Addiction Biology

HUMAN IMAGING BRIEF REPORT

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Regional homogeneity changes in heavy male smokers: a resting-state functional magnetic resonance imaging study

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ABSTRACT

Recent studies have documented declined global cognitive function and abnormal task-related brain activation in chronic cigarette smokers. However, the effects of long-term heavy smoking on task-independent baseline brain activity are still unknown. Here, we used a regional homogeneity (ReHo) method combined with functional magnetic resonance imaging (fMRI) to investigate spontaneous neural activity in the resting state in heavy smokers. Compared with controls, heavy smokers exhibited decreased ReHo in prefrontal regions, as well as increased ReHo in insula and posterior cingulate cortex. Our study may better our understanding of the neurobiological consequences of smoking.

Keywords Addiction, insula, magnetic resonance imaging, prefrontal cortex, resting state, smoking.

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Cigarette smoking, one of the biggest threats to world health, is responsible for more than 5.4 million preventable deaths in 2004 and is set to cause 8.3 million deaths by the year 2030 (Mathers & Loncar 2006). Recent functional magnetic resonance imaging (fMRI) studies have focused on exploring activation abnormalities in smokers during a task state (Vollstadt-Klein *et al.* 2011; Zhang *et al.* 2011). Recently, studies have begun to examine the effects of smoking on functional connectivity (FC) in paradigm-free resting state (Hong *et al.* 2009; Cole *et al.* 2010). However, as FC analysis only examines correlations between spatially distinct regions, the local features of spontaneous brain activity in smokers are still unknown.

Regional homogeneity (ReHo), which measures the functional coherence of a given voxel with its nearest neighbors within a single region, has been successfully used to detect local abnormality in subjects with different psychiatric disorders (Zang *et al.* 2004; Liu *et al.* 2010). We predicted that heavy smokers would exhibit abnormal ReHo in regions implicated in addiction, including prefrontal cortex (PFC) (Vollstadt-Klein *et al.* 2011; Zhang *et al.* 2011), insula (Naqvi *et al.* 2007) and cingulate cortex (Hong *et al.* 2009; Vollstadt-Klein *et al.* 2011).

Participants were recruited from the community through advertisements. Data were collected from 16 cigarette smokers and 16 matched healthy non-smoking controls. All subjects were screened for psychiatric and non-psychiatric medical disorders using the structured clinical interview for the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV). The cigarette use survey and Fagerström test for nicotine dependence (FTND) were administered to each smoker by interview (Fagerstrom & Schneider 1989). Prior to magnetic resonance imaging (MRI) scanning, urine drug screening was performed on all subjects to exclude substance abuse, with the exception of cigarettes. Additional inclusion criteria for smokers included men who met the DSM-IV criteria for current nicotine dependence (smokers) and smoked at least 15 cigarettes per day for at least 10 years. All non-smokers in this sample never had a history of smoking. All subjects were right handed and male, had no history of any neurological or psychiatric disorder, had no other drug dependence and were not currently taking any medications. All subjects gave written informed consent. The study was approved by the Peking University Research Ethics Board.

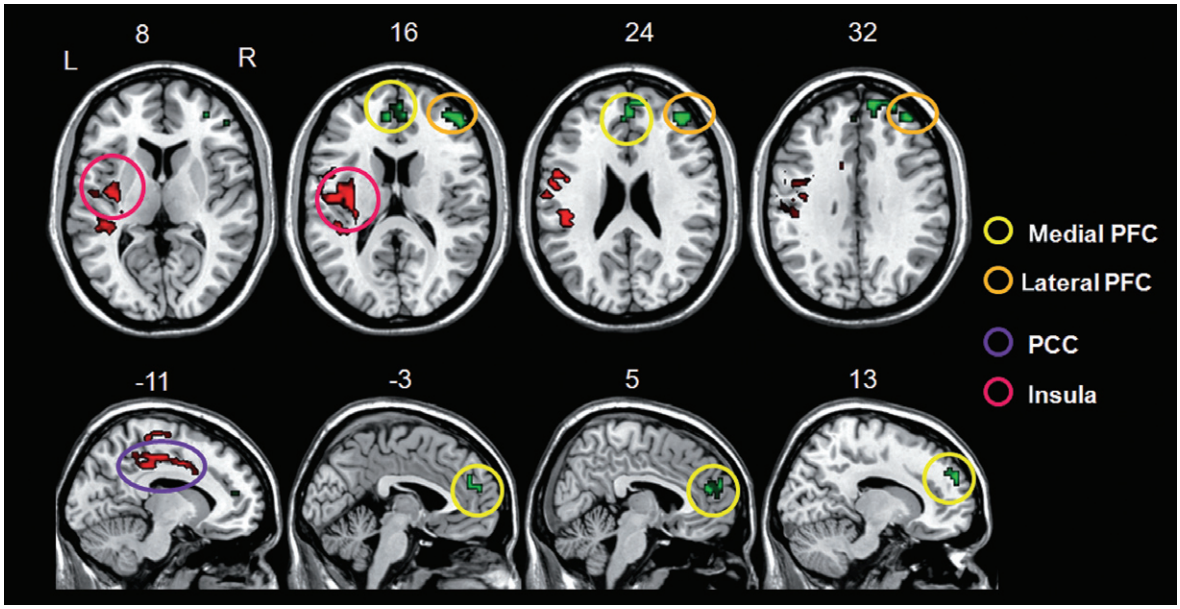

Figure 1 Regions that showed a significant regional homogeneity (ReHo) difference between heavy smokers and controls: lower ReHo in left medial prefrontal cortex (PFC) and the right lateral PFC; higher ReHo in the right posterior cingulate cortex (PCC) and the left posterior insula. For display purposes only, all statistical maps ($P < 0.001$, uncorrected) are overlaid on a T1-weighted MNI template using MRIcron

For MRI image acquisition, image processing and statistical analysis methods, see Supporting Information Fig. S1.

The smoker ($n = 16$) and the non-smoker ($n = 16$) groups were selected to be matched for age [mean ± standard deviation (SD): smokers 41.6 ± 5.5 versus non-smokers 39.2 ± 4.5] and for years of education (mean ± SD: smokers 10.9 ± 2.2 versus non-smokers 12.2 ± 2.5, mean ± SD), P values > 0.1. Smokers smoke 20.6 ± 7.4 (mean ± SD) cigarettes per day and the average smoke years are 21.1 ± 3.9 (mean ± SD). The mean score on the FTND questionnaire was 7.19 ± 1.42 (mean ± SD), indicating heavy nicotine dependence.

In comparison with non-smokers, the chronic smokers displayed significantly decreased ReHo in right medial frontal cortex [Montreal Neurological Institute (MNI) (12, 57, 30), peak $Z = 4.07$, cluster size = 79, $P < 0.001$, corrected, Fig. 1] and right inferior PFC [MNI (48, 45, 15), peak $Z = 4.12$, cluster size = 72, $P < 0.001$, corrected, Fig. 1], as well as increased ReHo in left posterior cingulate gyrus [MNI (−12, 18, 48), peak $Z = 4.90$, cluster size = 100, $P < 0.001$, corrected, Fig. 1] and left insula [MNI (−33, 15, 15), peak $Z = 4.98$, cluster size = 67, $P < 0.001$, corrected, Fig. 1]. No significant correlation with other measurement (e.g. FTND) was found.

Using a ReHo method, our study found that compared with controls, long-term heavy smokers exhibited significantly reduced ReHo in medial prefrontal and lateral prefrontal regions, as well as significantly increased ReHo in insula and posterior cingulate cortex (PCC) during resting state. Our findings demonstrate that smoking leads to abnormal coherence of spontaneous neural activity in the regional brain.

The PFC plays an important role in cognitive function and is hypothesized to account for the declined cognition associated with drug addiction (Robinson & Berridge 2003). Abnormal FC between medial PFC and lateral PFC in smokers has been found in a previous resting-state fMRI study (Zhang *et al.* 2011). Our study complements the earlier FC analysis by showing that heavy smokers exhibited decreased regional coherence or synchronization in both medial PFC and lateral PFC. Taken together, these findings highlight a key role of PFC in nicotine addiction.

The insula is implicated in conscious urges and is another critical neural substrate in addiction. Recent studies found that damage to the insula can disrupt addiction to cigarette smoking (Naqvi *et al.* 2007). In accord with these findings, the enhanced synchronization in local regional resting-state blood oxygen level dependent BOLD activity detected in heavy smokers in insula may reflect atypical smoking urge. Our results further support the abnormality of the insula in drug addiction.

The PCC is part of the default-mode network. A recent study found that nicotine enhanced a relatively 'local' circuit between the dorsal PCC and ventral PCC (Hong *et al.* 2009). These authors suggest that nicotine may also alter the resting-state default network (Hong *et al.* 2009). Our finding of enhanced ReHo in PCC in heavy smokers provides additional evidence for this hypothesis.

Some limitations in our study are worth mentioning. The sample size in this study is relatively small, which may explain why we did not find significant correlations between ReHo and smoking-related measurements. More work will, however, be required to investigate those relationships using a larger sample size. Also, we did not examine cognitive function in our sample. Future studies may test the relationships between ReHo alterations and cognition deficits.

In conclusion, this resting-state fMRI study revealed abnormal ReHo in prefrontal regions, insula and PCC in heavy smokers. These results may better our understanding of the neurobiological consequences of heavy smoking.

Acknowledgments

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Authors Contribution

Rongjun Yu undertook the MRI data analyses and wrote the manuscript; Liyan Zhao designed the study; wrote the protocol; collected the clinical and MRI data. Jie Tian, Wei Qin, Kai Yuan, Wei Wang and Qiang Li collected the MRI data; Lin Lu contributed to the study design. All authors contributed to and have approved the final manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1 One-sample *t*-test results for smokers (a, b, c) and controls (d, e, f) at threshold $P < 0.001$, uncorrected.