PC line were acquired with a total scan time of 480 s.

2.3. Data processing

Data processing was performed using the Data Processing & Analysis for (Resting-State) Brain Imaging (DPABI) (Yan et al., 2016) (DPABI V2.3), SPM12 and custom code written in MATLAB. Functional images were slice-timing corrected, realigned (cut off < 3 mm or 3°), spatially normalized to the Montreal Neurologic Institute space and re-sampled to 3 × 3 × 3 mm^3. Next, several spurious variances (24 head motion parameters, global signals, ventricular signals, and white matter signals) were regressed out using multiple linear regression analysis. Framewise displacement (FD) was calculated for each time point (Power et al., 2012), and participants with mean FD value exceeding 0.5 mm were excluded. Functional images were spatially smoothed using a Gaussian kernel of full-width at half-maximum of 8 mm. Subsequently, functional images were trended and temporal band-pass filtered between 0.01 Hz and 0.08 Hz.

2.4. Estimation of dALFF

The dALFF analysis was performed using the Dynamic Brain Connectome (DynamicBC) toolbox (Liao et al., 2014) (V2.0 http://restfmri.net/forum/DynamicBC). A sliding window approach was performed to characterize the temporal dynamic patterns. Previous studies have suggested that a frequency interval of [0 − 1 / w] Hz should be a target, due to the low pass filtering effect of the window, and that the minimum window length should be above $1 / f_{min}$ (Leonardi and Van De Ville, 2015). Thus, a window size of 50 TRs (100 s), and a window overlap of 80% (window shifted by 10 TRs) were selected (Liao et al.,

2018b). We also examined the effect with other window sizes, and they were included in the validation analyses. The resulting dALFF values for each voxel constituted were used for further second-level group analyses. To quantify temporal variations in dALFF, we computed the coefficient of variation [CV = standard deviation (SD) / mean] map over time for each subject (Yan et al., 2017). The CV maps were then m-standardized across all voxels within the gray matter template and were used for further second-level group analyses.

2.5. Statistical analyses

Demographic and clinical data were analyzed using the chi-squared test for sex and handedness. Two-sample *t*-tests or the Mann-Whitney *U* test were used for the other demographic characteristics and/or clinical scores. Differences were considered significant at $P < 0.05$.

A two-way analysis of variance (ANOVA) was employed for whole-brain dALFF comparisons to analyze the interaction effects between the diagnosis group (schizophrenia vs. controls) and smoking status (smokers vs. non-smokers). Age, sex, education level, mean FD and medication dose (chlorpromazine dose-years) (Andreasen et al., 2010) were entered as nuisance covariates. The results were set at a threshold of $P < 0.05$ (combined height threshold $P < 0.001$ and cluster extent threshold at $k > 20$, AlphaSim corrected), and the Monte Carlo simulation was applied, taking into consideration both the individual voxel thresholding and cluster size.

Each identified cluster where the CV of dALFF was found to be significant for the effect of both schizophrenia and smoking was set as the region of interest (ROI). The CV of the averaged dALFF was extracted from the ROI, and then post-hoc comparisons were performed using a two-sample *t*-test to correct for multiple comparisons ($P < 0.05/2$ for main effect analyses, $P < 0.05/4$ for interaction effect analyses, Bonferroni-corrected).

2.6. Correlation analyses

To examine the association of dALFF with disease severity and cigarette smoking, we carried out correlation analyses between PANSS scores, duration of disease, FTND, pack-years, and the dALFF of ROIs that showed main effects of schizophrenia and smoking. We also used Spearman's correlation as a more robust measure for dALFF-clinical correlation (Schwarzkopf et al., 2012).

2.7. Validation analyses

We carried out additional analyses to validate our findings. Demographic and clinical data showed that non-smokers differed from smokers in the percentage of males; therefore, we repeated the analysis using only male participants. We also examined the effect with other window sizes (30 TRs and 100 TRs) to validate our interaction results. The validation analyses were performed on ROI-derived values (using ROIs identified in the main analysis). To determine if there were differences between patients taking medication or not, we conducted an additional analysis that included 39 patients taking medication, and the remaining 10 sex-, age-, and education-matched patients not on medication.

3. Results

3.1. Participants

The patients with schizophrenia did not differ from healthy controls in terms of sex, age, or handedness. Patients with schizophrenia and healthy controls who were smokers did not differ from non-smokers in age, handedness or education level (Table 1). No differences were found in medication dose, duration of illness, FTND and lifetime smoking (pack-years). Demographic and clinical data showed that non-smokers differed from smokers in the percentage of males; therefore, we repeated the analysis using only male participants (see Validation analyses).

3.2. Main effects

The main effect of schizophrenia was found in the left superior parietal gyrus (SPG) (peak (MNI): −21, −48, 69; Brodmann area (BA): 5/7; cluster size: 20; peak F value: 20.6; Fig. 1A). No main effects were found for smoking. Planned post-hoc analysis revealed increased CV of dALFF in schizophrenic non-smokers, compared to healthy non-smokers ($t_{(46)} = 12.34$, $P < 0.0001$, Bonferroni corrected with twice planned comparisons); and increased CV of dALFF in schizophrenic smokers compared to healthy control smokers ($t_{(42)} = 6.28$, $P < 0.0001$; Bonferroni corrected with twice planned comparisons; Fig. 1B). The dALFF of the SPG positively correlated with the disease duration of schizophrenic patients ($Rho_{(46)} = 0.43$, $P = 0.002$; Fig. 2), whereas PANSS scores did not. One outlier was identified in the correlation analyses.

3.3. Interaction effects

An interaction effect of disease and smoking was found in the left dorsolateral prefrontal cortex [DLPFC; peak (MNI): −45, 33, 18; BA: 46; cluster size: 21; peak F value: 17.5; Fig. 3A]. Planned post-hoc analysis of the DLPFC showed significantly increased CVs of dALFF in schizophrenic smokers compared to schizophrenic non-smokers ($t_{(47)} = 3.66$, $P < 0.0001$, Bonferroni corrected with four times comparisons). No significant difference between smoking controls and non-smoking controls was observed ($U = 209$, $P = 0.6$; Fig. 3B).

3.4. Validation analyses

When other window sizes were included, such as 30 TRs and 100 TRs, the interaction effect of disease and smoking status in the left DLPFC remained significant (Fig. 4A–B).

Non-smoking participants differed from smoking participants in the percentage of males, which may have had an impact on the results. To clarify this, repeated analysis using only male subjects was carried out to examine how this difference affected the interaction findings. Results indicated that the interaction effect was observed in the left DLPFC (Fig. 4C).

Additional analysis showed that there was no significant drug effect on medication status, which may have indicated that antipsychotic drugs did not significantly impact regional brain dynamics.

4. Discussion

The current study used a 2×2 factorial design for diagnosis and smoking status. We identified the dynamic intrinsic brain activity among four groups of subjects using a novel temporal variation of the dALFF method. Compared to healthy controls, schizophrenic patients showed increased dynamic brain activity in the left SPG, irrespective of smoking status. In contrast, there were no main effects of smoking. More importantly, smoking restored the dynamic intrinsic brain activity in the left DLPFC of schizophrenic patients due to the interaction effect, an observation which may support the self-medication hypothesis.

Conventional ALFF can be a proxy for static intrinsic brain activity. Previous research has reported that static brain activity is altered in both patients with schizophrenia (Hoptman et al., 2010; Huang et al., 2010) and smokers (Wang et al., 2017). Moreover, abnormal static brain activity has been associated with the effects of both schizophrenia and smoking in the right caudate, right postcentral gyrus, and medial prefrontal cortex (Liu et al., 2018). However, ALFF only generates a single, static estimate of brain activity. Dynamic brain activity is captured using the temporal variability of dALFF, which describes the temporal changes in energy consumption and reflects the adaptability of neural

Table 1
Demographic and clinical characteristics of subjects.

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

networks, measures which are linked to various mental processes (Fu et al., 2018). This novel temporal variability may also allow clinical characterization (Cai et al., 2018; X. Guo et al., 2019; Li et al., 2019). Fractional ALFF (fALFF) is not highly sensitive to noise fluctuations from major arteries and veins (Zou et al., 2008), but ALFF has shown higher test-retest reliability than fALFF (Zuo and Xing, 2014). In addition, our previous work found a highly positive association between dALFF and dynamic fALFF (Liao et al., 2019). Thus, guided by previously reported results (Fu et al., 2018; Li et al., 2019; Liao et al., 2019), we used the dALFF to detect temporal dynamics of brain activity in the current study. However, further work should seek to elaborate on the reliability of dALFF or dynamic fALFF.

The fact that the temporal variability of intrinsic brain activity is abnormally related to the DLPFC in schizophrenia patients with nicotine dependence is worthy of consideration. The dynome beyond the brain network, expressed by rhythmic activity, has been found to be altered in morbid states (Kopell et al., 2014; Li et al., 2018). Compared to healthy controls, patients with schizophrenia show mixed results of left DLPFC activity in various cognitive tasks (Manoach et al., 2000; Minzenberg et al., 2009). These inconsistencies may be due to not controlling smoking as a confounder (Leyba et al., 2008). The strength of the current study is that we recruited four groups to control for cigarette smoking, which allowed us to investigate whether there was an interaction between disease diagnosis and smoking status.

Additionally, functional dysconnectivity associated with the left DLPFC is observed in patients with schizophrenia at rest, which may partially relate to a disturbance in intrinsic brain activity (Zhou et al., 2007). Our results indicated that smokers showed increased dynamic brain activity in the DLPFC, with and without schizophrenia. These results are supported by previous studies where smokers exposed to smoking stimuli showed significant activation of the DLPFC (McBride et al., 2006), and this activation was positively correlated with functional connectivity between the DLPFC and anterior cingulate cortex (Zhang et al., 2011). Smokers with high level of anhedonia were more likely to relapse (Cook et al., 2010; Leventhal et al., 2009), while anhedonia in patients with schizophrenia correlated negatively with metabolic activity in the DLPFC (Park et al., 2009). In line with these studies, we found that smoking did not result in a significant change in healthy controls, but restored the variability of brain activity in the DLPFC in patients with schizophrenia, which may support the self-medication hypothesis. We speculated that smoking improved the adaptability of the DLPFC in patients with schizophrenia, and compensated for regional disturbances that may be due to anhedonia (Haroon et al., 2018). Collectively, a multifactorial influence on the DLPFC in patients with schizophrenia and nicotine dependence was observed. Smoking was only allowed up until 30 min prior to scanning to avoid measuring withdrawal effects (Galvan et al., 2011), but we have not ruled out whether the remaining nicotine levels may have had an effect on brain dynamics. Future studies should employ a control group of non-smokers who are administered nicotine. From the perspective of the level of changes in brain activity, these results may guide the clinical treatment of schizophrenia with smoking comorbidity.

We also noted that the disease effects impacted the dALFF in the left SPG. Previous morphometry studies have reported brain volume deficits within parietal regions in patients with schizophrenia (Cannon et al., 2002; Thompson et al., 2001). Other functional studies found significantly increased ALFF in the left SPG of patients with schizophrenia receiving antipsychotic treatment (Lui et al., 2010), and significant activations in the parietal cortex during working memory performance tasks (Quintana et al., 2003). It is plausible that enhanced function in the SPG may be associated with dynamic brain activity improvements, consistent with the idea that resting state brain activity is highly co-evolved with brain connectivity over time (Fu et al., 2018).

4.1. Limitations

There were several limitations to this study. First, the demographic analysis showed that non-smoking participants differed from smoking participants in the percentage of male subjects, although the validation analysis results using only male subjects suggested that the interaction between schizophrenia and smoking was not significantly impacted by this factor. We also found a lower smoking prevalence in women with

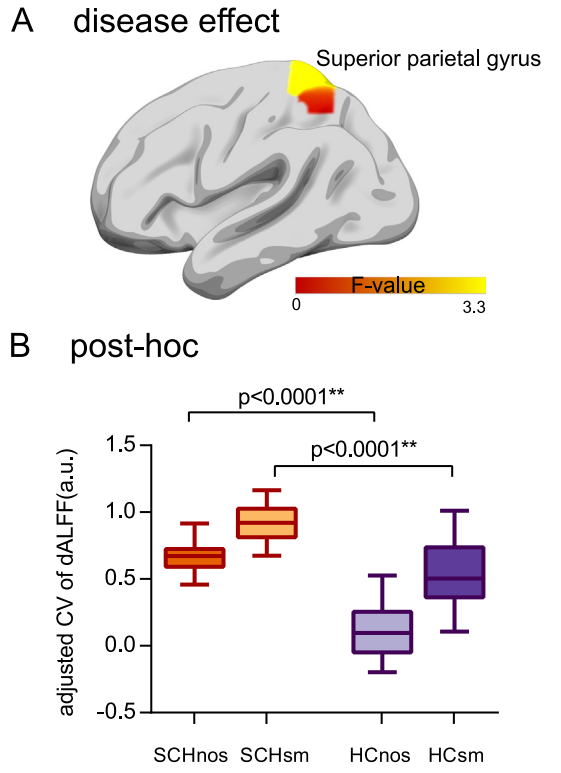

Fig. 1. The main effect of schizophrenia. (A) Dynamic ALFF shows the significant main effect of disease in the SPG using two-way ANOVA. The statistical significance level was set at P < 0.05 (combined height threshold P < 0.001 and cluster extent threshold at k > 20, AlphaSim corrected). (B) The inset box-and-whisker plot indicates the planned post-hoc analysis between SCHnos and HCnos, and SCHsm and HCsm using two-sample *t*-tests. The vertical bar indicates the maximum and minimum across subjects. ** denotes P < 0.05 Bonferroni correction with two times planned comparisons. ALFF; amplitude of low-frequency fluctuation; SPG, superior parietal gyrus; SCHnos, schizophrenic non-smokers; HCnos, healthy nonsmokers; SCHsm, schizophrenic smokers; HCsm, healthy smokers; CV, coefficient of variation.

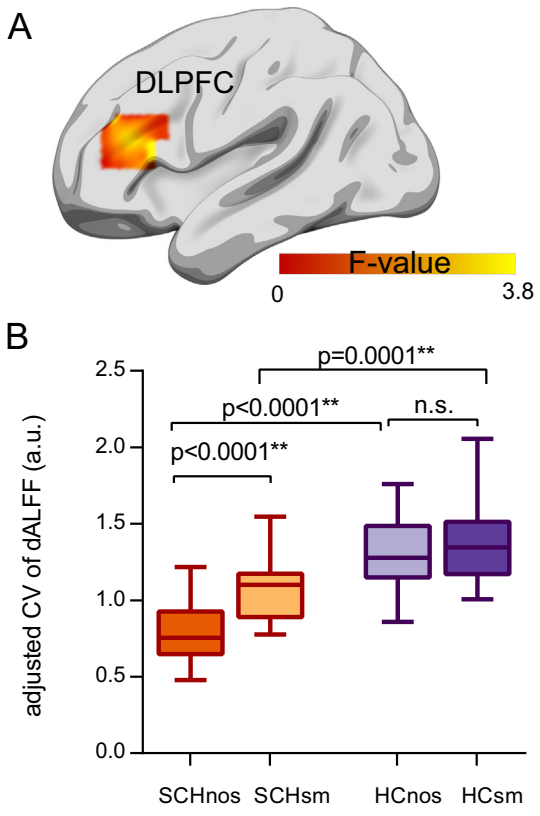

Fig. 3. The interaction effect of schizophrenia and smoking. (A) A significant interaction effect shown by dALFF in the DLPFC using two-way ANOVA. The statistical significance level was set at P < 0.05 (combined height threshold P < 0.001 and cluster extent threshold at k > 20, AlphaSim corrected). (B) Planned post-hoc analysis of the DLPFC among the four groups. The vertical bar indicates the maximum and minimum across subjects. ** denotes P < 0.05 Bonferroni correction with four times planned comparisons. DLPFC, dorsolateral prefrontal cortex.

and without schizophrenia than previously reported in western populations. The low prevalence rates in our study are consistent with previously reported statistics of Chinese patients with schizophrenia (Tang et al., 2007a; Tang et al., 2007b; Xu et al., 2014). Indeed, it appears the sex ratio imbalance among smokers we have observed is reflective of the Chinese population, as it is consistent with general population reports in the 2010 Global Adult Tobacco Survey (Giovino et al., 2012). This imbalance could be influenced by traditional sex roles, social norms, cultural resistance, and sex empowerment (Chen et al., 2015; Yang et al., 2016). It also reflected the cultural differences between China and other western countries (Xu et al., 2014; Yang et al., 2016), which would contribute to the sex ratio imbalance among Chinese smokers (Yang et al., 2016), which is also applicable to Chinese patients with schizophrenia (Tang et al., 2007b; Xu et al., 2014).

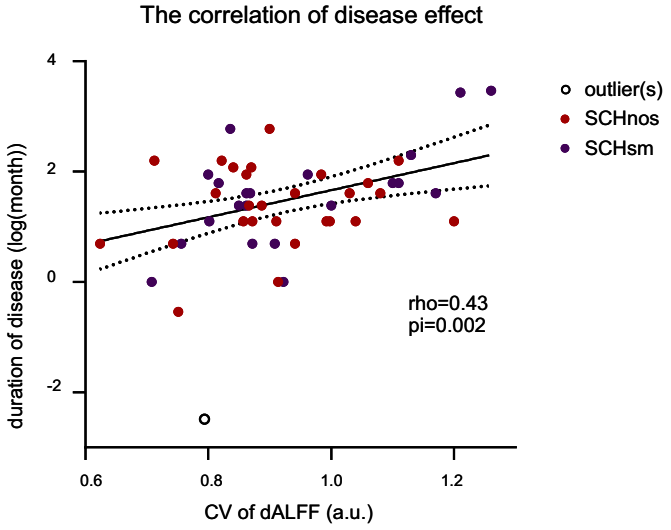

Fig. 2. The correlation between duration of disease (log(month)) and dALFF (CV value) of the SPG in patients with and without smoking (Rho = 0.43, P = 0.002). Of note, the correlation was significant after one outlier was removed by Shepherd's π correlation.

Second, whether antipsychotic drugs in patients with chronic schizophrenia have an influence on brain activity is controversial. We reduced the impact by using medication dose as a covariate in the regression analysis. Further studies should focus on assessing brain activity following chronic use of antipsychotics.

In addition, the oral nicotine dosage of smokers was not assessed. Further work on this topic would benefit from a controlled measure of nicotine concentration, e.g. derived from a blood sample at the time of the scan. In future work, the effect of nicotine on a non-smoking control group should also be investigated.

5. Conclusion

Smoking restored the temporal variability of the dALFF in the left DLPFC in patients with schizophrenia. Our results revealed that dynamic intrinsic brain activity contributed to schizophrenia and smoking comorbidity. These dynamic patterns may be effective indicators in future clinical studies.

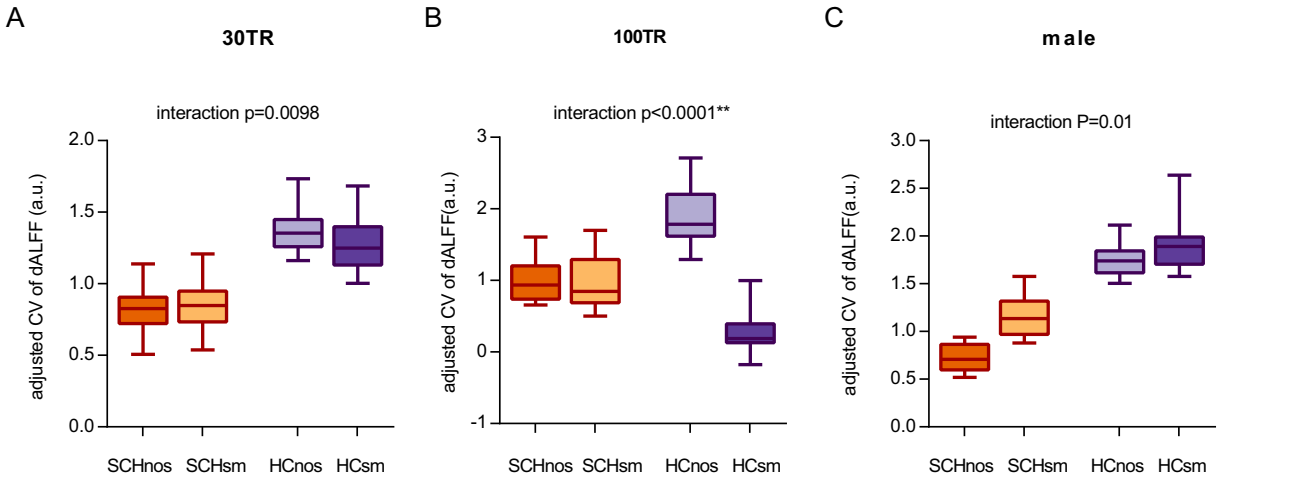

Fig. 4. Reproducibility results in different sliding-window length and only male subjects. Two additional sliding-window lengths chosen were 30 TRs (A) and 100 TRs (B) and using only male subjects were included to avoid a gender imbalance in smokers (C).

Contributors

Author Huafu Chen and Lian Du designed the study and wrote the protocol. Author Yao Meng managed the literature searches and analyses. Authors Jiao Li and Yun-shuang Fan undertook the statistical analysis, and author Siqi Yang and Wei Liao wrote the first draft of the manuscript.

All authors contributed to and have approved the final manuscript.

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Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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