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Research article

Altered thalamo-cortical resting state functional connectivity in smokers

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HIGHLIGHTS

- Thalamus showed reduced RSFC with caudate and insula in smokers.
- Thalamus showed reduced RSFC with dlPFC and ACC in smokers.
- RSFC between thalamus and dlPFC correlated with pack-years in smokers.

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ABSTRACT

The thalamus has widespread connections with the prefrontal cortex (PFC) and modulates communication between the striatum and PFC, which is crucial to the neural mechanisms of smoking. However, relatively few studies focused on the thalamic resting state functional connectivity (RSFC) patterns and their association with smoking behaviors in smokers. 24 young male smokers and 24 non-smokers were enrolled in our study. Fagerström Test for Nicotine Dependence (FTND) was used to assess the nicotine dependence level. The bilateral thalamic RSFC patterns were compared between smokers and non-smokers. The relationship between neuroimaging findings and smoking behaviors (FTND and pack-years) were also investigated in smokers. Relative to nonsmokers, smokers showed reduced RSFC strength between the left thalamus and several brain regions, *i.e.* the right dorsolateral prefrontal cortex (dlPFC), the anterior cingulate cortex (ACC) and the bilateral caudate. In addition, the right thalamus showed reduced RSFC with the right dlPFC as well as the bilateral insula in smokers. Therefore, the findings in the current study revealed the reduced RSFC of the thalamus with the dlPFC, the ACC, the insula and the caudate in smokers, which provided new insights into the roles of the thalamus in nicotine addiction from a function integration perspective.

1. Introduction

Nicotine plays an important role in the highly addictive properties of cigarettes [16] by acting as an agonist at presynaptic nicotinic acetylcholine receptors (nAChRs) and facilitating synaptic release of several neurotransmitters including dopamine and glutamate [8,39]. The crucial roles of dopaminergic transmission in reward mechanisms make the nAChRs the conduit for the delivery of signals that instigate and maintain nicotine addiction [47]. The thalamus has the highest density of nAChRs [19,40] and was therefore vulnerable to the addictive effects of nicotine [4]. Recently, functional and structural changes in the thalamus have been associated with the neural mechanism of substance addiction including cigarette smoking, such as reduced gray matter volume of the thalamus and the cerebral blood flow of the thalamus associated with craving in smokers [11,13,45,46]. Anatomically, due to the widespread influence of the thalamic connections with cortical and subcortical regions (such as the prefrontal cortex-PFC and striatum) [38,48]. The cognitive control (mainly associated with the PFC) and reward processing (mainly associated with the striatum) are important in the maintenance of smoking behaviors [6,45,53]. It is not surprising that the thalamic connections with these regions are considered to contribute to the neural mechanisms of smoking behaviors. However, little evidence exists about abnormal thalamic connections with PFC and striatum in smokers compared with nonsmokers. Even less is known about the relationship between

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thalamic connections with the PFC and striatum abnormalities and smoking behaviors in smokers.

Resting state functional connectivity (RSFC), which permits *in vivo* measurement of the degree of correlated activity (*i.e.*, the strength of the interaction) between macroscopic brain regions, offers us a unique opportunity to examine these interactions between brain regions in addiction [2,43,52]. Therefore, in the current study, the thalamic RSFC differences were investigated between smokers and nonsmokers. The RSFC findings were then correlated with smoking behavior variables (Fagerstrom Test for Nicotine Dependence-FTND and pack-years). Previous work had found that the thalamus may integrate activity by conveying information to dopamine adapter systems involved in reward, which is important in the development and maintenance of addiction [36]. In addition, the thalamus is a critical hub of the frontal-striatal-thalamic circuit, and the dysregulation of this circuit could be involved in the persistence of drug-seeking behaviors [12]. Thus, we hypothesized that smokers would exhibit a deficient RSFC between the thalamus and interconnected brain regions, such as the PFC and striatum. We hoped that our study focusing on the thalamic RSFC could provide new insights into the neurobiological mechanisms of smoking.

2. Materials and methods

2.1. Ethics statement

All study procedures were approved by the Ethical Committee of The First Affiliated Hospital of Zhengzhou University and were conducted in accordance with the Declaration of Helsinki. All subjects gave written informed consent after receiving a detailed explanation of the study.

2.2. Subjects

The latest national survey of youth smoking by the Chinese Center for Disease Control and Prevention (announced in May, 2014) revealed that the smoking rate of junior high school students was 10.6% for males and 1.8% for females in China (http://www.chinacdc.cn/). We focused on the young male smokers in the current study. Twenty-four young male smokers and 24 age- and education-matched healthy nonsmokers (18–24 years) were recruited from the local university. The smokers reported smoking more than 10 cigarettes per day and had no attempt to quit or undergo smoking abstinence in the past year. The expired air carbon monoxide (CO) was ≥10 parts per million (ppm) (by Smokelyzer, Bedfont Scientific, Kent, UK). Nicotine dependence severity was assessed with the Fagerstrom Test for Nicotine Dependence (FTND) [17]. Pack-years of smoking were also collected by multiplying the average number of packs of cigarettes smoked per day by the number of years the subjects smoked [28,51]. Nonsmokers were identified as those smoking less than five cigarettes in their lifetime with expired CO ≤ 3 ppm.

The exclusion criteria for both groups were as follows: (1) any physical illness such as a brain tumor, obstructive lung disease, hepatitis, or epilepsy; (2) any current medications that may affect cognitive functioning; (3) alcohol or other drug abuse (excluding nicotine); (4) existence of a neurological disease; and (5) claustrophobia. In the current study, we focused on the chronic effect of smoking, therefore, we asked the smokers to refrain from smoking during the 20 min immediately preceding the scan to exclude withdrawal symptoms. The clinical and demographic characteristics of subjects are displayed in Table 1.

Table 1
Clinical details of young smokers and nonsmokers.

Clinical details	Smoker (n = 24)	Nonsmoker (n = 24)
Age (years)	20.8 ± 1.8	20.6 ± 2.5
Education (years)	12.6 ± 1.2	12.8 ± 1.4
Initial smoking age	14.2 ± 1.9	–
Cigarettes smoked per day	16.6 ± 5.3	–
Years of smoking	4.7 ± 1.5	–
Pack-years	3.9 ± 1.8	–
FTND	6.1 ± 1.3	–

Data are means ± standard deviations.
Pack-years = years of smoking × cigarettes smoked per day/20.
FTND = Fagerström Test for Nicotine Dependence.

2.3. MRI data acquisition

Scanning procedures were conducted at a 3-Tesla MRI system with a 32-channel head coil (Discovery MR750, General Electric Medical Systems, Milwaukee, Wisconsin) in the MRI Department, The First Affiliated Hospital of Zhengzhou University, China. Subjects were instructed to keep their eyes closed but stay awake, and not to think about anything in particular. For each subject, a T1-weighted whole-brain anatomical images was collected with the following parameters: repetition time (TR) = 8.5 ms; echo time (TE) = 3.4 ms; flip angle (FA) = 12°; in-plane matrix resolution = 240 × 240; slices = 140; field of view (FOV) = 240 × 240 mm^2; slice thickness = 1 mm. The resting-state functional images were acquired with an echo-planar-imaging sequence (EPI) (30 axial slices with a 5 mm slice thickness and no slice gap; TR = 2000 ms; TE = 30 ms; FA = 90°; FOV = 240 × 240 mm^2; data matrix = 64 × 64), which lasted for 6 min 10 s.

2.4. Resting state functional data preprocessing

The fMRI resting-state images were processed using DPARSF (http://rfmri.org/DPARSF) and SPM12 (http://www.fil.ion.ucl.ac.uk/spm/) software. The first 10 volumes of the functional images were removed for the signal equilibrium and participants' adaptation to the scanning environment. Then, the following steps were carried out: slice timing correction; rigid-body head motion correction; obliquity transformation to the structural image; affine co-registration to the skull-stripped structural image; standard spatial transform to the MNI152 template; spatial smoothing (6 mm full width at half maximum); and linear de-trending. Nuisance regression and bandpass filtering alone are often insufficient to control head movement induced noise, therefore, wavelet despiking was used in this study [35]. Time series despiking (wavelet domain) was carried out to the processed resting state images and then nuisance signal regression was done by including the 6 motion parameters, their first order temporal derivatives, white matter and ventricular cerebrospinal fluid (CSF) signal as covariates. Finally, a temporal Fourier filter was employed (bandpassed 0.01–0.08 Hz) to reduce the low-frequency drift, as well as high-frequency physiological respiratory and cardiac noise.

2.5. Resting state functional connectivity of the thalamus

We extracted the left and right thalamus as our seeds from the Harvard-subcortical structural atlas (http://www.cma.mgh.harvard.edu/) respectively. The resting-state fMRI time series of each seed was extracted by averaging all of the voxels within each region at each time point in the preprocessed data. For each subject, a correlation map was produced by computing the correlation coefficient (r value) between the time series of the seeds and the time series of each voxel of the other brain regions. The r-value maps