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ORIGINAL RESEARCH

12-h abstinence-induced functional connectivity density changes and craving in young smokers: a resting-state study

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Abstract

Studying the neural correlates of craving to smoke is of great importance to improve treatment outcomes in smoking addiction. According to previous studies, the critical roles of striatum and frontal brain regions had been revealed in addiction. However, few studies focused on the hub of brain regions in the 12 h abstinence induced craving in young smokers. Thirty-one young male smokers were enrolled in the present study. A within-subject experiment design was carried out to compare functional connectivity density between 12-h smoking abstinence and smoking satiety conditions during resting state in young adult smokers by using functional connectivity density mapping (FCDM). Then, the functional connectivity density changes during smoking abstinence versus satiety were further used to examine correlations with abstinence-induced changes in subjective craving. We found young adult smokers in abstinence state (vs satiety) had higher local functional connectivity density (lFCD) and global functional connectivity density (gFCD) in brain regions including striatal subregions (i.e., bilateral caudate and putamen), frontal regions (i.e., anterior cingulate cortex (ACC) and orbital frontal cortex (OFC)) and bilateral insula. We also found higher lFCD during smoking abstinence (vs satiety) in bilateral thalamus. Additionally, the lFCD changes of the left ACC, bilateral caudate and right OFC were positively correlated with the changes in craving induced by abstinence (i.e., abstinence minus satiety) in young adult smokers. The present findings improve the understanding of the effects of acute smoking abstinence on the hubs of brain gray matter in the abstinence-induces craving and may contribute new insights into the neural mechanism of abstinence-induced craving in young smokers in smoking addiction.

Keywords Resting state · Functional connectivity density mapping (FCDM) · Abstinence-induced craving · Young adult smokers

Introduction

Cigarette smoking is a global public health problem (Bloomfield et al. 2014), and it is the most common preventable cause of morbidity and mortality in the developed world (Naqvi et al. 2007). In a recent Word Health Organization (WHO) report, smoking abstinence can slow down the progress of the disease in smokers and decrease chronic obstructive pulmonary disease (COPD)-related deaths (http://www.who.int/en/). Although being aware of the negative outcomes of smoking,

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most smokers found it hard to quit, and even those who had quit experience urge to smoke and tend to relapse (Cooper 2001; U.S. Department of Health and Human Services; USDHHS, 1988). Smoking abstinence can cause withdrawal symptoms such as craving and negative mood, and the severity of abstinence-induced craving is theorized to be a major motivator for continued smoking and a significant predictor of smoking relapse, especially during the early stage of smoking abstinence (Addicott et al. 2014; Lerman et al. 2007; Xue et al. 2012).

In a previous study, the striatal morphology (volume, surface area, and shape) was found to be associated with smoking craving assessed by the brief questionnaire of smoking urges (QSU) (Janes et al. 2015b). By using positron emission tomography (PET), researchers found that smoking could increase dopamine release in striatum region, thus leading to craving, withdrawal and smoking behavior (Le et al. 2014). According to previous substance use disorder (SUD) studies, it has been discovered that the vital roles of fronto-striatal circuits, which were mainly related to reward (striatum) and cognitive control (prefrontal cortex) mechanism (Feil et al. 2010; Kober and Ochsner 2010; Li et al. 2016; Yu et al. 2017; Yuan et al. 2017). Meanwhile, modular dysfunction and structural abnormity within fronto-striatal circuits had also been measured in smokers (Jasinska et al. 2014; Li et al. 2015, 2016; Martin-Soelch 2013; Yuan et al. 2016, 2017). For example, the structural and functional abnormities of striatum were detected separately in previous studies of smoking addiction (Hanlon et al. 2015; Li et al. 2015; Yip et al. 2014). The abnormalities in frontal brain regions had also been detected in smokers, such as reduced gray matter and dysfunction of orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and dorsolateral prefrontal cortex (DLPFC) (Feil et al. 2010; Yu et al. 2011; Zhao et al. 2012). Furthermore, the resting-state functional connectivity (RSFC) changes between caudate (striatum subregion) and dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC) were found in a resting-state study (Yuan et al. 2016), and the fiber tract integrity of the left DLPFC-caudate pathway was negatively correlated with functional coupling within this circuit and activation of the caudate induced by smoking cue in smokers (Yuan et al. 2017). In addition, both striatum and prefrontal cortex (PFC) dopamine system changes had been discovered in smokers (Newberg et al. 2007; Wing et al. 2015). Thus, we hypothesized that striatum and frontal brain regions are the key nodes of brain in the abstinence-induces craving in young smokers.

In the current study, by conducting a within-subject experiment, we explore the brain resting-state properties after 12-h smoking abstinence (vs satiety) in young adult smokers. In previous researches, functional connectivity density mapping (FCDM) approach was used in developing imaging biomarkers for diagnostics/prognosis, such as neuropsychiatric diseases of sex brain, Traumatic Axonal Injury (TAI), White matter lesions (WMLs), and schizophrenia (Caeyenberghs et al. 2015; Ding et al. 2016; Tomasi and Volkow 2012b). This method showed commendably high functional connectivity density of brain regions (hubs) and could reflect energy consumption of the brain tissue (Tomasi et al. 2013; Tomasi and Volkow 2011). However, few studies used FCDM method to examine the hub of brain gray matter in the abstinence-induces craving of young smokers. Therefore, we employed FCDM method to compare the resting-state properties between 12-h abstinence and satiety conditions in young adult smokers. We hypothesized that following 12 h of abstinence, smokers would display higher striatal and frontal functional connectivity density (hubs) values compared to satiety, and these changes would be related to changes in individual craving. We hope this work could facilitate the understanding of the roles of striatal and frontal brain regions in abstinence-induced craving in young smokers.

Materials and methods

Ethics statement

The procedures of present study were approved by the ethic committee of medical research in First Affiliated Hospital of Baotou Medical College, Inner Mongolia University of Science and Technology, Baotou, China. After understanding our research objectives, all participants gave the written informed consent. All experimental procedures followed the guidelines of human medical research (Declaration of Helsinki).

Participants

Thirty-one young male smokers (18.5 ± 1.5 years; $\geq$ 10 cigarettes/day for $\geq$1 year) with no attempt to quit or experience in smoking abstinence in the past 6 months had participated in this study (Table 1). All participants were right-handed as measured by the Edinburgh Handedness Inventor (Oldfield 1971). The nicotine-dependent level is evaluated by the Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al. 1991). Exclusion criteria for participates included any contraindications (e.g., non-reversible metal implants, claustrophobia, etc.) for MRI scanning, any physical illness (e.g., brain tumor, obstructive lung disease, etc.), or the neurological and mental disorders (e.g., mental disorders of the organism, bipolar depression, schizophrenia spectrum disorder, etc.). Alcohol use disorder measured by Alcohol Use Disorders Identification Test was also excluded. The IQ of subjects score > 90 (measured by Wechsler intelligence Scale). No any medications currently that may affect cognitive function.

Table 1 The age of each smoke and the craving scores in both sessions (satiety and abstinence)

Subjiect ID	Items		
	Age (year)	Craving scores	
		Satiety	Abstinence
1	20	12	13
2	19	25	64
3	18	24	54
4	20	31	55
5	19	15	41
6	20	49	52
7	18	10	40
8	19	29	32
9	18	17	33
10	19	42	52
11	18	28	45
12	18	30	58
13	19	45	52
14	20	20	68
15	17	20	56
16	18	37	45
17	17	10	29
18	18	14	18
19	18	20	48
20	17	16	41
21	19	20	37
22	18	18	39
23	18	49	68
24	19	13	17
25	18	11	34
26	19	24	41
27	17	34	52
28	18	18	26
29	19	27	43
30	20	16	25
31	19	11	12

Procedure

We used a within-subject design with two identical functional MRIs sessions occurring 1–3 weeks apart: the satisfied (smoking as usual) and abstinent (12 h abstinence) participants. The satisfied participants smoked as usual about 20 min before scanning. During the abstinent session, participants were prohibited from using cigarettes, alcohol or other drugs (including caffeine, nicotine) at least 12 h before scan, confirmed by results of a urine drug screen and a breath test for alcohol. In addition, expiratory carbon monoxide (CO) levels of all participants were measured by the Smokerlyzer system (Bedfont Scientific Ltd., Rochester, UK). During abstinence state, CO levels in the exhaled breath confirmed to ≤8 ppm (p.p.m), which showed a distinct reduction in CO levels for each participant compared to that measured in satiety state (> 10 p.p.m.). Before each scan, subjective craving was assessed by the brief 10-item Questionnaire for smoking urges (QSU) (Cox et al. 2001) and participants were required to agree or disagree with each item in the questionnaire using intensity of 1 (weakly agree) to 7 (weakly disagree).

Data acquisition

The experiment was carried out on a 3-Telsa Philips scanner (Achieva; Philips Medical Systems, Best, The Netherlands) at the First Affiliated Hospital of Baotou Medical College, Inner Mongolia University of Science and Technology, Baotou, China. Earplugs and a head cervical fixation with foam pads were used to lessen engine noise and head movements. Each individual high-resolution structural MR images were acquired using the three-dimensional MRI sequence of voxel size 1 mm^3 employing a fast axial spoiled gradient recalled sequence (TR = 1900 ms; TE = 2.26 ms; data matrix = 256 × 256; field of view = 256 × 256 mm^2). The structural images were examined to exclude the possibility of clinically silent lesions for all of the participants by two expert radiologists. The resting-state functional images were obtained with echo-planar imaging (30 contiguous slices with a slice thickness of 5 mm; TR = 2000 ms; TE = 30 ms; flip angle = 90°; field of view = 240 × 240 mm^2; data matrix = 64 × 64; total volumes = 180). During a 6-min functional scan, subjects were ordered to close their eyes, did not think anything, and stayed awake throughout the session. After the scan, the participants were asked whether or not they remained awake during the whole procedure.

Data analysis

All of the data preprocessing procedures were performed using in Analysis of Functional NeuroImages (AFNI, http://afni.nimh.nih.gov/) and FMRIB Software Library (FSL, www.fmrib.ox.ac.uk), which included skull-stripping, slice timing correction, and registration to a base EPI volume. Due to the instability of early MRI signals and the adaptation of the subjects in the scanning environment, the first 10 volumes of every functional time series removed from the analysis. The images were then corrected for the latency of acquisition between slices, aligned with the first image of each session for motion correction, and spatially normalized to the standard MNI_152_2mm template in the FSL. All data were resampled to 3 × 3 × 3 mm cubic voxels. No head motionhad been moved more than 1 mm or rotated 1° in any direction. The nuisance signal regression including the

motion parameters estimated in the rigid-body head motion correction, their first-order temporal derivatives, white matter and ventricular cerebrospinal fluid (CSF) signal. Lastly, the bandpass filter (0.01 Hz < f < 0.08 Hz) was applied to eliminate physiological and high frequency noise.

After data preprocessing, the number of significant functional connections per voxel in the local cluster (k) was used to evaluate functional connectivity density (Zhu et al. 2018; Tomasi and Volkow 2010; Hu et al. 2016), which was performed using Functional Connectivity Density Mapping toolbox (Addicott et al. 2014; Tomasi and Volkow 2010). Two parameters were used to calculate lFCD: the correlation threshold (T_C) and the MRI signal-to-noise ratio threshold (T_{SNR}). T_C was used to determine significant correlations between voxels, while T_{SNR} was used to evaluate which voxels of the image will be subject to correlation analyses (Tomasi and Volkow 2010; Zhu et al. 2017; Lei and Zhu 2017). In order to minimize the false positive rate of lFCD maps especially near air/tissue interfaces, we fixed $T_C = 0.6$ and $T_{SNR} = 50$ for all calculations of functional connectivity density. What's more, we used Pearson's linear correlation to establish the functional connectivity strength between voxels. The gFCD calculation had the same spatial resolution, preprocessing and postprocessing (spatial smoothing) steps as for lFCD, but the number of significant connections ($R > T_C$) without local cluster restrictions is different (Tomasi and Volkow 2010; Zhang et al. 2017; Zheng et al. 2017).

Statistical analysis was carried out using FMRIB Software Library (FSL, www.fmrib.ox.ac.uk). A paired t-tests was used to compare functional connectivity density alteration of smokers between the two smoking states [$p < 0.05$, family-wise error (FWE) corrected] (Fig. 1). Isotropic cubic masks were defined at the centers of relevant functional connectivity hubs to extract the average strength of the lFCD signal from individual lFCD maps. The average and standard deviation values of the lFCD were computed for each subject. Then, ROI values were extracted from the different brain regions and then the values were used to draw a bar chart with error bars (Fig. 1). Bonferroni correction was conducted for six higher local functional connectivity density (lFCD-hubs) at the whole brain level ($p < 0.001$). For each lFCD-hub, individual abstinence-induced lFCD map was generated by applying the individual lFCD map for each subject in abstinence state minus the lFCD map in satiety state. Then, to evaluate the possible relationship between the abstinence-induced lFCD changes of lFCD-hubs and subjective craving changes, voxelwise whole-brain multiple regression analysis with the craving changes (abstinence minus satiety) included as covariates was applied. Besides, a series of Pearson's correlation analysis were performed to evaluate the possible relationships between abstinence-induced craving changes and FTND, CO levels.

FCD

FCDM overcomes the limitations of seed-based approaches for the identification of hubs in the human brain (Tomasi and Volkow 2010). The gFCD-map reflects the total number of functional connections per voxel in the functional anatomy of the brain across subjects, while the searching algorithm computes the lFCD as $k(x_0)$ (the number of elements in the local functional connectivity cluster) when no new neighbors can be added to the list of neighbors of x_0 (Tomasi and Volkow 2011). The lFCD and the gFCD both reflects high functional connectivity density (hubs) with energy efficient and minimizing glucose consumption (Tomasi et al. 2013; Tomasi and Volkow 2010, 2011). We had used a single scaling factor for different states (abstinence and satiety), $1/k_0$, reflecting the mean lFCD across subjects and voxels in the brain, k_0, allowed us to normalize its distribution and merge the data sets from different participators (Tomasi and Volkow 2010, 2012b). Totally, the functional connectivity density (FCD) can reflect alterations in the connection number (Liu et al. 2017). A detailed description can be seen in Tomasi and Volkow.

Results

Descriptive data

All 31 young male smokers (all right-handed subjects) had a mean age of 18.5 (standard deviation, SD =0.9) years (range, 17–20 years) and a mean of 13.3 (SD = 1.1) years of education. They smoked a mean of 15.8 (SD = 2.0) cigarettes per day, had a mean FTND score of 4.9 (SD = 1.3), and smoked for a mean of 5.2 (SD = 2.1) years. As expected, the smoking abstinence manipulation produced significant differences in craving across the two sessions [average craving scores of 41.6 (SD = 15.3) vs. 23.7 (SD = 11.4) for abstinence and satiety, respectively; $p < 0.0001$].

FCDM results

Figure 1 showed the statistical map of average lFCD and gFCD distribution in smoking abstinence (vs satiety). Higher local functional connectivity density (lFCD-hubs) and global functional connectivity density (gFCD-hubs) both were found in anterior cingulate cortex (ACC), bilateral insula, orbital frontal cortex (OFC), bilateral putamen and bilateral caudate [$p < 0.05$, family-wise error (FWE) corrected]. lFCD-hubs were found in bilateral thalamus [$p < 0.05$, family-wise error (FWE) corrected]. No brain regions with lower lFCD and gFCD values during smoking abstinence (vs satiety) were found in this study. The prominent functional connectivity hubs are

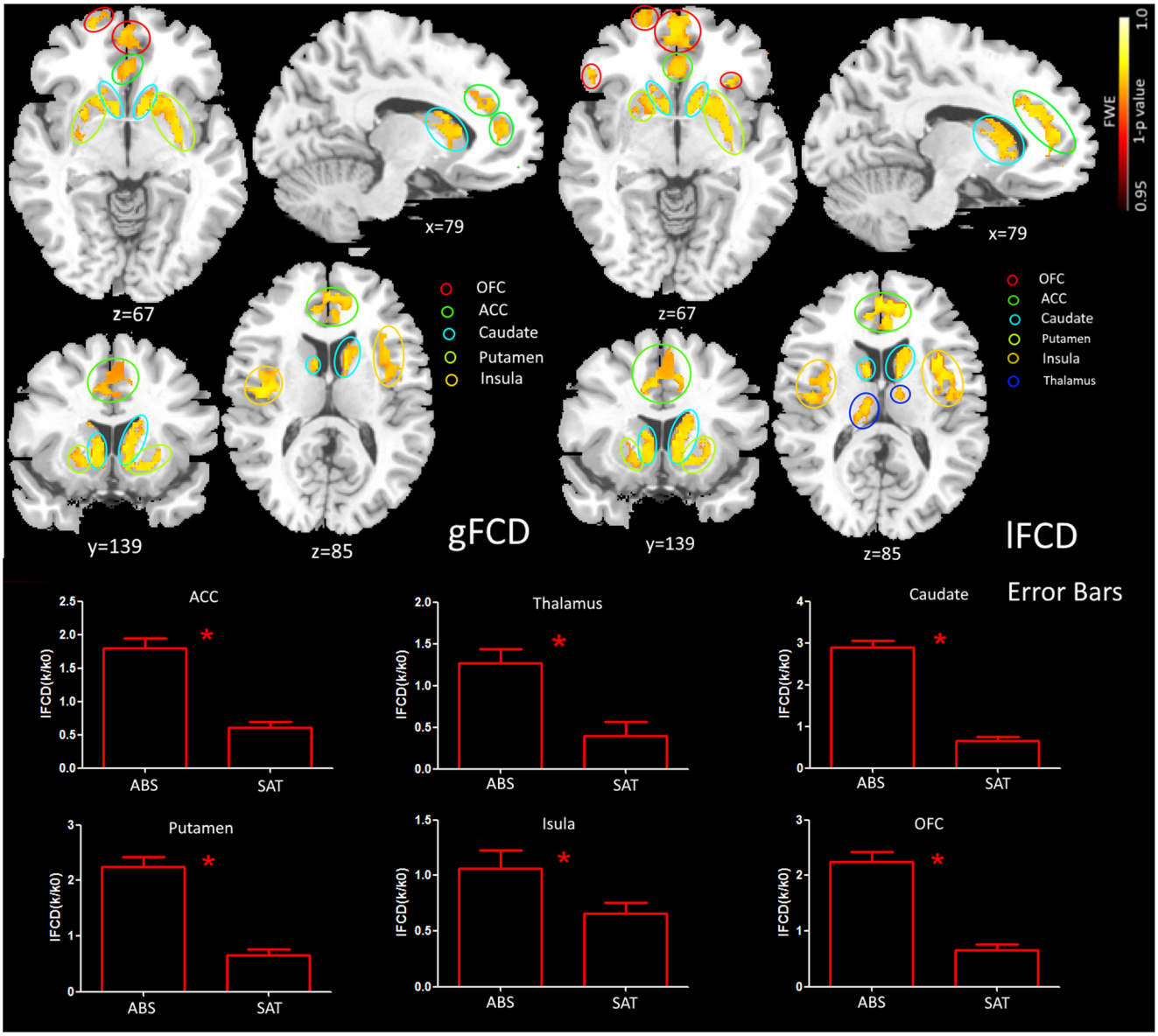

Fig. 1 Statistical map of average lFCD and gFCD distribution in smoking abstinence (vs satiety). gFCD- and lFCD-hubs (Tomasi and Volkow 2011) both were found in anterior cingulate cortex (ACC), bilateral Insula, orbital frontal cortex (OFC), bilateral putamen and bilateral caudate. [$p < 0.05$, family-wise error (FWE) corrected]. Higher lFCD was found in bilateral thalamus. [$p < 0.05$, family-wise error (FWE) corrected]. Error Bars plot was also proved the result of lFCD- and gFCD-hubs. lFCD: local functional connectivity density; gFCD: global functional connectivity density; lFCD-hubs: high local functional connectivity density; gFCD-hubs: high global functional connectivity density connectivity density

located in the brain regions with frontal-striatum circuit. Whole-brain multiple regression analysis discovered that the changes of craving (abstinence vs satiety) were significantly correlated with the lFCD changes in the left ACC, the bilateral caudate, the right orbital frontal cortex(OFC) (FWE corrected, $p < 0.05$; Fig. 2). The results of whole-brain correlation analysis were corrected for multiple comparisons by using family-wise error correction, while Bonferroni correction was used to examine the Pearson correlations analysis ($p < 0.001$). After correction, significant positive correlations were found in the left ACC ($r = 0.5581$, $p < 0.001$, Bonferroni correction), the right Caudate ($r = 0.6099$, $p < 0.001$, Bonferroni correction), the left Caudate ($r = 0.6273$, $p < 0.001$, Bonferroni correction), the right orbital frontal cortex(OFC) ($r = 0.5662$, $p < 0.001$, Bonferroni correction) (Fig. 2).

Discussion

The period from late adolescence to emerging adulthood is associated with the high prevalence of cigarette smoking (Bi et al. 2017b; Jin et al. 2016; Li et al. 2015,

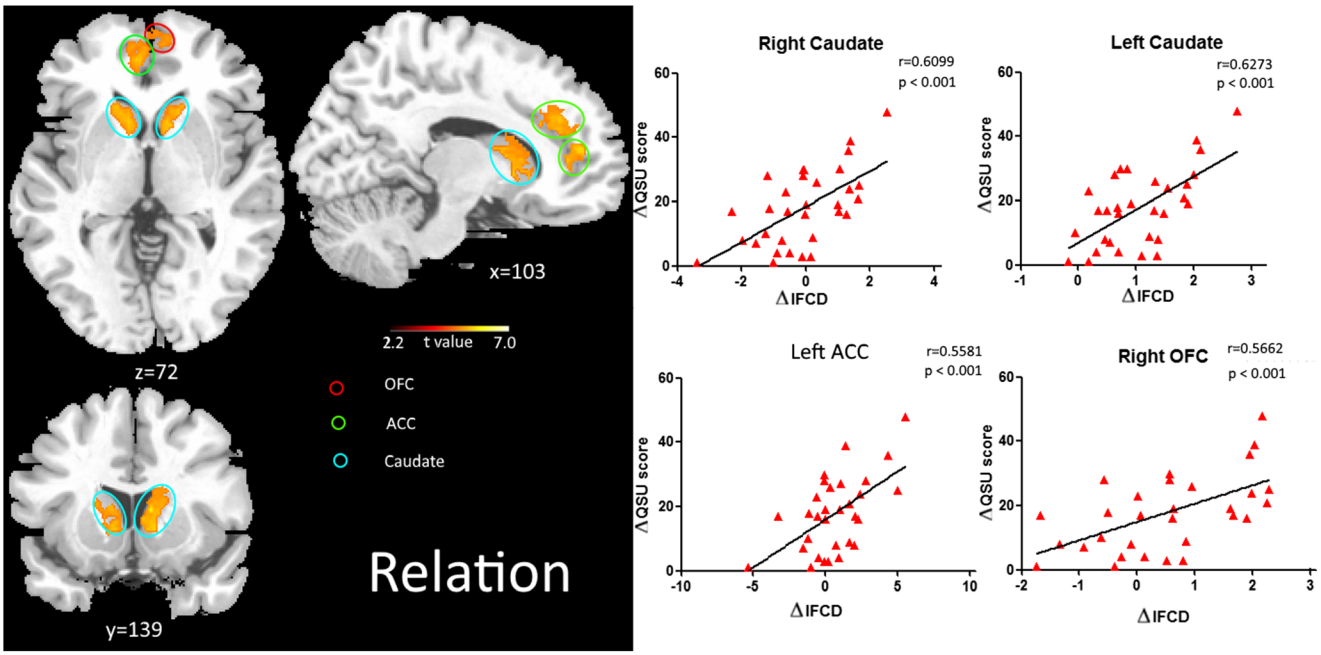

Fig. 2 Association of abstinence-induced craving with lFCD changes. Multiple regression analysis revealed significant positive correlations between the lFCD changes and the changes in craving induced by 12-h abstinence (i.e., abstinence minus satiety) in the left ACC, the bilateral caudate, the right orbital frontal cortex(OFC) (FWE corrected, $p < 0.05$). Significant positive correlations were also found in the left ACC ($r = 0.5581$, $p < 0.001$, Bonferroni correction), the right Caudate($r = 0.6099$, $p < 0.001$, Bonferroni correction), the left Caudate ($r = 0.6273$, $p < 0.001$, Bonferroni correction), the right orbital frontal cortex(OFC) ($r = 0.5662$, $p < 0.001$, Bonferroni correction) in the scatter plot

2016, 2017; Yu et al. 2017; Yuan et al. 2016, 2017). According to previous study, the early smokers are more likely to become life-long nicotine dependence than adulthood (Smith and Nichols 2009). Additionally, young people from late adolescence to emerging adulthood are characteristic of alterations in physical, psychological and social function, which were induced to a high prevalence of cigarette smoking (Li et al. 2016). Therefore, the study of adolescent smoking is particularly important.

The present study examined the effects of 12 h of smoking abstinence on the functional connectivity density (lFCD and gFCD) of brain gray matter in young smokers, as well as the correlations between the changes of abstinence-induced lFCD and the changes of abstinence-induced craving to smoke. We found that, after 12 h of abstinence from smoking, the brain regions within frontal-striatum circuit (i.e., OFC, ACC, bilateral caudate, bilateral putamen), bilateral thalamus and bilateral insula exhibited higher functional connectivity density in brain gray matter. These regions were commonly implicated in craving, which was consist with previous studies (Bi et al. 2017b; Goldstein and Volkow 2011; Hayashi et al. 2013; Li et al. 2016, 2017; Yu et al. 2017; Yuan et al. 2016, 2017). According to previous studies, brain regions with higher functional connectivity density (hubs) were associated with higher energy consumption and cerebral blood flow (CBF) (Tomasi et al. 2013; Tomasi and Volkow 2011). Therefore, we think that the brain regions with high functional connectivity density can predict higher energy consumption and cerebral blood flow (CBF) at rest during smoking abstinence.

As we expected, gFCD- and lFCD-hubs in striatum and frontal brain regions were found. In a previous study, Li et al. had found smoking abstinence can induce Regional homogeneity (ReHo) changes of brain regions within fronto-striatal circuits in smokers (Li et al. 2016). Our results were consisted with these previous findings. In other previous studies, DA and nAChRs (nicotinic acetylcholine receptors) changes that occur in the striatum as might be the case with cigarette smoking (Bloomfield et al. 2014; Hilario et al. 2012; Kim et al. 2014), and smoking was significantly associated with gray matter volume changes in the prefrontal cortex (PFC) and the anterior cingulate cortex (ACC) (Fritz et al. 2014; Yu et al. 2011). Additionally, the prefrontal cortex (PFC) was greatly crucial in cognitive control in smokers (Feil et al. 2010; Feng et al. 2016; Nees et al. 2013), and the striatum was mainly associated with reward (Feil et al. 2010; Li et al. 2016; Yuan et al. 2016). The interactions between reward and cognitive control play extremely crucial roles in investigating the underlying neural mechanisms of smoking craving (Chua et al. 2011; Kober and Ochsner 2010). The higher gFCD and lFCD in abstinence than satiety would predict higher energy consumption and higher CBF per unit weight of brain. Therefore, we suggested that smoking abstinence would greatly change neural mechanisms underlying information interactions, which in turn may affect the balance between rewards and cognitive controls.

Through the whole brain correlation analysis, we found that the abstinence-induced lFCD changes of left ACC, right OFC and bilateral caudate (striatum subregion) were significantly correlated with the craving changes in young smokers. According to previous studies, caudate showed a single relationship with craving measures (i.e., QSU) (Di et al. 2016; Janes et al. 2015b), and the smoking cues could activate the OFC brain region (Charboneau et al. 2013). Additionally, both OFC and ACC are implicated in reinforcement-guided decision-making, emotion and social behavior (Campbell-Meiklejohn et al. 2012; Rushworth et al. 2007; Walton et al. 2010). It has been shown that the ACC has the ability to control the urge to smoke, and the activation of this area is related with craving measures (Azizian et al. 2010; Li et al. 2013, 2015). The human OFC was linked with reward to hedonic experience (Elliott et al. 2000; Kringelbach 2005; Rolls 2000). On the circuit level, the dorsal ACC–insula coupling is associated with enhanced brain reactivity to smoking cues (Janes et al. 2015a). The intermittent dopaminergic activation of reward circuits secondary to drug self-administration can lead to dysfunction of the orbitofrontal cortex via the striato-thalamo-orbitofrontal circuit (Volkow and Fowler 2000; Volkow et al. 2013). Based on these observations, we speculated that abstinence can change the hubness of these brain regions, which was associated with neural mechanisms of craving and reward processing.

We also found gFCD- and lFCD-hubs in the bilateral insula. Through a converging lines of neuroimaging finding, insula paly critical roles in maintaining smoking addiction (Addicott et al. 2015; Naqvi et al. 2007), especially in the interoceptive awareness of smoking craving (Bi et al. 2017a; Moran-Santa Maria et al. 2015). The damage of the insula may cause no response to craving after quitting (Contreras et al. 2007; Gaznick et al. 2014; Naqvi et al. 2007). Our experimental result exactly verified that insula was closely related to smoking addiction. With respect to previous studies, the increased RSFC between ACC and insula was found to be correlated with the intensity of abstinence-induced smoking craving (Huang et al. 2014). Additionally, our previous study also showed that the right anterior insula plays an important roles in craving in young smokers (Bi et al. 2017a, b). Thus, abnormal functional connectivity density of the insula possibly reflects the inefficiency of inhibitory control ability of conscious feeling of urge. In addition, the lFCD-hubs in bilateral thalamus regions were found in this study. According to previous study, smoking has been demonstrated to be associated with the abnormity of structure and function in the thalamus, which plays a crucial role in distributing incoming sensory information (Sutherland et al. 2016; Scholpp and Lumsden 2010; Yu et al. 2017).

The FCDM method can accurately measure the most prominent functional hub with fast communication of minimal energy cost in the brain (Tomasi and Volkow 2010). The primary indicators of FCDM method include lFCD and gFCD, which indicate the energy-efficient regions (densely connected nodes), and the nodes serve as the interconnection hubs (Tomasi and Volkow 2010, 2011). In this study, we use both lFCD and gFCD indicators to evaluate FCDM during 12-h abstinence (vs satiety). The lFCD mainly reflects functional connectivity of the local cluster, while the gFCD included both local and distal functional connections (Ding et al. 2016; Tomasi and Volkow 2010; Tomasi and Volkow, 2012a). We had used both lFCD and gFCD to analyze the relationship between craving and these two indicators (lFCD and gFCD). However, only the changes of brain lFCD were related to the changes of craving in our experiment (Fig. 2). From Fig. 1, there is a strong coupling between gFCD- and lFCD-hubs results during 12-h abstinence (vs satiety). Particularly, the mostly coupling regions are the key nodes within fronto-striatal circuits. The present findings from functional connectivity density may provide new insights into the neurobiological mechanisms underlying the abstinence-induced craving.

Limitations

The strength of within-subject design extremely increased statistical power and reduced the error variance associated with individual differences (Li et al. 2016; Bi et al. 2017b). Several limitations should be considered. First, the lack of a neutral control condition made it difficulty to determine whether the status of abstinence or satiety can cause functional connectivity density changes. In future, we should use a design that would allow test–retest reliability to be determined, which may contribute to the following studies. Another limitation is that only male smokers were included in this study. In previous studies, abstinence-induced craving to smoke and the neural mechanism of craving (e.g. smoking cue-induced craving) differed by sex (Mcclernon et al. 2008; Bi et al. 2017b). In future studies, our findings should be generalized to female smokers.

Conclusion

In conclusion, we used the FCDM to assess the brain properties between 12 h of abstinence condition and satiety condition during resting state in young adult smokers by employing a within-subject design. We found young adult smokers in abstinence state (compared with satiety) had higher lFCD and gFCD in brain regions involved in fronto-striatal circuits and bilateral insula. Additionally, we found that significant positive correlations between the lFCD changes and the changes in craving induced by 12-h abstinence in the left ACC, right

OFC and bilateral caudate. The present findings improve the understanding of the effects of acute smoking abstinence on spontaneous brain activity and may contribute new insights into the neural mechanism of craving in smoking addiction.

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Compliance with ethical standards

Informed consent Informed consent was obtained from all individual participants included in the study.

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.

Conflict of interest The authors declare that they have no conflict of interest.

References

Addicott, M. A., Froeliger, B., Kozink, R. V., Van Wert, D. M., Westman, E. C., Rose, J. E., & McClernon, F. J. (2014). Nicotine and non-nicotine smoking factors differentially modulate craving, withdrawal and cerebral blood flow as measured with arterial spin labeling. *Neuropsychopharmacology, 39*, 2750.

Addicott, M. A., Sweitzer, M. M., Froeliger, B., Rose, J. E., & McLennan, F. J. (2015). Increased Functional Connectivity in an Insula-Based Network is Associated with Improved Smoking Cessation Outcomes. *Neuropsychopharmacology Official Publication of the American College of Neuropsychopharmacology, 40*, 2648.

Azizian, A., Nestor, L. J., Payer, D., Monterosso, J. R., Brody, A. L., & London, E. D. (2010). Smoking reduces conflict-related anterior cingulate activity in abstinent cigarette smokers performing a Stroop task. *Neuropsychopharmacology, 35*, 775.

Bi, Y., Yuan, K., Guan, Y., Cheng, J., Zhang, Y., Li, Y., Yu, D., Qin, W., & Tian, J. (2017a). Altered resting state functional connectivity of anterior insula in young smokers. *Brain Imaging and Behavior, 11*, 155.

Bi, Y., Zhang, Y., Li, Y., Yu, D., Yuan, K., & Tian, J. (2017b). 12h abstinence-induced right anterior insula network pattern changes in young smokers. *Drug and Alcohol Dependence, 176*, 162.

Bloomfield, M. A., Pepper, F., Egerton, A., Demjaha, A., Tomasi, G., Mouchlianitis, E., Maximen, L., Veronese, M., Turkheimer, F., & Selvaraj, S. (2014). Dopamine function in cigarette smokers: an [^{18}F]-DOPA PET study. *Neuropsychopharmacology Official Publication of the American College of Neuropsychopharmacology, 39*, 2397–2404.

Caeyenberghs, K., Siugzdaite, R., Drijkoningen, D., Marinazzo, D., & Swinnen, S. (2015). Functional connectivity density and balance in young patients with traumatic axonal injury. *Brain Connectivity, 5*(7), 423–432.

Campbell-Meiklejohn, D. K., Kanai, R., Bahrami, B., Bach, D. R., Dolan, R. J., Roepstorff, A., & Frith, C. D. (2012). Structure of orbitofrontal cortex predicts social influence. *Current Biology: CB, 22*, R123.

Charboneau, E. J., Dietrich, M. S., Park, S., Cao, A., Watkins, T. J., Blackford, J. U., Benningfield, M. M., Martin, P. R., Buchowski, M. S., & Cowan, R. L. (2013). Cannabis cue-induced brain activation correlates with drug craving in limbic and visual salience regions: Preliminary results. *Psychiatry Research, 214*, 122–131.

Chua, H. F., Ho, S. S., Jasinska, A. J., Polk, T. A., Welsh, R. C., Liberzon, I., & Strecher, V. J. (2011). Self-related neural response to tailored smoking-cessation messages predicts quitting. *Nature Neuroscience, 14*, 426–427.

Contreras, M., Ceric, F., & Torrealba, F. (2007). Inactivation of the interoceptive insula disrupts drug craving and malaise induced by lithium. *Science, 318*, 655–658.

Cooper, J. (2001). Diagnostic and Statistical Manual of Mental Disorders (4th edn, text revision) (DSM-IV-TR). *British Journal of Psychiatry, 179*, 97–98.

Cox, L. S., Tiffany, S. T., & Christen, A. G. (2001). Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco, 3*, 7.

Di, C. P., Guranda, M., Lagzdins, D., Tyndale, R. F., Gamaleddin, I., Selby, P., Boileau, I., & Le, F. B. (2016). Varenicline-Induced Elevation of Dopamine in Smokers: A Preliminary [(11)C]-(+)-PHNO PET Study. *Neuropsychopharmacology, 41*, 1513–1520.

Ding, J. R., Ding, X., Hua, B., Xiong, X., Wang, Q., & Chen, H. (2016). Abnormal functional connectivity density in patients with ischemic white matter lesions:An observational study. *Medicine, 95*, e4625.

Elliott, R., Dolan, R. J., & Frith, C. D. (2000). Dissociable Functions in the Medial and Lateral Orbitofrontal Cortex: Evidence from Human Neuroimaging Studies. *Cerebral Cortex, 10*, 308.

Feil, J., Sheppard, D., Fitzgerald, P. B., Yücel, M., Lubman, D. I., & Bradshaw, J. L. (2010). Addiction, compulsive drug seeking, and the role of frontostriatal mechanisms in regulating inhibitory control. *Neuroscience & Biobehavioral Reviews, 35*, 248.

Feng, D., Yuan, K., Li, Y., Cai, C., Yin, J., Bi, Y., Cheng, J., Guan, Y., Shi, S., & Yu, D. (2016). Intra-regional and inter-regional abnormalities and cognitive control deficits in young adult smokers. *Brain Imaging and Behavior, 10*, 506–516.

Fritz, H. C., Wittfeld, K., Schmidt, C. O., Domin, M., Grabe, H. J., Hegenscheid, K., Hosten, N., & Lotze, M. (2014). Current smoking and reduced gray matter volume-a voxel-based morphometry study. *Neuropsychopharmacology Official Publication of the American College of Neuropsychopharmacology, 39*, 2594.

Gaznick, N., Tranel, D., Mcnutt, A., & Bechara, A. (2014). Basal Ganglia Plus Insula Damage Yields Stronger Disruption of Smoking Addiction Than Basal Ganglia Damage Alone. *Nicotine & Tobacco Research Official Journal of the Society for Research on Nicotine & Tobacco, 16*, 445.

Goldstein, R. Z., & Volkow, N. D. (2011). Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nature Reviews Neuroscience, 12*, 652.

Hanlon, C. A., Devries, W., Dowdle, L. T., West, J. A., Siekman, B., Li, X., & George, M. S. (2015). A comprehensive study of sensorimotor cortex excitability in chronic cocaine users: Integrating TMS and functional MRI data ☆. *Drug and Alcohol Dependence, 157*, 28.

Hayashi, T., Ko, J. H., Strafella, A. P., & Dagher, A. (2013). Dorsolateral prefrontal and orbitofrontal cortex interactions during self-control of

cigarette craving. *Proceedings of the National Academy of Sciences of the United States of America, 110*, 4422–4427.

Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., & Fagerstrom, K. O. (1991). The Fagerström Test for Nicotine Dependence: a re-vision of the Fagerstrom Tolerance Questionnaire. *British Journal of Addiction, 86*, 1119.

Hilario, M. R., Turner, J. R., & Blendy, J. A. (2012). Reward Sensitization: Effects of Repeated Nicotine Exposure and Withdrawal in Mice. *Neuropsychopharmacology Official Publication of the American College of Neuropsychopharmacology, 37*, 2661–2670.

Hu, R., Zhu, X., Cheng, D., He, W., Yan, Y., Song, J., et al. (2016). Graph self-representation method for unsupervised feature selection. In *Neurocomputing*.

Huang, W., King, J. A., Sanouri Ursprung, W. W., Zheng, S., Zhang, N., Kennedy, D. N., Ziedonis, D., & DiFranza, J. R. (2014). The development and expression of physical nicotine dependence corresponds to structural and functional alterations in the anterior cingulate-precuneus pathway. *Brain and Behavior, 4*, 408–417.

Janes, A. C., Farmer, S., Peechatka, A. L., Frederick, B. B., & Lukas, S. E. (2015a). Insula-Dorsal Anterior Cingulate Cortex Coupling is Associated with Enhanced Brain Reactivity to Smoking Cues. *Neuropsychopharmacology, 40*, 1561–1568.

Janes, A. C., Park, M. T., Farmer, S., & Chakravarty, M. M. (2015b). Striatal morphology is associated with tobacco cigarette craving. *Neuropsychopharmacology Official Publication of the American College of Neuropsychopharmacology, 40*, 406–411.

Jasinska, A. J., Zorick, T., Brody, A. L., & Stein, E. A. (2014). Dual role of nicotine in addiction and cognition: a review of neuroimaging studies in humans. *Neuropharmacology, 84*, 111–122.

Jin, C., Zhang, T., Cai, C., Bi, Y., Li, Y., Yu, D., Zhang, M., & Yuan, K. (2016). Abnormal prefrontal cortex resting state functional connectivity and severity of internet gaming disorder. *Brain Imaging and Behavior, 10*, 719.

Kim, S. J., Sullivan, J. M., Wang, S., Cosgrove, K. P., & Morris, E. D. (2014). Voxelwise lp-ntPET for detecting localized, transient dopamine release of unknown timing: Sensitivity Analysis and Application to Cigarette Smoking in the PET Scanner. *Human Brain Mapping, 35*, 4876–4891.

Kober, H., & Ochsner, K. N. (2010). Prefrontal-striatal pathway underlies cognitive regulation of craving. *Proceedings of the National Academy of Sciences of the United States of America, 107*, 14811.

Kringelbach, M. L. (2005). The human orbitofrontal cortex: linking reward to hedonic experience. *Nature Reiviews Neuroscience, 6*, 691.

Le, F. B., Guranda, M., Wilson, A. A., Houle, S., Rusjan, P. M., Wing, V. C., Zawertailo, L., Busto, U., Selby, P., & Brody, A. L. (2014). Elevation of dopamine induced by cigarette smoking: novel insights from a [11C]−+-PHNO PET study in humans. *Neuropsychopharmacology Official Publication of the American College of Neuropsychopharmacology, 39*, 415–424.

Lei, C., & Zhu, X. (2017). Unsupervised feature selection via local structure learning and sparse learning. *Multimedia Tools & Applications*, (1). https://doi.org/10.1007/s11042-017-5381-7.

Lerman, C., Lesage, M. G., Perkins, K.A., O'Malley, S. S., Siegel, S. J., Benowitz, N. L., & Corrigall, W. A. (2007). Translational research in medication development for nicotine dependence. *Nature Reviews Drug Discovery, 6*, 746–762.

Li, X., Hartwell, K. J., Borckardt, J., Prisciandaro, J. J., Saladin, M. E., Morgan, P. S., Johnson, K. A., LeMatty, T., Brady, K. T., & George, M. S. (2013). Volitional reduction of anterior cingulate cortex activity produces decreased cue craving in smoking cessation: a preliminary real-time fMRI study. *Addiction Biology, 18*, 739–748.

Li, Y., Yuan, K., Cai, C., Feng, D., Yin, J., Bi, Y., Shi, S., Yu, D., Jin, C., & von Deneen, K. M. (2015). Reduced frontal cortical thickness and increased caudate volume within fronto-striatal circuits in young adult smokers. *Drug and Alcohol Dependence, 151*, 211.

Li, Y., Yuan, K., Bi, Y., Guan, Y., Cheng, J., Zhang, Y., Shi, S., Lu, X., Yu, D., & Tian, J. (2016). Neural correlates of 12-h abstinence-induced craving in young adult smokers: a resting-state study. *Brain Imaging and Behavior, 11*, 1–8.

Li, Y., Yuan, K., Guan, Y., Cheng, J., Bi, Y., Shi, S., Xue, T., Lu, X., Qin, W., & Yu, D. (2017). The implication of salience network abnormalities in young male adult smokers. *Brain Imaging and Behavior, 11*, 943–953.

Liu, C., Wei, Z., Chen, G., Tian, H., Jie, L., Qu, H., et al. (2017). Aberrant patterns of local and long-range functional connectivity densities in schizophrenia. *Oncotarget, 8*(29), 48196–48203.

Martin-Soelch, C. (2013). Neuroadaptive changes associated with smoking: structural and functional neural changes in nicotine dependence. *Brain Sciences, 3*, 159.

Mcclernon, F. J., Kozink, R. V., & Rose, J. E. (2008). Individual Differences in Nicotine Dependence, Withdrawal Symptoms, and Sex Predict Transient fMRI-BOLD Responses to Smoking Cues. *Neuropsychopharmacology Official Publication of the American College of Neuropsychopharmacology, 33*(9), 2148.

Moran-Santa Maria, M. M., Hartwell, K. J., Hanlon, C. A., Canterberry, M., Lematty, T., Owens, M., Brady, K. T., & George, M. S. (2015). Right anterior insula connectivity is important for cue-induced craving in nicotine-dependent smokers. *Addiction Biology, 20*, 407–414.

Naqvi, N. H., Rudrauf, D., Damasio, H., & Bechara, A. (2007). Damage to the insula disrupts addiction to cigarette smoking. *Science, 315*, 531.

Nees, F., Witt, S. H., Lourdusamy, A., Vollstädt-Klein, S., Steiner, S., Poustka, L., Banaschewski, T., Barker, G. J., Büchel, C., & Conrod, P. J. (2013). Genetic risk for nicotine dependence in the cholinergic system and activation of the brain reward system in healthy adolescents. *Neuropsychopharmacology Official Publication of the American College of Neuropsychopharmacology, 38*, 2081.

Newberg, A., Lerman, C., Wintering, N., Ploessl, K., & Mozley, P. D. (2007). Dopamine transporter binding in smokers and nonsmokers. *Clinical Nuclear Medicine, 32*, 452–455.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9*, 97–113.

Rolls, E. T. (2000). The Orbitofrontal Cortex and Reward. *Cerebral Cortex, 10*, 284–294.

Rushworth, M. F. S., Behrens, T. E. J., Rudebeck, P. H., & Walton, M. E. (2007). Contrasting roles for cingulate and orbitofrontal cortex in decisions and social behaviour. *Trends in Cognitive Sciences, 11*, 168–176.

Scholpp, S., & Lumsden, A. (2010). Building a bridal chamber: development of the thalamus. *Trends in Neurosciences, 33*, 373–380.

Smith, S. M., & Nichols, T. E. (2009). Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference. *Neuroimage, 44*, 83–98.

Sutherland, M. T., Riedel, M. C., Flannery, J. S., Yanes, J. A., Fox, P. T., Stein, E. A., & Laird, A. R. (2016). Chronic cigarette smoking is linked with structural alterations in brain regions showing acute nicotinic drug-induced functional modulations. *Behavioral and Brain Functions, 12*, 16.

Tomasi, D., & Volkow, N. D. (2010). Functional connectivity density mapping. *Proceedings of the National Academy of Sciences of the United States of America, 107*, 9885–9890.

Tomasi, D., & Volkow, N. D. (2011). Functional connectivity hubs in the human brain. *Neuroimage, 57*, 908–917.

Tomasi, D., & Volkow, N. D. (2012a). Abnormal Functional Connectivity in Children with Attention-Deficit/Hyperactivity Disorder. *Biological Psychiatry, 71*, 443.

Tomasi, D., & Volkow, N. D. (2012b). Gender differences in brain functional connectivity density. *Human Brain Mapping, 33*, 849.

Tomasi, D., Wang, G.-J., & Volkow, N. D. (2013). Energetic cost of brain functional connectivity. *Proceedings of the National Academy of Sciences of the United States of America, 110*, 13642–13647.

U.S. Department of Health and Human Services. (1988). *The health consequences of smoking: Nicotine addiction. A report of the surgeon general (DHHS Publication No. [CDC] 88-8406)*. Washington, DC: U.S. Dept. of Health and Human Services, Public Health Services.

Volkow, N. D., & Fowler, J. S. (2000). Addiction, a Disease of Compulsion and Drive: Involvement of the Orbitofrontal Cortex. *Cerebral Cortex, 10*, 318.

Volkow, N. D., Wang, G. J., Tomasi, D., & Baler, R. D. (2013). Unbalanced neuronal circuits in addiction. *Current Opinion in Neurobiology, 23*, 639–648.

Walton, M. E., Behrens, T. E. J., Buckley, M. J., Rudebeck, P. H., & Rushworth, M. F. S. (2010). Separable Learning Systems in the Macaque Brain and the Role of Orbitofrontal Cortex in Contingent Learning. *Neuron, 65*, 927.

Wing, V. C., Payer, D. E., Houle, S., George, T. P., & Boileau, I. (2015). Measuring cigarette smoking-induced cortical dopamine release: A [Â^{1}Â^{1}C]FLB-457 PET study. *Neuropsychopharmacology, 40*, 1417–1427.

Xue, Y., Luo, Y., Wu, P., Shi, H., Xue, L., Chen, C., Zhu, W., Ding, Z., Bao, Y., & Shi, J. (2012). A Memory Retrieval-Extinction Procedure to Prevent Drug Craving and Relapse. *Science (New York, N.Y.), 336*, 241.

Yip, S. W., Devito, E. E., Kober, H., Worhunsky, P. D., Carroll, K. M., & Potenza, M. N. (2014). Pretreatment measures of brain structure and reward-processing brain function in cannabis dependence: An exploratory study of relationships with abstinence during behavioral treatment 1. *Drug and Alcohol Dependence, 140*, 33–41.

Yu, R., Zhao, L., & Lu, L. (2011). Regional Grey and White Matter Changes in Heavy Male Smokers. *PLoS One, 6*, e27440.

Yu, D., Yuan, K., Bi, Y., Luo, L., Zhai, J., Liu, B., Li, Y., Cheng, J., Guan, Y., and Xue, T. (2017). Altered interhemispheric resting-state functional connectivity in young male smokers. *Addiction Biology, 23*(2), 772–780.

Yuan, K., Yu, D., Bi, Y., Li, Y., Guan, Y., Liu, J., Zhang, Y., Qin, W., Lu, X., & Tian, J. (2016). The implication of frontostriatal circuits in young smokers: A resting-state study. *Human Brain Mapping, 37*(6), 2013–2026.

Yuan, K., Yu, D., Bi, Y., Wang, R., Li, M., Zhang, Y., Dong, M., Zhai, J., Li, Y., and Lu, X. (2017). The left dorsolateral prefrontal cortex and caudate pathway: New evidence for cue-induced craving of smokers. *Human Brain Mapping, 38*(9), 4644–4656.

Zhang, S., Li, X., Ming, Z., Zhu, X., & Wang, R. (2017). Efficient kNN Classification With Different Numbers of Nearest Neighbors. *IEEE Transactions on Neural Networks and Learning Systems, PP*(99), 1–12.

Zhao, L. Y., Tian, J., Wang, W., Qin, W., Shi, J., Li, Q., Yuan, K., Dong, M. H., Yang, W. C., & Wang, Y. R. (2012). The Role of Dorsal Anterior Cingulate Cortex in the Regulation of Craving by Reappraisal in Smokers. *PLoS One, 7*, e43598.

Zheng, W., Zhu, X., Zhu, Y., Hu, R., & Lei, C. (2017). Dynamic graph learning for spectral feature selection. *Multimedia Tools and Applications*. https://doi.org/10.1007/s11042-017-5272-y.

Zhu, X., Li, X., Zhang, S., Xu, Z., Yu, L., & Wang, C. (2017). Graph PCA Hashing for Similarity Search. *IEEE Transactions on Multimedia, PP*(99). https://doi.org/10.1109/TMM.2017.2703636.

Zhu, X., Zhang, S., Hu, R., Zhu, Y., & Song, J. (2018). Local and Global Structure Preservation for Robust Unsupervised Spectral Feature Selection. *IEEE Transactions on Knowledge and Data Engineering, 30*(3), 517–529.