NeuroImage: Clinical 28 (2020) 102451

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Increased thalamic volume and decreased thalamo-precuneus functional connectivity are associated with smoking relapse

Chao Wang [a,*], Shuyue Wang [a], Zhujing Shen [a], Wei Qian [a], Yeerfan Jiaerken [a], Xiao Luo [a], Kaicheng Li [a], Qingze Zeng [a], Quanquan Gu [a], Yihong Yang [b], Peiyu Huang [a,*], Minming Zhang [a,*]

[a] Department of Radiology, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China
[b] Neuroimaging Research Branch, National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD, USA

ARTICLE INFO

Keywords:
Smoking relapse
Resting state functional connectivity
Thalamus
Precuneus

ABSTRACT

The thalamus, with the highest density of nicotinic acetylcholine receptor (nAChR) in the brain, plays a central role in thalamo-cortical circuits that are implicated in nicotine addiction. However, little is known about whether the thalamo-cortical circuits are potentially predictive of smoking relapse. In the current study, a total of 125 participants (84 treatment-seeking male smokers and 41 age-matched male nonsmokers) were recruited. Structural and functional magnetic resonance images (MRI) were acquired from all participants. After a 12-week smoking cessation treatment with varenicline, the smokers were then divided into relapsers (n = 54) and non-relapsers (n = 30). Then, we compared thalamic volume and seed-based thalamo-cortical resting state functional connectivity (rsFC) prior to the cessation treatment among relapsers, nonrelapsers and nonsmokers to investigate the associations between thalamic structure/function and smoking relapse. Increased thalamic volume was detected in smokers relative to nonsmokers, and in relapsers relative to nonrelapsers, especially on the left side. Moreover, decreased left thalamo-precuneus rsFC was detected in relapsers relative to nonrelapsers. Additionally, a logistic regression analysis showed that the thalamic volume and thalamo-precuneus rsFC predicted smoking relapse with an accuracy of 75.7%. These novel findings indicate that increased thalamic volume and decreased thalamo-precuneus rsFC are associated with smoking relapse, and these thalamic measures may be used to predict treatment efficacy of nicotine addiction and serve as a potential biomarker for personalized medicine.

1. Introduction

Cigarette smoking is the leading cause of preventable morbidity, causing 6 million preventable deaths per year and an estimated 8 million deaths worldwide by 2030 without effective interventions (Asma et al., 2014). Most nicotine-dependent smokers express the desire to quit smoking, but only 3–5% remain abstinent without the use of therapies (Hughes et al., 2004). Varenicline, a partial agonist of alpha4beta2 nicotinic acetylcholine receptor (nAChR), is a first-line drug for quitting smoking and has shown therapeutic efficacy in smoking cessation. However, smoking relapse rates remain very high even with varenicline treatment (Cahill et al., 2016).

Nicotine is the primary ingredient that acts as a presynaptic nAChR agonist, facilitating the release of synaptic dopamine and making cigarettes highly addictive (Wonnacott, 1997). The key role of dopamine in reward processing makes nAChR a mediator for signal delivery that instigates and maintains nicotine addiction. nAChRs are widely distributed in various brain regions, such as the ventral tegmental area (VTA) (Yang et al., 2009), thalamus (Gallezot et al., 2005; Kimes et al., 2003), striatum (Grady et al., 2007), hippocampus (Alkondon and Albuquerque, 2001), prefrontal cortex (PFC) (Gioanni et al., 1999), and amygdala (Klein and Yakel, 2006). The thalamus, with the highest nAChR density in the brain (Gallezot et al., 2005; Kimes et al., 2003), plays a central role in the cortico-striato-thalamo-cortical reward circuits that are critically implicated in drug addiction (Huang et al., 2018). Using voxel-based morphometry (VBM) analysis, previous studies have reported reduced gray matter volumes in several areas within the thalamus in smokers relative to nonsmokers (Hanlon et al., 2016; Liao et al., 2012). However, it remains largely unclear whether thalamic volume prior to the treatment is potentially predictive of smoking relapse. In

* Corresponding authors at: Department of Radiology, The Second Affiliated Hospital, Zhejiang University School of Medicine, No. 88 Jiefang Road, Hangzhou 310009, China.
E-mail addresses: 2514110@zju.edu.cn (C. Wang), huangpy@zju.edu.cn (P. Huang), zhangminming@zju.edu.cn (M. Zhang).

https://doi.org/10.1016/j.nicl.2020.102451
Received 11 April 2020; Received in revised form 22 September 2020; Accepted 23 September 2020
Available online 28 September 2020

addition, a task-state functional magnetic resonance imaging (fMRI) study has shown that smoking relapse is associated with decreased task-based functional connectivity (FC) between the thalamus and inferior frontal gyrus (Froeliger et al., 2017). Recently, resting-state fMRI (rs-fMRI) has been suggested as an important tool to reveal the pathophysiological mechanisms underlying psychiatric and neurological diseases (Barkhof et al., 2014). However, it remains largely unclear whether thalamo-cortical resting-state FC (rsFC) prior to the treatment is potentially predictive of smoking relapse.

In the current study, a total of 125 participants (84 treatment-seeking male smokers and 41 age-matched male nonsmokers) were recruited. Structural and functional MRI were acquired from all participants. Then, a 12-week varenicline treatment was conducted for these treatment-seeking smokers. According to the smoking cessation outcomes, the smokers were then divided into relapsers and nonrelapsers. Subcortical volumetric segmentation using FreeSurfer (http://surfer.nmr.mgh.harvard.edu) has been shown as a sensitive method for measuring the structural changes of gray matter (Hutton et al., 2009). Therefore, in our study, subcortical parcellation procedures were performed using FreeSurfer for all participants. Then, the thalamic volume and thalamus-based rsFC were compared among relapsers, nonrelapsers and nonsmokers to determine whether the thalamic measures prior to the treatment were related to smoking treatment outcomes.

2. Methods and materials

2.1. Participants and procedures

Eighty-four treatment-seeking male smokers and 41 age-matched healthy male nonsmokers were recruited via advertisements. All participants were Han Chinese, 22–55 years old and right-handed as measured by the Edinburgh Handedness Inventory. The inclusion criteria for smokers included: 1) smoked $\geq$ 10 cigarettes per day in the last one year; 2) the number of years having smoked $\geq$ 2; 3) meeting the DSM-IV criteria of nicotine dependence; 4) afternoon breath carbon monoxide (CO) level $>$ 10 ppm. Fagerström Test of Nicotine Dependence (FTND) was used to assess nicotine dependence levels for smokers (Fagerstrom and Schneider, 1989). The nonsmokers were defined as those smoked fewer than 20 cigarettes in their lifetime, and none in the past 10 years with exhaled CO level $\leq$ 3 ppm. Exclusion criteria for all participants included: 1) a history of major illnesses, neurological and psychiatric diseases; 2) systemic diseases, such as hypertension and diabetes; 3) psychotropic medication use, and other substance abuse (besides nicotine), such as heroin, cocaine and alcohol; 4) MRI contraindications (i.e., claustrophobia and metal implants). This study was approved by the institutional review boards of the Second Affiliated Hospital, Zhejiang University School of Medicine. All participants signed informed consents.

After the baseline MRI scan, all treatment-seeking smokers received a standard 12-week varenicline treatment (http://www.pfizer.com/products). Participants started with a recommended varenicline dosage of 0.5 mg once daily for 3 days, then increased to 0.5 mg twice daily for days 4 to 7, and then to the maintenance dose of 1 mg twice daily. Participants were asked to reduce their baseline smoking rate by 50% or more from baseline by week 4 with a further reduction to 75% or more from baseline before week 8 with the goal of quitting smoking completely by week 8. Weekly telephone visits were conducted to record their self-reports of smoking behavior and encourage them to reduce their smoking amount faster. Consistent with prior studies, 4-week continuous abstinence for the last 4 weeks (weeks 9–12) was regarded as the endpoint (Gonzales et al., 2006; Jorenby et al., 2006). According to their weekly self-reports of smoking behavior, those who smoked any cigarette during weeks 9–12 were considered as relapsers (n = 45). And those who remained continuously abstinent during weeks 9–12 were considered as nonrelapsers (n = 30), which were further cross-validated by an expired CO level ($\leq$6 ppm) after the 12-week treatment. In addition, nine smokers did not adhere to the standard 12-week varenicline treatment, and then they lost the weekly telephone visits. Consistent with the previous study (Froeliger et al., 2017), both those smokers who met the criterion for relapsers and those who were lost to contact were classified as relapsers in the current study. Therefore, a total of 54 smokers were classified as relapsers.

2.2. Image acquisition

All smokers received an MRI scanning session prior to the varenicline treatment. All scans were performed using a 3.0 T GE Signa MR scanner equipped with an 8-channel high-resolution phase array head coil. Conventional T1- and T2-weighted images were acquired to exclude structural abnormalities. High-resolution T1- weighted images were obtained using Sagittal 3D Fast Spoiled Gradient Recalled (3D-FSGPR) sequence: slices = 136, thickness = 1.2 mm, gap = 0 mm, repetition time (TR) = 5.056 ms, echo time (TE) = 1.116 ms, field of view (FOV) = 240 $\times$ 240 mm^2, matrix = 256 $\times$ 256, and flip angle = 15°. Resting-state functional images were obtained using Echo-planar imaging (EPI) sequence: slices = 30, thickness = 4 mm, gap = 1 mm, TR = 2000 ms, TE = 30 ms, matrix = 64 $\times$ 64, FOV = 240 $\times$ 240 mm^2, flip angle = 80°, and volumes = 185. During fMRI scanning (370 s), participants were instructed to lie still, keep eyes closed, and not to fall asleep. The purpose of this study was to investigate the effect of chronic smoking rather than acute abstinence. Therefore, in this study, smokers were allowed to smoke as usual approximately ten minutes before scanning to avoid withdrawal symptoms during scanning. Thus, smokers were scanned at satiated state in this study.

2.3. Image processing

2.3.1. Thalamic volume calculation

Subcortical segmentation of the whole brain was performed using FreeSurfer software package (v5.3.0, https://surfer.nmr.mgh.harvard.edu), which had been used in our previous studies (Huang et al., 2015; Shen et al., 2017). Details of FreeSurfer segmentation were described in Fischl's study (Fischl, 2012). Subcortical segmentation and labeling of the thalamus were performed with default parameters (http://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferAnalysisPipelineOverview). In more detail, automatic subcortical segmentation of the thalamus was done in the following five stages (Fischl et al., 2002, 2004): 1) an affine registration with MNI305 space specifically was designed to be insensitive to pathology and to maximize the accuracy of the final segmentation; 2) an initial volumetric labeling; 3) the variation in intensity was corrected due to the B1 bias field; 4) a high dimensional nonlinear volumetric alignment to the MNI305 atlas; 5) labeling the volume. The segmented thalamus was visually inspected by an experienced neuroradiologist. Specifically, the thalamic mask was overlaid on the T1-weighted images in ITK-SNAP (http://www.itksnap.org/). The neuroradiologist inspected the gray/white matter boundaries segmentation results, and manual corrections would be made if there were mis-segmentations. After preprocessing, the thalamic volume was extracted and normalized by intracranial volume (ICV) (structure/ICV $*10^6$) to correct for differences of head size.

2.3.2. Resting state fMRI data processing

Preprocessing and statistical analyses of resting-state fMRI data were performed using the toolbox for Data Processing & Analysis of Brain Imaging (DPABI) (Yan et al., 2016) and SPM12 (http://www.fil.ion.ucl.ac.uk/spm/), which were based on the MATLAB (The Mathworks, Inc., USA). The first 10 volumes were discarded to reduce magnetization disequilibrium, and then slice-timing correction and head motion correction were performed. The exclusion criterion of head motion was $>$2 mm/degree (5 smokers were excluded). After segmentation of T1 images with diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL), functional images were co-registered to

T1 images and registered to Montreal Neurological Institute (MNI) template, and then resampled into 3 × 3 × 3 mm voxel size. Spatial smoothing was conducted with an isotropic 6 mm Gaussian kernel. Finally, linear detrending and temporal band-pass filtering (0.01–0.08 Hz) were performed to remove low- and high-frequency noise. To minimize physiological noise, nuisance covariates were regressed out using the Friston-24 head motion parameters (6 head motion parameters, 6 head motion parameters from the previous time point, and the 12 corresponding squared items), as well as white matter signal and corticospinal fluid signal.

Each thalamic mask was extracted as a seed from the AAL template respectively (Fig. 1a). Then, each resliced mask was used for a seed-based rsFC analysis. Pearson's correlation between the time course of each thalamic seed and the whole brain was calculated to obtain rsFC maps. Finally, the resulting rsFC maps were transformed to Z maps using Fisher's Z transformation.

2.4. Statistical analyses

Statistical analyses were conducted using SPSS (IBM SPSS Statistics, Version 20.0, Armonk, NY). Independent two-sample t-tests were used to compare the demographic characteristics and thalamic volume between smokers and nonsmokers. For bilateral thalamic volume results, Bonferroni corrections were used for multiple comparisons ($p < 0.05/2 = 0.025$). Subsequent correlations between bilateral thalamic volume and smoking behaviors (i.e., smoking onset, years smoked, cigarettes per day (CPD), pack-years, FTND) were assessed by Pearson correlations ($p < 0.05/10 = 0.005$, Bonferroni corrected). In addition, one-way analysis of variance (ANOVA) was used to compare the demographic characteristics and thalamic volume among relapsers, nonrelapsers and nonsmokers. Independent two-sample t-tests were used to compare the smoking behavior variables between relapsers and nonrelapsers.

For the baseline fMRI data, 10 smokers were excluded from the analyses (5 smokers for incomplete fMRI data, and 5 for head motion). Thus a sample of 74 smokers (47 relapsers and 27 nonrelapsers) were finally included in the statistical analyses. The differences of thalamus-based rsFC maps between relapsers and nonrelapsers were calculated using independent two-sample t-tests. Then, the resulting statistical rsFC maps were corrected for multiple comparisons with Gaussian random field (GRF), and clusters survived GRF correction if voxel-level $p < 0.005$, cluster-level $p < 0.025$ ($p < 0.05/2$, two-tailed, Bonferroni corrected). Then, rsFC values of the significantly different clusters between relapsers and nonrelapsers were extracted. Finally, the thalamic volume and rsFC values of the significantly different clusters were entered into logistic regression models as predictors of smoking relapse. The area under curve (AUC), accuracy (accuracy = number of correct predictions/total number of predictions), sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the receiver operating characteristic (ROC) curve were calculated to assess these models. All the logistic regression models employed a classification cut-off of 0.5.

3. Results

3.1. Demographic and smoking data

No significant differences were detected in age and education between smokers and nonsmokers (Table 1). Additionally, no significant differences were detected in age and education among relapsers, nonrelapsers and nonsmokers (Table 2).

Table 1
Characteristics of smokers and nonsmokers.

	Smokers	Nonsmokers	t	p
Age (years)	38.2 ± 6.8	38.5 ± 8.6	−0.209	0.835
Education (years)	14.0 ± 2.9	15.4 ± 4.7	−1.669	0.10
Smoking initiation (years)	20.9 ± 5.1	–	–	–
Years smoked	17.3 ± 6.6	–	–	–
Cigarettes/day	23.5 ± 9.6	–	–	–
Pack-years	20.6 ± 12.4	–	–	–
FTND	5.2 ± 2.2	–	–	–

Pack-years = cigarettes/day*years smoked/20; FTND: Fagerström Test for Nicotine Dependence.

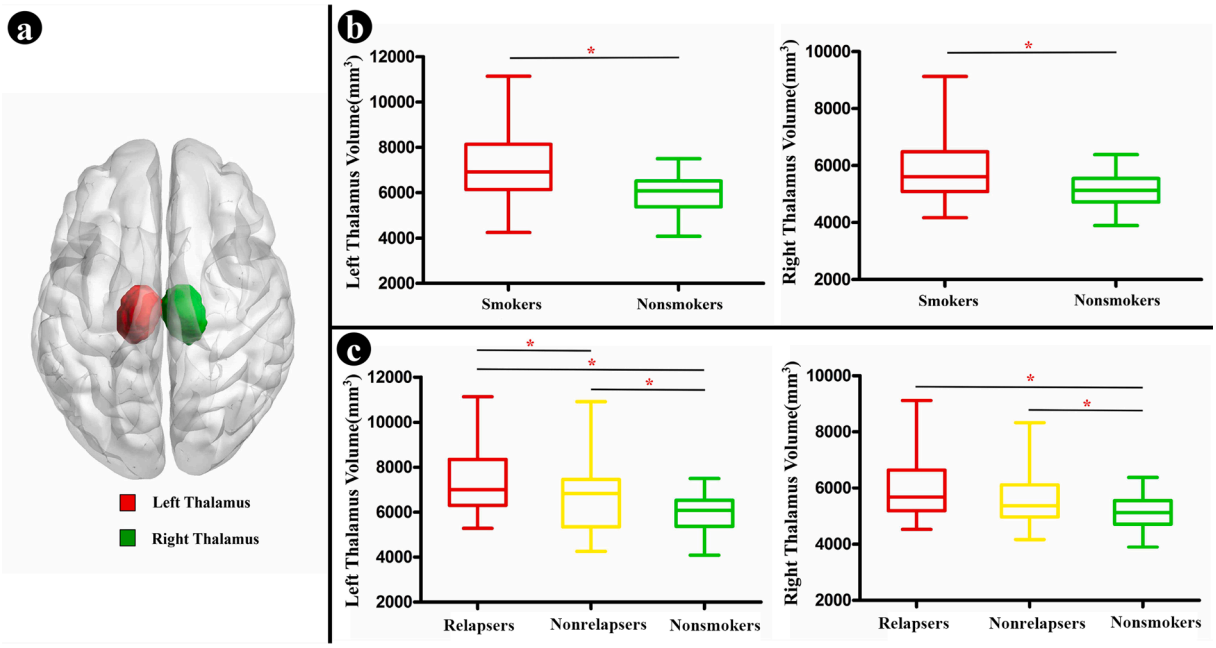

Fig. 1. Schematic of the left and right thalamus (a). Smokers showed increased normalized volume in the left ($p < 0.001$) and right ($p < 0.001$) thalamus relative to nonsmokers (b). The left thalamic volume was increased in relapsers ($p < 0.001$) and nonrelapsers ($p = 0.028$) relative to nonsmokers (c). The left thalamic volume was increased in relapsers ($p = 0.005$) relative to nonrelapsers (c). Additionally, the right thalamic volume was increased in relapsers ($p < 0.001$) and nonrelapsers ($p = 0.03$) relative to nonsmokers (c).

Table 2
Characteristics of relapsers, nonrelapsers and nonsmokers.

	Relapsers	Nonrelapsers	Nonsmokers	F/t	p
Age (years)	38.1 ± 6.6	38.3 ± 7.3	38.5 ± 8.6	0.029	0.971
Education (years)	14.0 ± 3.0	14.1 ± 2.8	15.4 ± 4.7	1.869	0.159
Smoking initiation (years)	20.3 ± 4.4	21.9 ± 6.1	–	−1.451	0.151
Years smoked	17.8 ± 6.6	16.4 ± 6.6	–	0.976	0.332
Cigarettes/day	23.8 ± 9.9	23.0 ± 9.1	–	0.331	0.742
Pack-years	21.3 ± 12.7	19.4 ± 11.9	–	0.642	0.523
FTND	5.2 ± 2.3	5.2 ± 1.9	–	0.111	0.912

Pack-years = cigarettes/day*years smoked/20; FTND: Fagerström Test for Nicotine Dependence.

3.2. Thalamic volume

No significant ICV difference was detected between smokers (1310001 ± 152634 mm^3) and nonsmokers (1357300 ± 136800 mm^3) ($p = 0.095$). Relative to nonsmokers, smokers showed increased normalized volume in the left thalamus (smokers: 7185 ± 1578 mm^3, nonsmokers: 5954 ± 810 mm^3, $t = 5.906$, $p < 0.001$, Bonferroni corrected) and right thalamus (smokers: 5838 ± 982 mm^3, nonsmokers: 5136 ± 585 mm^3, $t = 4.980$, $p < 0.001$, Bonferroni corrected) (Fig. 1b). In the whole cohort of smokers, correlation analysis revealed that left thalamic volume was negatively correlated with FTND scores ($p = 0.03$, $r = -0.236$, Bonferroni uncorrected) (Fig. 2). However, correlation analysis between thalamic volume and other smoking behavior measures (i.e., smoking onset, years smoked, CPD, and pack-years) did not reveal any significant associations.

One-way ANOVA analysis of left thalamic volume demonstrated significant differences among relapsers, nonrelapsers and nonsmokers ($F(2, 122) = 16.572$, $p < 0.001$, Bonferroni corrected) (Table 3). Post-hoc analysis demonstrated that left thalamic volume was larger in relapsers ($p < 0.001$) and nonrelapsers ($p = 0.028$) than nonsmokers (Fig. 1c). In addition, left thalamic volume was larger in relapsers ($p = 0.005$) than nonrelapsers (Fig. 1c). One-way ANOVA analysis of right thalamic volume also demonstrated significant differences among relapsers, nonrelapsers and nonsmokers ($F(2, 122) = 10.966$, $p < 0.001$, Bonferroni corrected) (Table 3). Post-hoc analysis demonstrated that right thalamic volume was larger in relapsers ($p < 0.001$) and nonrelapsers ($p = 0.03$) than nonsmokers (Fig. 1c). Relative to nonrelapsers, relapsers also tended to show increased volume in the right thalamus ($p = 0.55$), though it was not statistically significant. In addition, the statistical analyses of thalamic volume among relapsers (excluded the nine smokers who were lost to contact), nonrelapsers and nonsmokers showed the same findings (relapsers > nonrelapsers > nonsmokers) (Table S1).

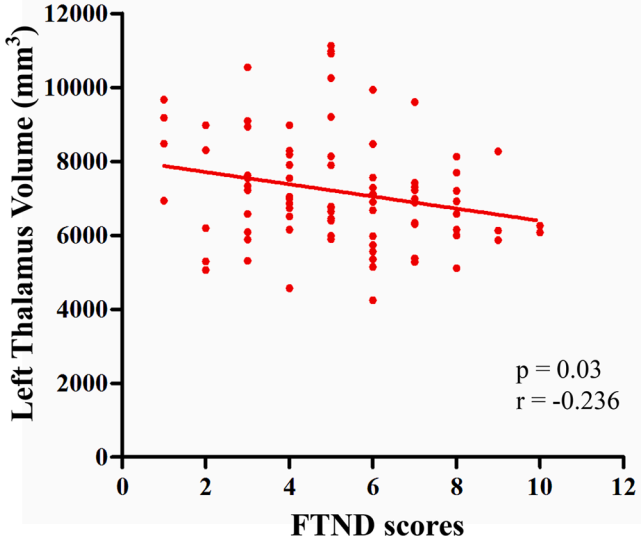

Fig. 2. The left normalized thalamic volume was negatively correlated with FTND scores.

Table 3
Thalamic volume between relapsers, nonrelapsers and nonsmokers.

	Relapsers	Nonrelapsers	Nonsmokers	F	p
Left thalamic volume	7485 ± 1484	6644 ± 1449	5954 ± 810	16.572	<0.001
Right thalamic volume	5974 ± 997	5593 ± 920	5136 ± 585	10.966	<0.001

3.3. Thalamus-based rsFC

Table 4 and Fig. 3 showed the results of thalamus-based rsFC analysis. Relapsers ($n = 54$) showed significantly lower left thalamo-precuneus rsFC than nonrelapsers. In addition, after excluding the nine smokers who were lost to contact, relapsers ($n = 45$) also showed significantly lower left thalamo-precuneus rsFC than nonrelapsers (Table S2).

3.4. Prediction of relapse by thalamic volume and thalamus-based rsFC

Table 5 and Fig. 4 illustrated the results of three models for predicting relapse with two thalamic measures, including left thalamic volume and thalamo-precuneus rsFC value. Model 1 and model 2 examined the predictors of left thalamic volume and thalamo-precuneus rsFC value in univariate models, respectively (model 1: $\chi^2 = 6.500$, $df = 1$, $p = 0.011$; model 2: $\chi^2 = 16.905$, $df = 1$, $p < 0.001$). With the two thalamic measures included, model 3 ($\chi^2 = 20.276$, $df = 2$, $p < 0.001$) improved AUC to 0.814, and the accuracy, sensitivity, specificity, PPV and NPV of this classification model were 75.7%, 85.1%, 59.3%, 78.4% and 69.6%, respectively.

4. Discussion

In the present study, smokers showed larger thalamic volume than nonsmokers, and relapsers showed larger thalamic volume than nonrelapsers, especially in the left thalamus. Moreover, relapsers showed lower left thalamo-precuneus rsFC than nonrelapsers. To explore the clinical implications of these thalamic measures, we further assessed the potential role of these thalamic measures to predict the risk of smoking relapse. And we found that thalamic volume and rsFC predicted smoking relapse over a 12-week period of varenicline treatment in smokers with an accuracy of 75.7%.

As an intermediately core node within the cortico-striato-thalamo-cortical reward circuit (Huang et al., 2018), the thalamus is integral to this circuit that underlies the reward (Haber and Calzavara, 2009; Rieck et al., 2004) and response inhibition processes mediating salience and

Table 4
Between-group differences of thalamus-based rsFC in relapsers and nonrelapsers.

Seed	Location	MNI coordinates			Cluster size	T values
		x	y	z		
Left thalamus	Relapser < nonrelapser Right precuneus	18	−57	27	165	−4.0019

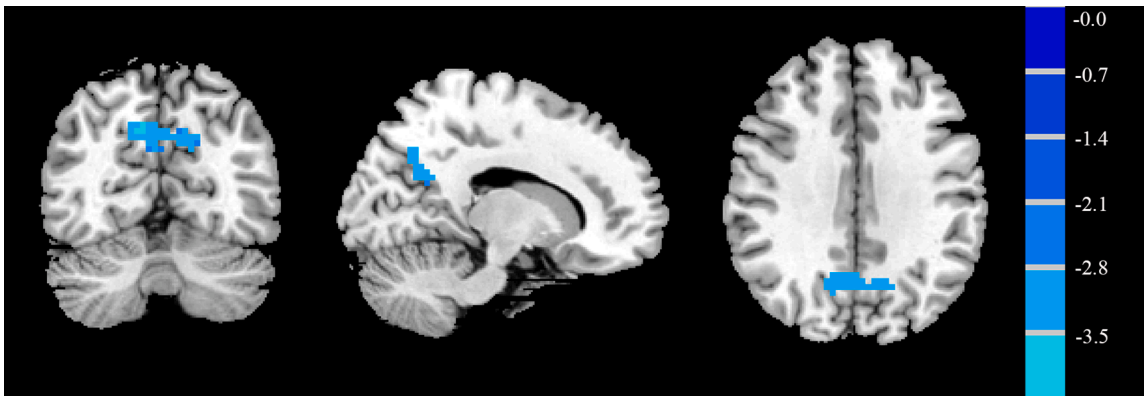

Fig. 3. The results of thalamus-based rsFC analysis. Relapsers showed significantly decreased left thalamo-precuneus rsFC relative to nonrelapsers. Colored bar represents t-values.

Table 5
Models predicting relapse status based on thalamic volume and thalamus-based rsFC.

Models	AUC (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Model 1: Left thalamic volume	65.1	72.6	96.3	30.0	71.2	81.8
Model 2: rsFC value of right precuneus	77.7	75.7	87.2	55.6	77.4	71.4
Model 3: Left thalamic volume + rsFC value of right precuneus	81.4	75.7	85.1	59.3	78.4	69.6

AUC: area under curve; PPV: positive predictive value; NPV: negative predictive value.

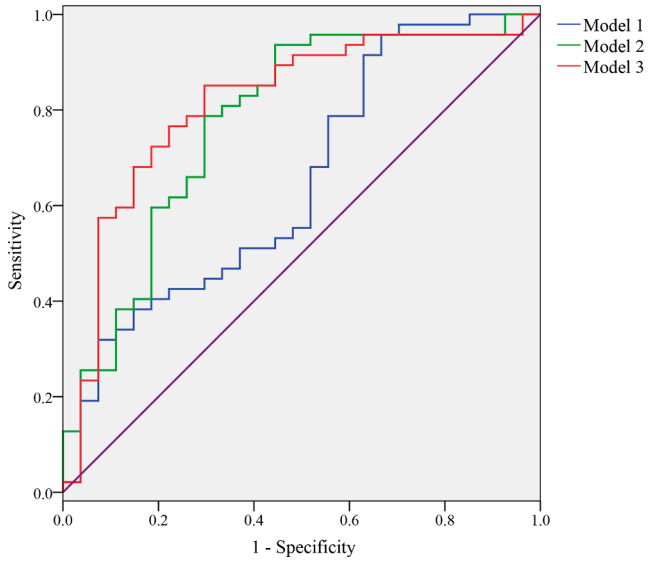

Fig. 4. The receiver operating characteristic (ROC) curve for the prediction of smoking relapse by the left thalamic volume and thalamo-precuneus rsFC in smokers.

control processes in goal-oriented behaviors (de Bourbon-Teles et al., 2014; Parnaudeau et al., 2015; Phillips et al., 2016). Using VBM analysis of the whole brain, several studies revealed a reduced thalamic nuclei within the thalamus in smokers, such as the pulvinar (Liao et al., 2012) or the dorsomedial thalamus (Qian et al., 2019). Further, using VBM analysis, Wetherill et al. found that cannabis-dependent individuals who smoked or did not smoke tobacco showed a reduced cluster within the thalamus compared to healthy controls (Wetherill et al., 2015). Using FreeSurfer segmentation, Yu et al. found that smokers (mean age: 20.8 years, mean pack-years: 3.5) showed reduced thalamic volume relative to nonsmokers (Yu et al., 2018). However, several other VBM studies did not reveal any significant differences of the thalamic volume between smokers and nonsmokers (Brody et al., 2004; Yu et al., 2011). Recently, a VBM study by Hanlon et al. simultaneously compared the subcortical gray matter volume in both younger smokers (mean age: 23.9 years, mean pack-years: 5.2) and older established smokers (mean age: 40 years, mean pack-years: 19.8) relative to their age-matched nonsmokers (Hanlon et al., 2016). Notably, younger smokers showed a reduced cluster within the left thalamus relative to age-matched nonsmokers, but no differences were detected between older established smokers and age-matched nonsmokers (Hanlon et al., 2016). Nevertheless, in this study, using FreeSurfer segmentation, smokers (mean age: 38.2 years, mean pack-years: 20.6) showed larger thalamic volume than non-smokers. Inconsistencies in reported findings may be due to methodological issues such as variations in age or pack-years of the sample (young or old, low or high pack-years), different analysis methods for the neuroimaging data (VBM or FreeSurfer), or structural heterogeneity of the thalamus (a cluster within thalamus or the whole thalamus).

Using FreeSurfer segmentation, Yu et al. found decreased thalamic volume in young male smokers (mean age: 20.8 years, mean pack-years: 3.5) (Yu et al., 2018). However, in this study, using the same analysis method (FreeSurfer segmentation), we found increased thalamic volume in old male smokers (mean age: 38.2 years, mean pack-years: 20.6). One possible explanation for this inconsistency is that thalamic volume may be decreased during adolescence and young adulthood, and then increased with long-term continued smoking during adulthood. Further, consistent with the previous study (Yu et al., 2018), we found that left thalamic volume was negatively correlated with FTND scores rather than pack-years or years smoked in smokers in this study. The severity of nicotine dependence, as measured by FTND (Dijkstra and Tromp, 2002), is a relatively stable trait in established smokers who are not trying to quit (Janson, 1999; McCarthy et al., 2001). Moreover, FTND is a highly heritable trait (Li, 2008; Vink et al., 2005). Therefore, one interpretation for the decreased thalamic volume in younger smokers or the negative correlation between thalamic volume and FTND is that pre-existing abnormalities in the thalamus may potentially predispose individuals to the initiation of smoking and the development of nicotine dependence, such as the genetic factor. About 80% of nicotine-dependent

smokers have progressed to nicotine dependence by the age of 18 years (Sussman, 2002). Developmental plasticity makes the brain of adolescents and young adults vulnerable to the effects of nicotine (Mathers et al., 2006). During this particular period of development, the adolescent brain continues to develop structurally and functionally (Casey et al., 2005), which is thought to be a cause of maladaptive decision-making associated with immature cognitive control (Pine et al., 2001). In addition, decreased thalamic volume in adolescents has been found to be correlated with increased levels of impulsivity, a factor known to contribute to the initiation of smoking (Liu et al., 2013).

In this study, increased thalamic volume was detected in older smokers, which may be associated with long-term continued smoking during adulthood. The thalamus has a very high concentration of nAChR in the brain (Wonnacott, 1997; Zubieta et al., 2001). Nicotine acts as an agonist at nAChR (Wonnacott, 1997), which stimulates glial activity, proliferation, the expression of genes involved in neurogenesis, and upregulates calcium-binding proteins and nerve growth factor (Garrido et al., 2003; Liu et al., 2005; Opanashuk et al., 2001). Thus, we speculate that repeated stimulation by long-term cigarette smoking may result in the increased thalamic volume. Similarly, increased subcortical volume, such as increased striatal volume, has been reported in the addiction disorders, such as nicotine addiction (Franklin et al., 2014b; Li et al., 2015; Yu et al., 2011), and cannabis addiction (Wetherill et al., 2015). Additionally, increased thalamic volume has also been reported in other psychiatric disorders characterized by repetitive, compulsive behaviors, such as obsessive–compulsive personality disorder (Atmaca et al., 2019). The mechanism for increased thalamic volume in older established smokers is still unknown. Nicotine disrupts the blood–brain barrier and then plasma fluid may leak into the parenchymal interstitial space, leading to vasogenic swelling (Hawkins et al., 2002). Alternatively, elevated carboxyhaemoglobin levels (Deveci et al., 2004) and decreased cerebral blood flow (a secondary issue to the cerebral arteriosclerosis) in chronic smokers (Yamamoto et al., 2003) may lead to reduced blood oxygen levels for cellular energy production, leading to an osmotic imbalance and then to cytotoxic cell swelling. Either nicotine-induced vasogenic swelling (Hawkins et al., 2002) or cytotoxic cell swelling (Deveci et al., 2004; Yamamoto et al., 2003) might lead to an increase in the subcortical structures, such as the thalamus. Thus, the functional consequence of enlarged thalamus in smokers may be not beneficial, but detrimental.

Another possible explanation for the inconsistency of thalamic volume may be due to transient volumetric changes caused by recent smoking. In this study, smokers were allowed to smoke as usual approximately 10 min before scanning to avoid withdrawal symptoms during scanning, thus these smokers were scanned at satiated state. In Yu et al.'s study (Yu et al., 2018), smokers were also scanned at satiated state that was described in detail in another paper of the group using the same sample (Bi et al., 2017). However, in their study, smokers were allowed to smoke as usual approximately 30 min before scanning (Bi et al., 2017). Several studies showed that transient states could alter regional brain volume. Franklin et al. found that a single dose of medication altered regional brain volume that overlapped with cerebral blood flow changes (Franklin et al., 2013). In addition, Franklin et al. compared gray-matter volume between satiated state (scanned 45 min after smoking) and abstinent state (scanned 5 h after smoking) in smokers (Franklin et al., 2014a). They found significantly increased gray-matter volume at the satiated state compared to the abstinent state in the bilateral ventral striatum. Again, the gray-matter volume results overlapped with changes in blood flow (Franklin et al., 2014a). These studies unambiguously demonstrated that a transient volumetric change was associated with a transient change in blood flow. In addition, the smokers (CPD: 23.5 $\pm$ 9.6) in our study had greater CPD than the smokers (CPD: 15.4 $\pm$ 4.5) in Yu et al.'s study (Yu et al., 2018). CPD, a smoking parameter, is related to recent smoking. Thus, greater CPD may result in more obvious transient volumetric change. Further, in our study, we observed larger thalamus in relapsers than nonrelapsers, suggesting that increased thalamic volume was associated with smoking relapse vulnerability in smokers. Taken together, the above results of thalamic volume changes (relapers > nonrelapsers > nonsmokers) indicate that increased thalamic volume may be associated with both the maintenance of smoking behavior and smoking relapse.

Using event-related fMRI, McClernon et al. found that weaker baseline responses to smoking cues in the thalamus were related to worse smoking cessation outcomes (McClernon et al., 2007). In this study, using resting-state fMRI, we further revealed significantly decreased thalamo-precuneus rsFC in relapsers relative to nonrelapsers. The precuneus is a core component of the default mode network (DMN), which is involved in internal self-referential and reflective activity, such as personal introspection, thoughts about the future, and autobiographical memories (Zhang and Raichle, 2010). Our prior study demonstrated that decreased spontaneous neural activity in the precuneus was correlated with the maintenance of smoking behavior (Wang et al., 2017). Further, this study revealed that decreased thalamo-precuneus rsFC was correlated with smoking relapse. Taken together, these findings suggest that thalamo-precuneus rsFC degradation may be associated with both the maintenance of smoking behavior and smoking relapse. In addition, in our prior study, based on the result of VBM analysis, the left dorsomedial thalamus (a cluster within the thalamus, Figure S1) was used as a seed region to perform a rsFC analysis (Qian et al., 2019). And then we found decreased rsFC between the left dorsomedial thalamus and cerebellum in relapsers relative to nonrelapsers. However, in this study, decreased thalamo-cerebellum rsFC was not detected in relapsers. This study is a hypothesis-driven study rather than a pure exploratory study. Based on *a priori* knowledge, the whole thalamus (Figure S2) was chosen as a seed region to perform a rsFC analysis in this study. Therefore, we speculate that the different results may be attributable to the different seed regions used in the two rsFC analyses.

Our study revealed a laterality observation that the alterations of thalamic volume and thalamus-based rsFC in relapsers relative to nonrelapsers were on the left side. Such a hemispheric laterality difference may be due to the lateralization of dopaminergic systems. The lateralization on the left side can also be found in other dopaminergic dysfunction disorders, such as Parkinson's disease. Previous studies demonstrated that right-handed Parkinson's patients had greater vulnerability of left-sided substantia nigra dopaminergic neurons (Scherfler et al., 2012), and a stronger left-sided nigrostriatal FC was associated with a lower risk for Parkinson's disease (Ellmore et al., 2013). This was further supported by the fact that nicotine intake can be affected in humans via dopaminergic agonists and antagonists (Caskey et al., 2002). Moreover, many reward-related fMRI studies revealed an obvious left-sided bias to the activation of cortical and subcortical regions involved in reward processing (Delgado et al., 2000; Koepp et al., 1998; Thut et al., 1997). Additionally, structural MRI studies demonstrated a strong left-sided bias to the alterations of cortical and subcortical regions in smokers, such as left prefrontal cortex and insula (Zhang et al., 2011), left anterior cingulate cortex (Liao et al., 2012), left thalamus and amygdala (Hanlon et al., 2016).

In the present study, increased thalamic volume was detected in smokers relative to nonsmokers, and in relapsers relative to nonrelapsers, especially on the left side. Moreover, decreased rsFC in left thalamo-precuneus circuit was detected in relapsers relative to nonrelapsers. In addition, a logistic regression analysis showed that the thalamic volume and thalamo-precuneus rsFC predicted smoking relapse with an accuracy of 75.7%. These novel findings indicate that increased thalamic volume and decreased thalamo-precuneus rsFC are associated with smoking relapse, and these thalamic measures may be used to predict treatment efficacy of nicotine addiction and serve as a potential biomarker for personalized medicine.

5. Limitation

Several limitations of our study warrant discussion. First, in this

study, participants were all right-handed and male. Therefore, the findings may be specific to right-handed male smokers. In the future, left-handed and female smokers should be further recruited to determine whether these results apply to different handedness and genders. Second, the prediction accuracy of 75.7% in itself might not be a robust value to make an unequivocal claim of prediction of smoking relapse. Third, this study was a cross-sectional study which could not clearly determine the etiology of structural and functional abnormalities. The reported differences in smokers may be the direct result of cigarette smoking or may reflect pre-existing abnormalities (such as the genetic factor) that predispose to the development of nicotine addiction. In the future, prospective longitudinal imaging studies should be employed to investigate thalamic alterations before and after smoking initiation. Fourth, this study did not subdivide thalamic nuclei to explore the role of different thalamic regions in nicotine addiction. Future studies should seek to better delineate the role of different thalamic regions in nicotine addiction through the application of advanced imaging protocols at higher magnetic fields (i.e. 7 Tesla). Last, blood flow scan was not performed in this study so that we could not investigate the association between blood flow and regional brain volume in the thalamus. In the future, blood flow scan, such as arterial spin labeling (scanned 10 min, 30 min or 1 h after smoking), should be performed to investigate the association between transient volumetric changes and blood flow changes caused by recent smoking.

CRediT authorship contribution statement

Chao Wang: Conceptualization, Methodology, Data curation, Formal analysis, Writing - review & editing. **Shuyue Wang:** Data curation, Formal analysis. **Zhujing Shen:** Data curation, Formal analysis. **Wei Qian:** Data curation, Formal analysis. **Yeerfan Jiaerken:** Writing - review & editing, Software. **Xiao Luo:** Software. **Kaicheng Li:** Software. **Qingze Zeng:** Software. **Quanquan Gu:** Writing - review & editing. **Yihong Yang:** Conceptualization. **Peiyu Huang:** Conceptualization, Methodology. **Minming Zhang:** Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This research was supported by Zhejiang Provincial Natural Science Foundation of China under Grant Nos. LY21H180017 and LQ18H180001, Zhejiang Medicine Health Science and Technology Program under Grant Nos. 2017KY080 and 2018KY418, National Natural Science Foundation of China under Grant Nos. 81901721, 81171310 and 81701647. YY was supported by the Intramural Research Program of the National Institute on Drug Abuse, the National Institutes of Health.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2020.102451.

References

Alkondon, M., Albuquerque, E.X., 2001. Nicotinic acetylcholine receptor alpha7 and alpha4beta2 subtypes differentially control GABAergic input to CA1 neurons in rat hippocampus. J. Neurophysiol. 86, 3043–3055.

Asma, S., Song, Y., Cohen, J., Eriksen, M., Pechacek, T., Cohen, N., Iskander, J., 2014. CDC Grand Rounds: global tobacco control. MMWR Morb. Mortal Wkly. Rep. 63, 277–280.

Atmaca, M., Korucu, T., Tabara, M.F., Yildirim, H., Kılıç, M.C., 2019. Volumetric MRI study of orbito-frontal cortex and thalamus in obsessive-compulsive personality disorder. J. Clinical Neurosci. 64, 89–93.

Barkhof, F., Haller, S., Rombouts, S.A.R.B., 2014. Resting-state functional MR imaging: a new window to the brain. Radiology 272 (1), 29–49.

Bi, Y., Yuan, K., Guan, Y., Cheng, J., Zhang, Y., Li, Y., Yu, D., Qin, W., Tian, J., 2017. Altered resting state functional connectivity of anterior insula in young smokers. Brain Imaging Behav. 11 (1), 155–165.

Brody, A.L., Mandelkern, M.A., Jarvik, M.E., Lee, G.S., Smith, E.C., Huang, J.C., Bota, R. G., Bartzokis, G., London, E.D., 2004. Differences between smokers and nonsmokers in regional gray matter volumes and densities. Biol. Psychiatry 55 (1), 77–84.

Cahill, K., Lindson-Hawley, N., Thomas, K.H., Fanshawe, T.R., Lancaster, T., 2016. Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst. Rev. Cd006103.

Casey, B., Tottenham, N., Liston, C., Durston, S., 2005. Imaging the developing brain: what have we learned about cognitive development? Trends Cognitive Sci. 9 (3), 104–110.

Caskey, N.H., Jarvik, M.E., Wirshing, W.C., Madsen, D.C., Olmstead, R.E., Iwamoto-Schaap, P.N., Eisenberger, N.I., Huerta, L., Terrace, S.M., 2002. Modulating tobacco smoking rates by dopaminergic stimulation and blockade. Nicotine Tob. Res. 4 (3), 259–266.

de Bourbon-Teles, J., Bentley, P., Koshino, S., Shah, K., Dutta, A., Malhotra, P., Egner, T., Husain, M., Soto, D., 2014. Thalamic control of human attention driven by memory and learning. Curr. Biol. 24, 993–999.

Delgado, M.R., Nystrom, L.E., Fissell, C., Noll, D.C., Fiez, J.A., 2000. Tracking the hemodynamic responses to reward and punishment in the striatum. J. Neurophysiol. 84 (6), 3072–3077.

Deveci, S.E., Deveci, F., Açik, Y., Ozan, A.T., 2004. The measurement of exhaled carbon monoxide in healthy smokers and non-smokers. Respir. Med. 98 (6), 551–556.

Dijkstra, A., Tromp, D., 2002. Is the FTND a measure of physical as well as psychological tobacco dependence? J. Subst. Abuse Treat. 23 (4), 367–374.

Ellmore, T.M., Castriotta, R.J., Hendley, K.L., Aalbers, B.M., Furr-Stimming, E., Hood, A. J., Suescun, J., Beurlot, M.R., Hendley, R.T., Schiess, M.C., 2013. Altered nigrostriatal and nigrocortical functional connectivity in rapid eye movement sleep behavior disorder. Sleep 36, 1885–1892.

Fagerstrom, K.-O., Schneider, N.G., 1989. Measuring nicotine dependence: a review of the Fagerstrom Tolerance Questionnaire. J. Behav. Med. 12 (2), 159–182.

Fischl, B., 2012. FreeSurfer. NeuroImage 62 (2), 774–781.

Fischl, B., Salat, D.H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., van der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., Dale, A.M., 2002. Whole Brain Segmentation. Neuron 33 (3), 341–355.

Fischl, B., van der Kouwe, A., Destrieux, C., Halgren, E., Ségonne, F., Salat, D.H., Busa, E., Seidman, L.J., Goldstein, J., Kennedy, D., Caviness, V., Makris, N., Rosen, B., Dale, A. M., 2004. Automatically parcellating the human cerebral cortex. Cereb Cortex 14, 11–22.

Franklin, T.R., Wang, Z.e., Shin, J., Jagannathan, K., Suh, J.J., Detre, J.A., O'Brien, C.P., Childress, A.R., 2013. A VBM study demonstrating 'apparent' effects of a single dose of medication on T1-weighted MRIs. Brain Struct. Funct. 218 (1), 97–104.

Franklin, T.R., Wetherill, R.R., Jagannathan, K., Hager, N., O'Brien, C.P., Childress, A.R., 2014a. Limitations of the use of the MP-RAGE to identify neural changes in the brain: recent cigarette smoking alters gray matter indices in the striatum. Front. Hum. Neurosci. 8, 1052.

Franklin, T.R., Wetherill, R.R., Jagannathan, K., Johnson, B., Mumma, J., Hager, N., Rao, H., Childress, A.R., 2014b. The effects of chronic cigarette smoking on gray matter volume: influence of sex. PLoS One 9, e104102.

Froeliger, B., McConnell, P.A., Bell, S., Sweitzer, M., Kozink, R.V., Eichberg, C., Hallyburton, M., Kaiser, N., Gray, K.M., McClernon, F.J., 2017. Association between baseline corticothalamic-mediated inhibitory control and smoking relapse vulnerability. JAMA Psychiatry 74 (4), 379. https://doi.org/10.1001/jamapsychiatry.2017.0017.

Gallezot, J.D., Bottlaender, M., Grégoire, M.C., Roumenov, D., Deverre, J.R., Coulon, C., Ottaviani, M., Dollé, F., Syrota, A., Valette, H., 2005. In vivo imaging of human cerebral nicotinic acetylcholine receptors with 2–18F-fluoro-A-85380 and PET. J. Nucl. Med. 46, 240–247.

Garrido, R., King-Pospisil, K., Son, K.W., Hennig, B., Toborek, M., 2003. Nicotine upregulates nerve growth factor expression and prevents apoptosis of cultured spinal cord neurons. Neurosci. Res. 47 (3), 349–355.

Gioanni, Y., Rougeot, C., Clarke, P.B.S., Lepousé, C., Thierry, A.M., Vidal, C., 1999. Nicotinic receptors in the rat prefrontal cortex: increase in glutamate release and facilitation of mediodorsal thalamo-cortical transmission: nicotinic receptors in the rat prefrontal cortex. Eur. J. Neurosci. 11 (1), 18–30.

Gonzales, D., Rennard, S.I., Nides, M., Oncken, C., Azoulay, S., Billing, C.B., Watsky, E.J., Gong, J., Williams, K.E., Reeves, K.R., 2006. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA 296, 47–55.

Grady, S.R., Salminen, O., Laverty, D.C., Whiteaker, P., McIntosh, J.M., Collins, A.C., Marks, M.J., 2007. The subtypes of nicotinic acetylcholine receptors on dopaminergic terminals of mouse striatum. Biochem. Pharmacol. 74 (8), 1235–1246.

Haber, S.N., Calzavara, R., 2009. The cortico-basal ganglia integrative network: the role of the thalamus. Brain Res. Bull. 78 (2-3), 69–74.

Hanlon, C.A., Owens, M.M., Joseph, J.E., Zhu, X., George, M.S., Brady, K.T., Hartwell, K. J., 2016. Lower subcortical gray matter volume in both younger smokers and established smokers relative to non-smokers: Gray matter differences. Addict. Biol. 21 (1), 185–195.

Hawkins, B.T., Brown, R.C., Davis, T.P., 2002. Smoking and ischemic stroke: a role for nicotine? Trends Pharmacol. Sci. 23 (2), 78–82.

Huang, A.S., Mitchell, J.A., Haber, S.N., Alia-Klein, N., Goldstein, R.Z., 2018. The thalamus in drug addiction: from rodents to humans. Phil. Trans. R. Soc. B 373 (1742), 20170028. https://doi.org/10.1098/rstb.2017.0028.
Huang, P., Xuan, M., Gu, Q., Yu, X., Xu, X., Luo, W., Zhang, M., 2015. Abnormal amygdala function in Parkinson's disease patients and its relationship to depression. J. Affect. Disord. 183, 263–268.
Hughes, J.R., Keely, J., Naud, S., 2004. Shape of the relapse curve and long-term abstinence among untreated smokers. Addiction 99, 29–38.
Hutton, C., Draganski, B., Ashburner, J., Weiskopf, N., 2009. A comparison between voxel-based cortical thickness and voxel-based morphometry in normal aging. NeuroImage 48 (2), 371–380.
Janson, H., 1999. Longitudinal patterns of tobacco smoking from childhood to middle age. Addict. Behav. 24 (2), 239–249.
Jorenby, D.E., Hays, J.T., Rigotti, N.A., Azoulay, S., Watsky, E.J., Williams, K.E., Billing, C.B., Gong, J., Reeves, K.R., 2006. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. JAMA 296, 56–63.
Kimes, A.S., Horti, A.G., London, E.D., Chefer, S.I., Contoreggi, C., Ernst, M., Friello, P., Koren, A.O., Kurian, V., Matochik, J.A., Pavlova, O., Bruce Vaupel, D., Mukhin, A.G., 2003. 2 [18 F]F-A85380: PET imaging of brain nicotinic acetylcholine receptors and whole body distribution in humans. FASEB J. 17 (10), 1331–1333.
Klein, R.C., Yakel, J.L., 2006. Functional somato-dendritic alpha7-containing nicotinic acetylcholine receptors in the rat basolateral amygdala complex. J. Physiol. 576, 865–872.
Koepp, M.J., Gunn, R.N., Lawrence, A.D., Cunningham, V.J., Dagher, A., Jones, T., Brooks, D.J., Bench, C.J., Grasby, P.M., 1998. Evidence for striatal dopamine release during a video game. Nature 393 (6682), 266–268.
Li, M.D., 2008. Identifying susceptibility loci for nicotine dependence: 2008 update based on recent genome-wide linkage analyses. Hum. Genet. 123 (2), 119–131.
Li, Y., Yuan, K., Cai, C., Feng, D., Yin, J., Bi, Y., Shi, S., Yu, D., Jin, C., von Deneen, K.M., Qin, W., Tian, J., 2015. Reduced frontal cortical thickness and increased caudate volume within fronto-striatal circuits in young adult smokers. Drug Alcohol Depend. 151, 211–219.
Liao, Y., Tang, J., Liu, T., Chen, X., Hao, W., 2012. Differences between smokers and non-smokers in regional gray matter volumes: a voxel-based morphometry study. Addict. Biol. 17, 977–980.
Liu, J., Lester, B.M., Neyzi, N., Sheinkopf, S.J., Gracia, L., Kekatpure, M., Kosofsky, B.E., 2013. Regional brain morphometry and impulsivity in adolescents following prenatal exposure to cocaine and tobacco. JAMA Pediatr. 167 (4), 348. https://doi.org/10.1001/jamapediatrics.2013.550.
Liu, J.J., Mohila, C.A., Gong, Y., Govindarajan, N., Onn, S.P., 2005. Chronic nicotine exposure during adolescence differentially influences calcium-binding proteins in rat anterior cingulate cortex. Eur. J. Neurosci. 22, 2462–2474.
Mathers, M., Toumbourou, J.W., Catalano, R.F., Williams, J., Patton, G.C., 2006. Consequences of youth tobacco use: a review of prospective behavioural studies. Addiction 101, 948–958.
McCarthy, W.J., Zhou, Y., Hser, Y.-I., 2001. Individual change amid stable smoking patterns in polydrug users over 3 years. Addict. Behav. 26 (1), 143–149.
McClernon, F.J., Hiott, F.B., Liu, J., Salley, A.N., Behm, F.M., Rose, J.E., 2007. Selectively reduced responses to smoking cues in amygdala following extinction-based smoking cessation: results of a preliminary functional magnetic resonance imaging study. Addict. Biol. 12 (3-4), 503–512.
Opanashuk, L.A., Pauly, J.R., Hauser, K.F., 2001. Effect of nicotine on cerebellar granule neuron development. Eur. J. Neurosci. 13 (1), 48–56.
Parnaudeau, S., Taylor, K., Bolkan, S.S., Ward, R.D., Balsam, P.D., Kellendonk, C., 2015. Mediodorsal thalamus hypofunction impairs flexible goal-directed behavior. Biol. Psychiatry 77 (5), 445–453.
Phillips, J.M., Kambi, N.A., Saalmann, Y.B., 2016. A subcortical pathway for rapid, goal-driven, attentional filtering. Trends Neurosci. 39 (2), 49–51.
Pine, D.S., Cohen, P., Brook, J.S., 2001. Emotional reactivity and risk for psychopathology among adolescents. CNS Spectr. 6 (1), 27–35.
Qian, W., Huang, P., Shen, Z., Wang, C., Yang, Y., Zhang, M., 2019. Brain gray matter volume and functional connectivity are associated with smoking cessation outcomes. Front. Hum. Neurosci. 13, 361.
Rieck, R.W., Ansari, M.S., Whetsell Jr, W.O., Deutch, A.Y., Kessler, R.M., 2004. Distribution of Dopamine D2-Like Receptors in the Human Thalamus: Autoradiographic and PET Studies. Neuropsychopharmacol 29 (2), 362–372.
Scherfler, C., Seppi, K., Mair, K.J., Donnemiller, E., Virgolini, I., Wenning, G.K., Poewe, W., 2012. Left hemispheric predominance of nigrostriatal dysfunction in Parkinson's disease. Brain 135, 3348–3354.
Shen, Z., Huang, P., Wang, C., Qian, W., Luo, X., Guan, X., Qiu, T., Yang, Y., Zhang, M., 2017. Altered function but not structure of the amygdala in nicotine-dependent individuals. Neuropsychologia 107, 102–107.
Sussman, S., 2002. Effects of sixty six adolescent tobacco use cessation trials and seventeen prospective studies of self-initiated quitting. Tob. Induced Dis. 1 (1), 35. https://doi.org/10.1186/1617-9625-1-1-35.
Thut, G., Schultz, W., Roelcke, U., Nienhusmeier, M., Missimer, J., Maguire, R.P., Leenders, K.L., 1997. Activation of the human brain by monetary reward. NeuroReport 8 (5), 1225–1228.
Vink, J.M., Willemsen, G., Boomsma, D.I., 2005. Heritability of smoking initiation and nicotine dependence. Behav. Genet. 35 (4), 397–406.
Wang, C., Shen, Z., Huang, P., Yu, H., Qian, W., Guan, X., Gu, Q., Yang, Y., Zhang, M., 2017. Altered spontaneous brain activity in chronic smokers revealed by fractional ramplitude of low-frequency fluctuation analysis: a preliminary study. Sci. Rep. 7 (1) https://doi.org/10.1038/s41598-017-00463-7.
Wetherill, R.R., Jagannathan, K., Hager, N., Childress, A.R., Rao, H., Franklin, T.R., 2015. Cannabis, cigarettes, and their co-occurring use: disentangling differences in gray matter volume. IJNPPY 18 (10), pyv061. https://doi.org/10.1093/ijnp/pyv061.
Wonnacott, S., 1997. Presynaptic nicotinic ACh receptors. Trends Neurosci. 20 (2), 92–98.
Yamamoto, Y., Nishiyama, Y., Monden, T., Satoh, K., Ohkawa, M., 2003. A study of the acute effect of smoking on cerebral blood flow using 99mTc-ECD SPET. Eur. J. Nucl. Med. Mol. Imaging 30 (4), 612–614.
Yan, C.G., Wang, X.D., Zuo, X.N., Zang, Y.F., 2016. DPABI: data processing & analysis for (resting-state) brain imaging. Neuroinformatics 14, 339–351.
Yang, K., Hu, J., Lucero, L., Liu, Q., Zheng, C., Zhen, X., Jin, G., Lukas, R.J., Wu, J., 2009. Distinctive nicotinic acetylcholine receptor functional phenotypes of rat ventral tegmental area dopaminergic neurons. J. Physiol. 587, 345–361.
Yu, D., Yuan, K., Cheng, J., Guan, Y., Li, Y., Bi, Y., Zhai, J., Luo, L., Liu, B., Xue, T., Lu, X., 2018. Reduced Thalamus Volume May Reflect Nicotine Severity in Young Male Smokers. Nicotine Tob. Res. 20, 434–439.
Yu, R., Zhao, L., Lu, L., 2011. Regional grey and white matter changes in heavy male smokers. PLoS One 6, e27440.
Zhang, D., Raichle, M.E., 2010. Disease and the brain's dark energy. Nat. Rev. Neurol. 6 (1), 15–28.
Zhang, X., Salmeron, B.J., Ross, T.J., Geng, X., Yang, Y., Stein, E.A., 2011. Factors underlying prefrontal and insula structural alterations in smokers. NeuroImage 54 (1), 42–48.
Zubieta, J.-K., Lombardi, U., Minoshima, S., Guthrie, S., Ni, LiSong, Ohl, L.E., Koeppe, R. A., Domino, E.F., 2001. Regional cerebral blood flow effects of nicotine in overnight abstinent smokers. Biol. Psychiatry 49 (11), 906–913.