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Tiantian Qiu

Linyi People's Hospital <https://orcid.org/0000-0002-9428-4117>

Fei Xie

Linyi People's Hospital

Qingze Zeng

Zhejiang University School of Medicine Second Affiliated Hospital

Zhujing Shen

Zhejiang University School of Medicine Second Affiliated Hospital

guijin Du

Linyi People's Hospital

Xiaopei Xu

Zhejiang University School of Medicine Second Affiliated Hospital

Chao Wang

Zhejiang University School of Medicine Second Affiliated Hospital

Xiaodong Li

Linyi People's Hospital

Xiao Luo

Zhejiang University School of Medicine Second Affiliated Hospital

Kaicheng Li

Zhejiang University School of Medicine Second Affiliated Hospital

Peiyu Huang

Zhejiang University School of Medicine Second Affiliated Hospital

Tianyi Zhang

Tongde Hospital Of Zhejiang Province

Jinling Zhang

Linyi People's Hospital

Shouping Dai

Linyi People's Hospital

Minming Zhang (✉ zhangminming@zju.edu.cn)

Zhejiang University School of Medicine Second Affiliated Hospital

Research Article

Keywords: Mild cognitive impairment, cigarette smoking, striatum, corticostriatal circuits, resting-state functional connectivity.

Posted Date: October 18th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-959685/v1>

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Tiantian Qiu^{a,†}, Fei Xie^{b,†}, Qingze Zeng^{c,†}, Zhujing Shen^c, Guijin, Du^a, Xiaopei Xu^c, Chao Wang^c, Xiaodong Li^a, Xiao Luo^c, Kaicheng Li^c, Peiyu Huang^c, Tianyi Zhang^d, Jinling Zhang^{e,*}, Shouping Dai^{a,*}, Minming Zhang^{c,*}, for the Alzheimer's Disease Neuroimaging

^aDepartment of Radiology, Linyi People's Hospital, Linyi, China

^bDepartment of Equipment and medical engineering, Linyi People's Hospital, Linyi, China

^cDepartment of Radiology, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China

^dDepartment of Neurology, Tongde Hospital of Zhejiang Province, Hangzhou, China

^eCancer Center, Linyi People's Hospital, Linyi, China

[†]These authors have contributed equally to this work and share first authorship.

^{*}These authors have contributed equally to this work and share senior authorship.

A running title: Cigarette smoking effects on MCI

Abstract: 245 words

Manuscript :2991 words

Correspondence author:

Minming Zhang, zhangminming@zju.edu.cn

Tel./Fax: +86 057187315255

Department of Radiology, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China

Address: No.88 Jiefang Road, Shang-cheng District, Hangzhou 310009, China.

Shouping, Dai, daishouping@sina.cn

Tel./Fax: +86 05398225769

Department of Radiology, Linyi People's Hospital, Linyi, China

Address: No.27 east section of Jiefang Road, Lanshan District, Linyi 276000, China

Jinling Zhang, jinlingzhang931@163.com

Tel./Fax: +86 05398097161

Cancer Center, Linyi People's Hospital, Linyi, China

Address: No.27 east section of Jiefang Road, Lanshan District, Linyi 276000, China

Abstract

To explore the interaction effects of smoking status (non-smoking vs. smoking) and disease (cognitively normal (CN) vs. MCI) based on resting-state functional connectivity (rsFC) of the corticostriatal circuits. We included 304 CN non-smokers, 44 CN smokers, 130 MCI non-smokers, and 33 MCI smokers. The seed-based rsFC of striatal subregions (caudate, putamen, and nucleus accumbens [NAc]) with the whole-brain voxel was calculated. Furthermore, we performed mixed effect analysis to explore the interaction effects between smoking status and disease. Significant interaction effects were detected between: (1) right caudate and left inferior parietal lobule (IPL); (2) right putamen and bilateral cuneus; (3) bilateral NAc and bilateral anterior cingulate cortex (ACC). The *post-hoc* analyses revealed that the CN smokers showed increased rsFC between right caudate and left IPL compared to non-smokers; while the MCI smokers demonstrated decreased rsFC between right putamen and cuneus, and increased rsFC between bilateral NAc and ACC compared to non-smokers. In MCI smokers, the rsFC value between left NAc and ACC was positively correlated with Semantic Verbal Fluency (SVF, $r = 0.387$, $p = 0.026$), and the rsFC value between right NAc and ACC was positively correlated with SVF ($r = 0.390$, $p = 0.025$), Wechsler memory scale-logical memory (WMS-LM) immediate recall ($r = 0.378$, $p = 0.03$), and WMS-LM delayed recall ($r = 0.367$, $p = 0.036$). Our findings suggest that chronic nicotine exposure may lead to functional connectivity alterations of corticostriatal circuits in MCI patients, and the pattern is different from CN smokers.

Keywords: Mild cognitive impairment; cigarette smoking; striatum; corticostriatal circuits; resting-state functional connectivity.

Introduction

Alzheimer's disease (AD) is the most common type of dementia in elderly, which is characterized by progressive and irreversible cognitive decline. Mild cognitive impairment (MCI) is the prodromal phase of AD and is associated with a high risk of progression to AD (Larrieu et al., 2002). Recent clinical trials of AD targeting the amyloid hypothesis have failed (Knopman, 2019), which led us to think that controlling risk factors could curb the progression of AD. Cigarette smoking is recognized as one of the important risk factors of AD (Rusanen et al., 2011). Therefore, exploring the effects of smoking on brain functional activity in MCI patients is of great significance for guiding early clinical intervention.

Nicotine is the psychoactive component of cigarette smoking which causes the addiction process. It excites dopaminergic neurons of the mesencephalon by activating the nicotinic acetylcholine receptors (nAChRs) on the dopaminergic somata (Livingstone and Wonnacott, 2009), inducing the dopamine release in the target areas, particularly the striatum (Pontieri et al., 1996; Balfour, 2004; Subramaniyan and Dani, 2015). Striatum dopamine system dysfunction, such as lower dopamine receptors availability (Okita et al., 2016) and reduced [¹¹C]raclopride binding potential (an indirect measure of dopamine release) by positron emission tomography (Brody et al., 2004) has been reported in nicotine addiction. Specifically, the striatum is comprised of the dorsal striatum (DS) and ventral striatum (VS). The DS (mainly the caudate and putamen) is involved in motor control and cognitive functions; while VS (mainly the nucleus accumbens [NAc]), the ventral extension of the DS, plays a central role in reward, development of addictive behaviors and habit formation (Haber, 2016). Furthermore, the DS and VS showed wide connections with cortical and limbic regions, such as the prefrontal cortex (PFC), orbital frontal cortex, anterior cingulate cortex (ACC), insula, and hippocampus, which constitutes the close corticostriatal circuits that contribute to the

processes of addiction and cognition(Looi and Walterfang, 2013; Steiner and Van Waes, 2013).

The abnormal functional connectivity (FC) of the corticostriatal circuits has been observed in healthy smokers and AD/MCI patients. For example, the FC of the striatum with dorsal ACC was negatively correlated with the severity of nicotine addiction in healthy smokers(Hong et al., 2009). In addition, AD and MCI patients exhibited abnormal connectivity between the striatum and cortical regions, including the PFC, medial frontal cortex, and middle temporal cortex(Tam et al., 2015; Quan et al., 2020; Wang et al., 2020). Another study also found that reduced FC of striatum with precuneus was correlated with memory decline in patients with AD (Anderkova et al., 2017). However, the exact effects of smoking on FC alterations of corticostriatal circuits in MCI patients remains unclear.

This study aimed to investigate the smoking effects on the FC alterations of the corticostriatal circuits in patients with MCI. Both DS and VS subregions (caudate, putamen, and NAc) were chosen as the seeds for FC analyses. Based on the converging target of corticostriatal circuits in both cigarette smoking and AD, we hypothesized that there is an interaction effect between smoking status and disease.

Methods

Study participants

The data in this study was obtained from the Alzheimer's disease Neuroimaging Initiative (ADNI) database (<http://adni.loni.usc.edu/>). The Institutional Review Board approved the study of all the participating institutions. Informed written consent was obtained from all participants at each site. Based on the ADNI 3 databases, we identified 378 right-handed cognitively normal subjects and 182 MCI patients with complete neuropsychological evaluations, structural magnetic resonance imaging (MRI), and resting-state functional MRI (rsfMRI) scans. We downloaded data from the

ADNI database before March 2021. The criteria for MCI and CN have been described in detail in previous studies (Qiu et al., 2016). Then, we classified MCI and CN subjects into non-smoking and smoking subgroups based on self-report smoking history. Non-smoking was defined as participants who reported they never smoked cigarettes during their lifetime, and smoking was defined as the presence of any history of smoking. After screening, 49 participants (including 29 CN non-smokers, 1 CN smoker, and 19 MCI non-smokers) were excluded for excessive head motion (details later). Finally, 304 CN non-smokers, 44 CN smokers, 130 MCI non-smokers, and 33 MCI smokers entered subsequent analyses.

Demographic and clinical characteristics

Demographic factors including age, sex, and education level, and vascular risk factors including hypertension, diabetes mellitus, and hypercholesterolemia were assessed. Hypertension was defined as systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, medical history of hypertension, or with antihypertensive medication treatment. Diabetes mellitus was defined as random blood glucose ≥ 11 mmol/dL, medical history of diabetes mellitus, or treatment with glucose-lowering medication. Hypercholesterolemia was defined as random blood cholesterol ≥ 11 mmol/L, medical history of hypercholesterolemia, or treatment with lipid-lowering medication. Neuropsychological tests in different cognitive domains, including memory (Wechsler memory scale-logical memory, WMS-LM, immediate and delayed recall); attention (Trail-Making Test, Part A, TMT-A); execution (Trail-Making Test, Part B, TMT-B); and language (Semantic Verbal Fluency, SVF) were included.

Imaging data acquisition

All subjects were scanned using a 3.0-Tesla Philips MRI scanner. The structural MRI images were acquired using a 3D MPRAGE T1-weighted sequence with the following parameters: repetition

time (TR) = 2300 ms; echo time (TE) = 2.98 ms; inversion time (TI) = 900 ms; 170 sagittal slices; within plane FOV = 256×240 mm²; voxel size = 1×1×1 mm³; flip angle = 9°; bandwidth = 240 Hz/pix. The rsfMRI images were obtained using an echo-planar imaging sequence with the following parameters: 197 time points; TR = 3000 ms; TE = 30 ms; slice thickness = 3.39 mm; spatial resolution = 3.39×3.39×3.39 mm³; flip angle = 90°; and matrix = 64×64.

Preprocessing of rsfMRI and structural MRI data

We preprocessed rsfMRI data using the Data Processing & Analysis for Brain Imaging (DPABI, <http://rfmri.org/dpabi>) (Yan et al., 2016) with Statistical Parametric Mapping software (SPM12, <http://www.fil.ion.ucl.ac.uk/spm/>) on the MATLAB platform (MathWorks, Natick, MA, USA). The first ten time points of rsfMRI data were discarded due to the instability of the initial MRI signal and the subjects' adaptation to the scanning noise. The remaining 187 images were corrected for timing differences between each slice and head motion (6-parameter rigid body). Subjects with more than 3.0 mm maximum displacement in any of the x, y, or z directions or 3.0° of any angular motion were discarded (including 29 CN non-smokers, 1 CN smoker, and 19 MCI non-smokers). Subsequently, rsfMRI images were spatially normalized to the standard EPI template and resampled into 3 × 3 × 3 mm³. The rsfMRI images were spatially smoothed with a Gaussian kernel of 6×6×6 mm³ full width at half maximum. Finally, linear trends and temporally filter (0.01 Hz < f < 0.08 Hz) were performed. Nuisance covariate regression was performed to minimize physiological noise using the Friston-24 head motion parameters (six head motion parameters, six head motion parameters from the previous time point, and the 12 corresponding squared items), as well as white matter (WM) signal and corticospinal fluid (CSF) signal. In addition, the framewise displacement (FD) jenkinson value of each subject was calculated to correct for the head motion artifacts.

The T1-weighted images were preprocessed and analyzed using the Computational Anatomy Toolbox (CAT12, <http://dbm.neuro.uni-jena.de/cat/>) and SPM12. The images were bias-corrected, tissue-classified (grey matter (GM), WM, and CSF), and registered using linear (12 parameter affine) and non-linear transformations (warping) within the CAT12 default preprocessing pipeline.

Striatum-based resting-state functional connectivity (rsFC) analysis

In order to explore the interaction effects between smoking status and disease on striatum-based rsFC, both left and right striatal subregions (i.e., caudate, putamen, and NAc) were chosen as the seeds for rsFC analyses according to Harvard-Oxford subcortical structural atlas. Dynamic brain connectome (DynamicBC) analysis toolbox (<http://restfmri.net/forum/DynamicBC>) (Liao et al., 2014) was used to create individual subject seed-to-voxel connectivity maps. First, each mask was resampled to the dimension of our normalized functional image with $3 \times 3 \times 3$ voxel size for seed-based rsFC analyses. Next, the rsFC maps were generated by calculating the Pearson correlation between the time course of striatal subregions and whole brain areas. Finally, the resulting rsFC maps were transformed to Z maps using Fisher's Z transformation.

Propensity score matching

Propensity score matching (PSM) implanted in SPSS version 26 was performed to balance the differences in demographic features between non-smoking and smoking subgroups in CN and MCI, and to reduce the bias due to confounding factors. A 1: 2 matching was used to pair subjects with CN smokers and MCI smokers based on the following covariates: age, sex, and education level. After PSM, 86 CN non-smokers, 44 CN smokers, 62 MCI non-smokers, and 32 MCI smokers were selected from the initial population. The demographic and clinical data were summarized in **Supplementary Table 1**. The interaction regions on rsFC of the striatal subregions were displayed in **Supplementary Fig 1 and Table 2**, and the results are consistent with those before PSM.

Statistical analysis

The statistical analyses of demographics and neuropsychological data were performed using SPSS 26.0 statistical software. We performed a group-level analysis using one-way analysis of variance (ANOVA) for continuous variables. If group-level test results were significant, *post-hoc* pairwise comparisons were performed (Bonferroni multiple comparison correction in parametric tests, Dunn multiple comparison tests in nonparametric tests). Binary data, such as sex, hypertension, diabetes mellitus, and hypercholesterolemia were compared between groups using a chi-square test.

The statistical analyses of the rsFC of striatal subregions(left and right caudate, putamen, and NAc) were performed using the DPABI toolbox(Yan et al., 2016). Specifically, we performed a 2×2 mixed effect analysis to explore the interaction effects of smoking status (non-smoking vs. smoking) and disease (CN vs. MCI). Age, sex, education level, head motion (FD value) and vascular risk factors were used as covariates. To control the effect of cortical atrophy on the functional analysis, normalized modulated (with the volumetric information encoded) GM maps were used as covariate images. The threshold was set to the voxel level at $p < 0.005$ and the cluster level at $p < 0.05$ after Gaussian random field (GRF) correction. To further understand how smoking status and disease interacted on the rsFC of the striatal subregions, we extracted the mean rsFC values from the interaction regions and further performed *post-hoc* pairwise comparisons ($p < 0.05$, Bonferroni correction). At last, partial correlation analysis was performed to investigate the correlation between the mean rsFC values of interaction regions and neuropsychological scores with age, sex, and education level as covariates ($p < 0.05$).

Results

Demographic and clinical characteristics

The demographic and clinical characteristics of the four subgroups were summarized in **Table 1**.

The MCI smokers (76.61 ± 7.54 years) were older ($p < 0.05$) than MCI non-smokers (72.98 ± 7.25 years). The CN smokers had a predominance of females than other subgroups ($p = 0.001$). There were no significant differences between subgroups in vascular risk factors ($p > 0.05$). The MCI patients (smokers and non-smokers) showed significantly lower neuropsychological performance on memory, attention, execution, and language than CN subjects ($p < 0.05$). The smokers (CN and MCI) showed no significant differences in neuropsychological performance compared to non-smokers ($p > 0.05$).

Smoking status $\times$ disease interaction on rsFC of the striatal subregions

The significant interaction effects of smoking status (non-smoking vs. smoking) $\times$ disease (CN vs. MCI) on rsFC of the striatal subregions were detected between: (1) right caudate and left inferior parietal lobule (IPL) (**Fig. 1A**); (2) right putamen and bilateral cuneus (**Fig. 1B**); (3) left NAc and bilateral anterior cingulate cortex (ACC) (**Fig. 1C**); and (4) right NAc and bilateral ACC (**Fig. 1D**). The interaction effects results of rsFC analyses were summarized in **Table 2**.

Then, *post-hoc* region-of-interest analyses were performed for the brain regions showing interaction effects (**Fig. 2**). Especially, the CN smokers showed increased rsFC of right caudate to left IPL than other subgroups. In MCI smokers, decreased rsFC of right putamen to cuneus and increased rsFC of bilateral NAc to ACC were observed when compared to MCI non-smokers.

Correlation between rsFC of the striatal subregions and cognition

We studied the relationships between rsFC values of the interaction regions (left IPL, bilateral cuneus, and bilateral ACC) and different cognition domains (**Table 3**). In MCI smokers, we found that the rsFC value between left NAc and ACC was positively correlated with language (SVF, $r = 0.387$, $p = 0.026$); the rsFC value between right NAc and ACC was positively associated with language (SVF, $r = 0.390$, $p = 0.025$) and memory (WMS-LM immediate recall, $r = 0.378$, $p = 0.03$;

delayed recall, $r = 0.367$, $p = 0.036$) (**Fig. 3**). After Bonferroni correction ($p < 0.05/20$) for multiple comparisons, there was no significant correlation between rsFC values of the interaction regions and neuropsychological scores.

Discussion

Our study explored the interaction effects between cigarette smoking status and disease based on the rsFC of the striatal subregions. In CN subjects, the smokers showed increased rsFC between the caudate and IPL compared to non-smokers. In MCI patients, the smokers demonstrated decreased rsFC between the putamen and cuneus, and increased rsFC between NAc and ACC compared to non-smokers. Our findings suggested that the effects of cigarette smoking exerted on corticostriatal circuits connectivity are different in CN smokers and MCI smokers.

The CN smokers showed increased rsFC between the caudate and IPL compared to non-smokers. There is increasing evidence that habitual mechanism plays a vital role in addiction (Yalachkov et al., 2009; Jasinska et al., 2014). Individuals with greater nicotine dependence severity had increased engagement of motor preparation circuits, suggesting increased reliance on habitual behavior (Claus et al., 2013). Specifically, the IPL is the key brain region controlling the conscious motor intention ‘wanting to move’, which specifies a general goal to be reached before movement planning (Desmurget and Sirigu, 2012). Previous studies demonstrated that smoking cue-induced activation in the IPL, which is associated with nicotine dependence severity (Engelmann et al., 2012; Yalachkov et al., 2013). Therefore, increased connectivity between the caudate and IPL indicated that smokers could have intense motor intention on craving for smoking before act to smoke. Furthermore, we observed decreased rsFC between the caudate and IPL in MCI smokers when compared with CN smokers. Besides the function of motor intention, the IPL is also a functional core of the default mode network (DMN), which plays a crucial role in episodic memory

retrieval(Buckner et al., 2008) and is vulnerable to AD neuropathology(Palmqvist et al., 2017; Chhatwal et al., 2018). Disrupted FC of the IPL/DMN has been widely reported in MCI and AD patients(Dennis and Thompson, 2014; Zhou and Seeley, 2014; Ibrahim et al., 2021). Moreover, a progressive declining trend of structural and functional connections within the DMN has also been observed from NC to MCI and then to AD patients(Zhu et al., 2013). Taken together, the IPL could be a key interaction region associated with smoking-related motor intention and cognition decline.

In MCI smokers, we found decreased rsFC of the putamen to cuneus when compared to non-smokers. The cuneus is a part of the visual associated cortex and participates in visual selective attention by relaying top-down information from the attention network to the visual cortex(Ninomiya et al., 2012). In addiction-related studies, chronic tobacco smoking could cause a decline in attention(Conti et al., 2019; Nadar et al., 2021). Moreover, chronic smokers also showed reduced gray matter volume and density in visual attention-related regions, such as the cuneus, lingual gyrus, and other occipital cortices(Gallinat et al., 2006). In patients with MCI, cognitive decline involve in episodic memory, visuospatial skills, and attention have been frequently reported(Nelson and O'Connor, 2008). Importantly, some declines in episodic memory might stem from early deteriorations in visual attention which might influence later memory(McDonough et al., 2019). In some rsfMRI studies, aberrant spontaneous low-frequency brain activity and regional homogeneity in the visual network have been observed in MCI patients(Pan et al., 2017; Zhen et al., 2018). Additionally, based on large-scale brain networks analysis, MCI patients also showed abnormal FC in the attention network(Wang et al., 2015; Sullivan et al., 2019).

It is worth noting that the MCI smokers also showed increased rsFC between the NAc and ACC compared to non-smokers. Increased intrinsic brain activity in MCI smokers had been reported in previous work(Zhang et al., 2020), which supports our finding. The ACC shows specific

interconnections with other PFC and dopaminergic striatal subregions, particularly the NAc, constituting the important frontostriatal reward circuit, which plays a key role in nicotine addiction (Haber and Knutson, 2010). As the primary ingredient of tobacco, nicotine shows a high affinity to nAChRs, which are widely distributed in the functional nodes of frontostriatal circuit (Hampel et al., 2018). Importantly, the nicotine could stimulate nAChRs, especially the $\alpha 4\beta 2$ and $\alpha 7$ subtypes, which protected neurons from A β -induced toxicity in vitro (Mehta et al., 2012). Therefore, the increased rsFC within the frontostriatal reward circuit in MCI smokers might indicate the compensatory mechanism of smoking against disrupted brain function caused by AD pathology to some extent. Furthermore, correlation analysis revealed that increased rsFC between NAc and ACC was positively correlated with memory and language in MCI smokers, which further emphasized the role of frontostriatal reward circuit in integrating information across the addiction and cognition.

The current study has several limitations. First, despite the large sample size of the ADNI database, the smoking subgroups are relatively small due to a positive selection from the population in respect to health and lifestyle in ADNI. Future studies with a larger sample size are needed to verify our work. Second, smoking history in the ADNI database is defined by subjective self-report from the medical record, including former and current smokers. Most participants lack detailed records such as the number, duration, and status (former or current). Future studies may further explore the effects of different smoking degrees or statuses on cognition. Finally, this cross-sectional study lacks clinical follow-up to make any possible inference between smoking and AD. Thus, longitudinal studies are needed to determine whether the FC alterations of corticostriatal circuits in smokers are related to disease progression.

Conclusions

In conclusion, chronic nicotine exposure may lead to functional connectivity disruption between striatum, cuneus and ACC in patients with MCI. Moreover, the effects of cigarette smoking exerted on corticostriatal circuits connectivity are different in CN smokers and MCI smokers.

Acknowledgements

None.

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.

Consent to Participate

Written informed consent was obtained from all participants and/or authorized representatives and the study partners before any protocol-specific procedures were carried out in the ADNI study.

Consent to Publish

All authors agree to publish this article in Brain Imaging and Behavior.

Authors Contributions

Author contributions included conception and study design (TTQ, FX, JLZ, SPD, and MMZ), data collection or acquisition (TTQ, QZZ, ZJS, and GJD), statistical analysis (TTQ), interpretation of results (TTQ, FX, and XPX), drafting the manuscript work or revising it critically for important intellectual content (CW, XDL, XL, KCL, PYH, and TYZ) and approval of final version to be published and agreement to be accountable for the integrity and accuracy of all aspects of the work (All authors).

Fundings

This study was funded by the National Key Research and Development Program of China (Grant

No. 2016YFC1306600), Linyi Science and Technology Development Program (Grant No. 202020024), Shandong Medicine and Health Science and Technology Program (Grant No. 202009010844), Zhejiang Provincial Natural Science Foundation of China (Grant No. LY21H180003), and National Natural Science Foundation of China (Grant No. 81901707, 82001766 and 81901721). The data collection and sharing for this project were funded by the ADNI (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense Award No. W81XWH-12-2-0012).

Competing interests

The authors declare that they have no conflict of interest.

Availability of data and materials

The data used in the preparation of this article were obtained from the Alzheimer's disease Neuroimaging Initiative (ADNI) database: <http://adni.loni.usc.edu/>.

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Fig. 1. The interaction effects of smoking status $\times$ disease on rsFC of the striatal subregions. (A) between right caudate and left IPL; (B) between right putamen and bilateral cuneus; (C) between left NAc and bilateral ACC; and (D) between right NAc and bilateral ACC. IPL, inferior parietal lobule; NAc, nucleus accumbens; ACC, anterior cingulate cortex. The statistical threshold was set at $p < 0.005$ with a cluster-level of $p < 0.05$ (two-tailed, GRF corrected).

Fig. 2. The *post-hoc* analysis of rsFC values of the interaction regions. The CN smokers showed increased rsFC of right caudate to left IPL than other subgroups (A). The MCI smokers showed decreased rsFC of right putamen to cuneus (B) and increased rsFC of bilateral NAc to ACC (C and D) compared to other subgroups. IPL, inferior parietal lobule; NAc, nucleus accumbens; ACC, anterior cingulate cortex. $*p < 0.05$, $**p < 0.01$, $***p < 0.005$.

Fig. 3. Correlation between rsFC of the striatal subregions and neuropsychological scores. In MCI smokers, the rsFC value between left NAc and ACC was positively correlated with language (SVF, $r = 0.387$, $p = 0.026$); the rsFC value between right NAc and ACC was positively associated with language (SVF, $r = 0.390$, $p = 0.025$) and memory (WMS-LM immediate recall, $r = 0.378$, $p = 0.03$; delayed recall, $r = 0.367$, $p = 0.036$). NAc, nucleus accumbens; ACC, anterior cingulate cortex; WMS-LM, Wechsler memory scale-logical memory; SVF, Semantic Verbal Fluency.

Table 1. The demographic and clinical characteristics.

Variables	CN non-smokers (n=304)	CN smokers (n=44)	MCI non-smokers (n=130)	MCI smokers (n=33)	F/ χ^2	<i>p</i>
Demographic factors						
Age(years)	72.98±7.25	75.83±7.64	74.33±7.87	76.61±7.54	4.09	0.007 ^b
Sex(F:M)	183:121	21:23	56:74	12:21	15.62	0.001
Education(years)	16.88±2.33	16.27±2.61	16.71±2.54	15.79±2.40	2.56	0.054
Vascular risk factors						
Hypertension, n(%)	118(38.80)	21(47.70)	59(45.40)	20(60.60)	7.04	0.071
Diabetes mellitus, n(%)	7(2.30)	1(2.30)	5(3.80)	0(0.00)	1.84	0.607
Hypercholesterolemia, n(%)	149(49.00)	22(50.00)	73(56.20)	20(60.60)	3.01	0.390
Neuropsychological tests						
Memory						
WMS-LM immediate recall	14.64±3.61	15.23±3.36	10.62±4.30	11.64±4.76	38.55	<0.001 ^{abcd}
WMS-LM delayed recall	13.53±3.80	14.20±3.62	8.58±4.37	9.61±4.59	54.94	<0.001 ^{abcd}
Attention						
TMT-A	31.30±9.51	29.84±6.69	36.15±13.05	37.76±12.91	9.96	<0.001 ^{abcd}
Execution						
TMT-B	74.85±35.90	70.50±27.23	96.23±51.98	110.39±64.58	14.21	<0.001 ^{abcd}
Language						
SVF (animal)	21.68±5.12	21.32±5.87	19.02±5.07	18.67±5.23	10.08	<0.001 ^{ab}
Head Motion (FD value)	0.11±0.07	0.12±0.07	0.11±0.06	0.13±0.07	1.04	0.374

Values are expressed as mean ± standard deviation, number or percentage of participants.

Abbreviation: CN, Cognitively normal; MCI, Mild Cognitive Impairment; WMS-LM, Wechsler memory scale-logical memory; TMT, Trail-Making Test; SVF, Semantic Verbal Fluency; FD, framewise displacement.

^{a-d}Post hoc analysis further revealed the source of ANOVA difference (^a CN non-smokers vs. MCI non-smokers; ^b CN non-smokers vs. MCI smokers; ^c CN smokers vs. MCI non-smokers; ^d CN smokers vs. MCI smokers) (*p* < 0.05, significant difference between the two groups)

Table 2. Smoking status × disease interaction on rsFC of the striatal subregions.

Seeds	Interaction effect regions	Peak MNI coordinate			Peak intensity	Cluster voxels
		X	Y	Z		
Right caudate	Left IPL	-42	-54	54	18.5931	21
Right putamen	Bilateral cuneus	6	-81	27	14.368	42
Left NAc	Bilateral ACC	-3	21	24	15.4675	35
Right NAc	Bilateral ACC	-3	18	27	20.4041	28

The statistical threshold was set at $p < 0.005$ with a cluster-level of $p < 0.05$ (two-tailed, GRF corrected). MNI, Montreal Neurological Institute; IPL, inferior parietal lobule; ACC, anterior cingulate cortex.

Table 3. Correlations between rsFC values and neuropsychological scores.

	WMS-LM immediate recall	WMS-LM delayed recall	TMT-A	TMT-B	SVF
Across all groups					
Left IPL	-0.059	-0.025	0.099	0.035	-0.042
Bilateral cuneus	-0.028	-0.019	0.054	0.034	-0.045
Bilateral ACC ^a	-0.024	-0.03	0.098	0.031	0.042
Bilateral ACC ^b	-0.003	-0.007	0.063	0.01	0.003
CN smokers					
Left IPL	0.178	0.115	0.241	0.147	0.096
Bilateral cuneus	-0.229	-0.221	-0.034	0.156	0.14
Bilateral ACC ^a	0.203	0.169	-0.298	-0.177	0.131
Bilateral ACC ^b	0.021	0.062	-0.144	-0.029	-0.129
MCI smokers					
Left IPL	-0.027	0.009	0.078	0.27	-0.096
Bilateral cuneus	0.174	0.167	-0.199	0.11	-0.026
Bilateral ACC ^a	0.145	0.153	0.046	-0.257	0.387*
Bilateral ACC ^b	0.378*	0.367*	0.03	-0.261	0.39*

Data represent correlation coefficients. WMS-LM, Wechsler memory scale-logical memory; TMT, Trail-Making Test; SVF, Semantic Verbal Fluency; IPL, inferior parietal lobule; ACC, anterior cingulate cortex. ^arepresents rsFC value between left NAc and bilateral ACC. ^brepresents rsFC value between right NAc and bilateral ACC. * $p < 0.05$, uncorrected.

Figures

Figure 1

The interaction effects of smoking status $\times$ disease on rsFC of the striatal subregions. (A) between right caudate and left IPL; (B) between right putamen and bilateral cuneus; (C) between left NAc and bilateral ACC; and (D) between right NAc and bilateral ACC. IPL, inferior parietal lobule; NAc, nucleus accumbens; ACC, anterior cingulate cortex. The statistical threshold was set at $p < 0.005$ with a cluster-level of $p < 0.05$ (two-tailed, GRF corrected).

Figure 2

The post-hoc analysis of rsFC values of the interaction regions. The CN smokers showed increased rsFC of right caudate to left IPL than other subgroups (A). The MCI smokers showed decreased rsFC of right putamen to cuneus (B) and increased rsFC of bilateral NAc to ACC (C and D) compared to other subgroups. IPL, inferior parietal lobule; NAc, nucleus accumbens; ACC, anterior cingulate cortex. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$.

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