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Original Investigation

Associations Between the Wisconsin Inventory of Smoking Dependence Motives and Regional Brain Volumes in Adult Smokers

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Abstract

Introduction: The Wisconsin Inventory of Smoking Dependence Motives (WISDM-68) is a 68-item questionnaire to assess nicotine dependence as a multifactorial construct based on 13 theoretically derived smoking motives. Chronic smoking is associated with structural changes in brain regions implicated in the maintenance of smoking behavior; however, associations between brain morphometry and the various reinforcing components of smoking behavior remain unexamined. The present study investigated the potential association between smoking dependence motives and regional brain volumes in a cohort of 254 adult smokers.

Aims and Methods: The WISDM-68 was administered to participants at the baseline session. Structural magnetic resonance brain imaging (MRI) data from 254 adult smokers (M_{age} = 42.7 ± 11.4) with moderate to severe nicotine dependence (M_{FTND} = 5.4 ± 2.0) smoking for at least 2 years (M_{years} = 24.3 ± 11.8) were collected and analyzed with Freesurfer.

Results: Vertex-wise cluster analysis revealed that high scores on the WISDM-68 composite, secondary dependence motives (SDM) composite, and multiple SDM subscales were associated with lower cortical volume in the right lateral prefrontal cortex (cluster-wise *p's* < .035). Analysis of subcortical volumes (ie, nucleus accumbens, amygdala, caudate, and pallidum) revealed several significant associations with WISDM-68 subscales, dependence severity (Fagerström Test for Nicotine Dependence), and overall exposure (pack-years). No significant associations between cortical volume and other nicotine dependence measures or pack-years were observed.

Conclusions: Results suggest that smoking motives may play a larger role in cortical abnormalities than addiction severity and smoking exposure per se, whereas subcortical volumes are associated with smoking motives, addiction severity, and smoking exposure.

Implications: The present study reports novel associations between the various reinforcing components of smoking behavior assessed by the WISDM-68 and regional brain volumes. Results suggest that the underlying emotional, cognitive, and sensory processes that drive non-compulsive smoking behaviors may play a larger role in gray matter abnormalities of smokers than smoking exposure or addiction severity.

Introduction

Despite the well-known, detrimental effects of smoking tobacco, smoking continues to be the leading cause of preventable death and disease.[1] Why is smoking still so prevalent? The consensus is that nicotine dependence drives the maintenance of smoking behaviors and is largely responsible for smoking prevalence. Indeed, individuals with nicotine dependence are often unable to quit smoking, experience withdrawal symptoms after making a quit attempt, and continue to smoke despite awareness of the negative health consequences. Neurobiologically, cigarette smokers with nicotine addiction have demonstrated abnormalities in brain structure such as decreased brain volume[2–4] and accelerated cortical thinning[5,6] compared to nonsmokers.

Prevailing nicotine dependence assessments such as the Fagerström Test for Nicotine Dependence (FTND)[7] and the Diagnostic and Statistical Manual of the American Psychiatric Association provide value by measuring nicotine dependence outcomes such as smoking heaviness and abstinence tolerability. FTND scores have been shown to be predictive of smoking relapse among individuals making a quit attempt.[8] However, smoking and nicotine reinforcement is a manifold process and most nicotine dependence assessments do not attempt to assess the underlying nature or mechanisms of nicotine dependence and do not investigate what characteristics of smoking may differentially reinforce the maintenance of smoking behavior.

In effort to elucidate the nature and behavioral mechanisms of nicotine addiction, Piper et al.[9] developed the Wisconsin Inventory of Smoking Dependence Motives (WISDM-68), a 68-item questionnaire that attempts to define and measure dependence as a multifactorial construct on the basis of 13 theoretically derived smoking motives (see Supplementary Table A1). A follow-up study by Piper et al.[10] performed latent class and factor analyses and suggested that four subscales (automaticity, craving, loss of control, and tolerance) represent the core features of dependence, and designated them as primary dependence motives (PDM). The remaining nine subscales

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(affiliative attachment, behavioral choice, cognitive enhancement, cue exposure and associative processes, negative reinforcement, positive reinforcement, social and environmental goads, taste and sensory properties, and weight control) were designated as secondary dependence motives (SDM) and are hypothesized to reflect the reasons people choose to smoke non-compulsively.

Multiple studies have found the PDM composite to be predictive of core nicotine dependence measures such as cigarettes per day (CPD), FTND scores, habitual or automatic motives for smoking cigarettes, and relapse.[10–15] The SDM composite has shown to be a stronger predictor of instrumental and situational smoking and withdrawal-induced cravings and distress.[10–12,14]

In an effort to further advance mechanistic understanding of the factors that reinforce the ongoing maintenance of smoking, the present study focused on examining how WISDM-68 smoking dependence motives are associated with brain morphometry. This is the first study to investigate neuroanatomical associations of smoking dependence motives. Specifically, the primary goal was to examine and characterize the extent to which cortical and subcortical brain morphometry explained shared and unique variance in PDM and SDM. Provided the WISDM-68s concurrent validity with other dependence measures (FTND, CPD, and pack-years) that have shown to be associated with brain morphometry, we hypothesized that specific aspects of smoking dependence motives would be differentially associated with brain volume. However, given the relative lack of extant literature in this domain, the pattern of associations were exploratory in nature. Using data from high-resolution MRI brain scans, the present study utilized advanced surface-based morphometric analysis to assess the potential relationship between WISDM-68 smoking dependence motives and regional brain volumes in a community sample of nicotine-dependent adult smokers.

Methods

Participants

The data analyzed in the present study were compiled from seven smoking studies conducted at the University of Missouri-Columbia and the Medical University of South Carolina (MUSC). Primary findings of these studies are reported in prior publications.[16–21] All studies were approved by the University of Missouri-Columbia or MUSC Internal Review Boards and were completed in accordance with the provisions of the World Medical Association Declaration of Helsinki. Informed consent was received from all participants prior to participation. Smokers (n = 254, M_{age} = 42.7 years ± 11.4) with moderate to severe nicotine addiction (M_{FTND} = 5.4 ± 2.0) who had been smoking for at least 2 years (M = 24.3 years ± 11.8) were recruited from the local communities at both MUSC (n = 151) and the University of Missouri (n = 103).

The present study's cohort was gathered from previous smoking studies where various neuropsychiatric and substance use data were collected and utilized for inclusion and exclusion criteria. All subjects in the present study did not have a current, non-nicotinic substance use disorder. Subjects in the present study were administered the Center for Epidemiological Studies-Depression (CES-D), Beck's Anxiety Inventory (BAI), and were asked to report current or past psychosis, which if reported excluded participants from studies. One hundred and thirty-one subjects (51.57%) of the present study's cohort were tested for current substance use and were administered the Mini-International Neuropsychiatric Interview. These 131 subjects did not test positive for current substance use and did not test positive for a psychiatric disorder when assessed by the MINI. The other 123 subjects in the present study's cohort were not excluded from their parent study if they reported or tested positive for current substance use or reported a history of substance use disorder. Sample characteristics are detailed in Table 1.

Measures

The WISDM-68 and FTND were administered to all participants at their baseline session. Average CPD during the 30 days preceding the baseline session and the number of years of smoking were self-reported at the baseline session.

Table 1. Sample Characteristics

Demographics	
Sample Size (Female)	254 (126)
Race - *N* (%)	
White	185 (72.8%)
Black	57 (22.4%)
Other	12 (4.7%)
Age - mean (SD)	42.7 (11.4)
Education - mean (SD)	14.1 (2.2)
Baseline Measures - mean (SD)	
Nicotine dependence (FTND score)	5.4 (2.0)
Pack-years	22.5 (16.0)
Years smoking	24.3 (11.8)
Cigarettes per day (30-day average)	17.6 (7.5)
WISDM composites and subscale scores - mean (SD)	
Total[a]	56.0 (15.4)
Primary dependence motives[b]	4.4 (1.3)
Secondary dependence motives[c]	3.8 (1.1)
Affiliative attachment	2.9 (1.6)
Automaticity	4.0 (1.7)
Loss of control	4.4 (1.6)
Behavioral choice and melioration	3.4 (1.4)
Cognitive enhancement	3.6 (1.6)
Craving	4.5 (1.5)
Cue exposure and associative processes	4.6 (1.3)
Negative reinforcement	4.5 (1.5)
Positive reinforcement	4.1 (1.6)
Social and environmental goads	3.7 (1.9)
Taste and sensory properties	4.3 (1.5)
Tolerance	4.6 (1.4)
Weight control	2.8 (1.6)

[a]WISDM total score = sum of the 13 WISDM subscales
[b]Primary dependence motives = mean of automaticity, loss of control, craving, and tolerance
[c]Secondary dependence motives = mean of affiliative attachment, behavioral choice and melioration, cognitive enhancement, cue exposure and associative processes, negative reinforcement, positive reinforcement, social and environmental goads, taste, and weight control

Pack-years were calculated as (CPD/20) × (years smoking). Scores for the 13 WISDM-68 subscales were calculated by taking the average score of all items belonging to the specified subscale. The WISDM-68 composite score was calculated as the sum of the 13 WISDM-68 subscales. The PDM composite score was calculated as the mean of automaticity, craving, loss of control, and tolerance subscales. The SDM composite was calculated as the mean score of affiliative attachment, behavioral choice and amelioration, cognitive enhancement, cue exposure and associative processes, negative reinforcement, positive reinforcement, social and environmental goads, taste and sensory properties, and weight control subscales.

MRI Data Acquisition

3T MRI scanners (Siemens Prisma Fit – University of Missouri and MUSC [n = 173]; Siemens Tim Trio – MUSC [n = 81]), were used to acquire sets of high-resolution (1mm^3) T1-weighted structural brain images. Images were collected using standard T1-weighted magnetization prepared – rapid gradient echo (MPRAGE) pulse sequences (TR = 2300 ms [1900ms on Trio], TE = 2.26 ms, flip angle = 9°, 192 slices, 1 mm^3 voxels, FOV = 256 mm). Participants were sated and smoked a cigarette within 30 minutes of their MRI scan.

Data Processing and Analysis

Acquired T1s were visually inspected for quality assurance before being used as input for Freesurfer's (version 6.0.0) cortical reconstruction and volumetric segmentation pipelines. Participants with distorted T1s because of motion or artifact were excluded from the study. The technical details of Freesurfer's cortical reconstruction and volumetric segmentation pipelines are described in prior publications. Once the cortical models were complete, a number of deformable procedures were performed for further data processing and analysis including surface inflation,[22] registration to a spherical atlas which is based on individual cortical folding patterns to match cortical geometry across subjects,[23] parcellation of the cerebral cortex into units with respect to gyral and sulcal structure from the Desikan–Killiany atlas,[24] and creation of a variety of surface-based data including maps of curvature and sulcal depth. Critically, all Freesurfer-generated segmentations and cortical reconstructions were inspected and edited where needed to ensure accurate segmentations.

The potential relationship between cortical volume and nicotine dependence measures (WISDM-68, FTND, and CPD) and smoking exposure (pack-years) were examined using Freesurfer's surface-based, vertex-wise, general linear model cluster analyses, where general linear models are run at each vertex of the brain surface. Clusters in these analyses refer to brain regions where adjacent vertices share similar relationships at a specified statistical threshold for a specified general linear model.

For models assessing the relationship between cortical volume and nicotine dependence measures, each nicotine dependence measure was examined individually with age, education, sex, estimated total intracranial volumes (eTIV), and pack-years entered as nuisance variables. Pack-years were not included as a nuisance variable in models assessing the relationship between cortical volume and pack-years. Cortical surface reconstructions for each participant were registered to Freesurfer's template brain—fsaverage—and were smoothed with a 10-millimeter full-width half-maximum Gaussian spatial smoothing kernel. Clusters were corrected for multiple comparisons via permutation simulation (n = 5000) with a cluster forming threshold of $p < .05$. Only surviving clusters with a cluster-wise $p < .05$ were considered significant. Participants' total volumes from significant resultant clusters were extracted and further analyzed using hierarchical linear regression models in SPSS (version 28.0). Partial correlations from the regression models are reported in the results.

The potential relationships between subcortical volumes, nicotine dependence measures, and smoking exposure were assessed using hierarchical linear regression models in SPSS. For models assessing the relationship between subcortical volumes and nicotine dependence measures, age, education, sex, eTIV, and pack-years were entered as nuisance variables. Pack-years were not included as a nuisance variable in models assessing the relationship between subcortical volumes and pack-years. Partial correlations from the regression models are reported in the results.

Results

Cortical Volume Analysis

Vertex-wise cluster analysis revealed significant negative associations between cortical volume and WISDM total, SDM composite, and SDM subscales (affiliative attachment, behavioral choice and melioration, cue exposure and associative processes, negative reinforcement, and positive reinforcement). Interestingly, all significant clusters were localized to the right lateral prefrontal cortex (lPFC) (Figure 1); specifically, the inferior frontal gyrus, rostral middle frontal, and lateral orbitofrontal cortex (all cluster-wise p's < .035). The overlapping region of all clusters is displayed in Figure 1. Additional details of cluster analysis results are described in Table 2.

Each participant's total volume within each resultant cluster was extracted and used to further analyze the WISDM—cortical volume relationships via linear regression in SPSS (t [247] < -4.560, r < –0.278, p < .001 in all instances). Scatter plots displaying the residual volumes and residual WISDM scores of the significant associations are displayed in Supplementary Figure A1. No significant associations were observed between cortical volume and PDM, FTND, CPD, or pack-years.

Subcortical Volume Analysis

PDM and Subcortical Volumes

High scores on the automaticity subscale were associated with larger left nucleus accumbens volumes (t [247] = 2.079, r = 0.131, p = .039) and right nucleus accumbens volumes showed a similar trend (t [247] = 1.868, r = 0.118, p = .063). Tolerance showed a positive relationship with left caudate volumes (t [247] = 2.05, r = 0.129, p = .041).

Secondary Dependence Motives and Subcortical Volumes

Positive reinforcement was negatively associated with right nucleus accumbens volumes (t [247] = -2.179, r = –0.137, p = .03). Taste and sensory properties showed both negative and positive associations with subcortical volumes. Bilateral nucleus accumbens and left amygdala volumes were negatively associated with taste and sensory properties (t [247] < –2.662, r < –0.166, p < .009 in all instances), whereas

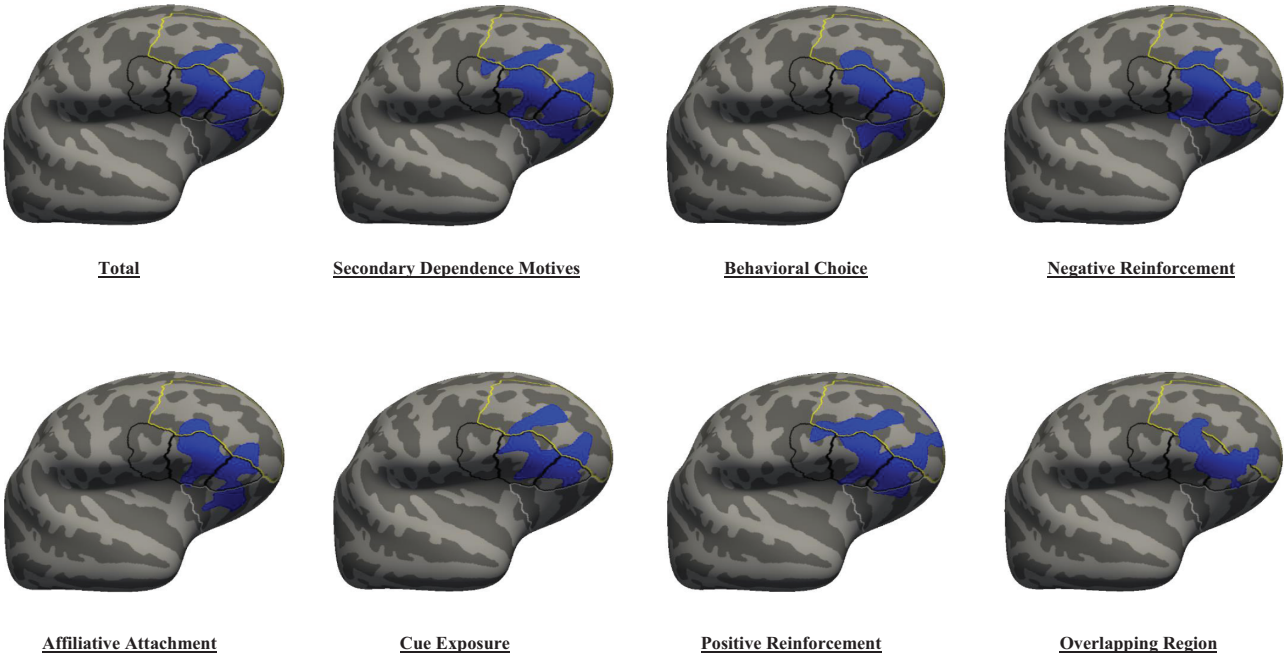

Figure 1. Corrected cluster analysis results (blue) overlaid on the Freesurfer template (fsaverage) inflated surface displaying the negative associations between cortical volume and WISDM composite and subscale scores controlling for age, education, sex, estimated total intracranial volume, and pack-years (all cluster-wise *p*-values <.035). The overlapping region of all clusters is displayed on the bottom right. Outlines of the right inferior frontal gyrus (black), rostral middle frontal (yellow), and lateral orbitofrontal cortex (white) from the Desikan–Killiany atlas are also overlaid on the inflated surface.

Table 2. Cluster Analysis Results

WISDM scale	Peak region	MNI coordinates of peak vertex			Peak vertex *t*-statistic	Cluster-wise *p*	Cluster-wise *p* 90% CI	Cluster size (mm²)
		X	Y	Z				
Total	Pars orbitalis	46	36.9	−9.6	−4.941	.025	0.023 to 0.028	2055.80
Secondary dependence motives	Pars orbitalis	46	36.9	−9.6	−4.907	.014	0.012 to 0.016	2482.07
Affiliative attachment	Pars orbitalis	46.9	35.5	−9.2	−3.698	.033	0.030 to 0.037	1894.20
Behavioral choice - melioration	Pars orbitalis	46	36.9	−9.6	−4.379	.034	0.031 to 0.037	1901.59
Cue exposure - associative processes	Pars orbitalis	46.4	35.6	−8.2	−5.29	.033	0.030 to 0.037	1878.58
Negative reinforcement	Pars orbitalis	46	36.9	−9.6	−6.177	.007	0.006 to 0.009	2840.88
Positive reinforcement	Pars orbitalis	46.5	37.7	−10.9	−6.609	.022	0.019 to 0.024	2164.31

bilateral pallidum volumes were positively associated with taste and sensory properties (t [247] > 2.910, r > 0.181, p < .005 in both instances).

FTND, CPD, Pack-years, and Subcortical Volumes

FTND scores were positively associated with bilateral caudate volumes (t [247] > 2.342, r > 0.146, p < .021 in both instances). Pack-years was negatively associated with bilateral amygdala volumes (t [248] < −2.273, r < −0.142, p < .025 in both instances). No significant associations were observed between CPD and subcortical volumes. Significant subcortical volume associations are further detailed in Table 3.

Discussion

The present study is the first to assess the relationship between WISDM-68 smoking dependence motives and brain morphometry. Primary findings include: (1) High scores on the WISDM-68 total, SDM composite, and multiple SDM subscales were associated with less cortical volume in the right lateral prefrontal cortex (lPFC), (2) subcortical volumes (ie, nucleus accumbens, amygdala, caudate, and pallidum) revealed several significant associations with WISDM-68 subscales. Associations between subcortical volumes and PDM subscales were positive, whereas associations between subcortical volumes and SDM subscales were negative, (3)

Table 3. Subcortical Volume Associations

Subcortical structure	Associated measure	t	Partial correlation	*p*
Right nucleus accumbens	Positive reinforcement	−2.179	−0.137	.03
	Taste - sensory properties	−3.266	−0.203	.001
Left nucleus accumbens	Taste - sensory properties	−3.946	−0.243	<.001
	Automaticity	2.079	0.131	.039
Right amygdala	Pack-years	−2.274	−0.143	.024
Left amygdala	Pack-years	−3.126	−0.195	.002
	Taste - sensory properties	−2.663	−0.167	.008
Right caudate	FTND	2.531	0.159	.012
Left caudate	FTND	2.343	0.147	.02
	Tolerance	2.05	0.129	.041
Right pallidum	Taste - sensory properties	3.091	0.193	.002
Left pallidum	Taste - sensory properties	2.911	0.182	.004

amygdala volumes were negatively associated with pack-years and caudate volumes were positively associated with FTND, (4) no significant associations between cortical volume and other nicotine dependence measures (FTND, CPD) or smoking exposure (pack-years) were observed.

Cortical Volume

Cluster analysis revealed significant negative associations between right lateral prefrontal cortex (lPFC) volumes and WISDM-68 total, SDM composite, and the SDM subscales affiliative attachment, behavioral choice and melioration, cue exposure and associative processes, negative reinforcement, and positive reinforcement. Negative reinforcement, a subscale representing the tendency or desire to smoke to ameliorate negative internal states, displayed the strongest association with cortical volume. The majority of the clusters were localized to the right inferior frontal gyrus (rIFG), a cortical region considered to be a locus of inhibitory control[25] and a prefrontal node of the hyper-direct pathway—a corticothalamic circuit involved in executing inhibitory control that has been shown to be dysregulated among individuals with nicotine dependence.[16,17,26–28] Previous studies have shown smokers to exhibit less rIFG gray matter volume than nonsmokers,[4,29,30] and that smokers who relapsed following a quit attempt had less rIFG volume than those who remained abstinent.[17] Additionally, a recent study found that rIFG volume was positively associated with inhibitory control and rIFG thickness was positively associated with the ability to inhibit ad lib smoking during a smoking relapse analog task in a cohort of nicotine-dependent adult smokers.[19]

Interestingly, pack-years, FTND, CPD, PDM composite, and PDM subscales were *not* significantly associated with cortical volumes. The lack of significant associations between cortical volume and FTND and CPD may be due in part to the homogeneity of the cohort as few participants reported low CPD and FTND scores. Additionally, many studies that have found associations between nicotine dependence severity and cortical volume have utilized ROI analyses which can be more liberal than surface-based, vertex-wise, whole-brain analysis.

Although surprising, this is not the first imaging study of smokers to observe a lack of significant associations between FTND or pack-years and brain volume. For example, Hanlon et al.[31] found no associations between cortical volume and pack-years, FTND, or years of smoking when collapsing across age groups. Taken in conjunction with the volumetric associations observed in the present study, these results may suggest that alterations in cortical volume of smokers may reflect the progressive dysregulation of the cognitive and emotional processes that reinforce smoking behaviors. Future studies exploring the dissociable effects of smoking exposure, nicotine dependence, and smoking dependence motives on brain morphometry may provide valuable insight into the underlying mechanisms affecting brain morphometry in smokers.

Subcortical Volumes

Automaticity

Nucleus accumbens volume was positively associated with the PDM subscale automaticity. The nucleus accumbens is of particular interest in addiction research as the reinforcing effects of most drugs of abuse such as nicotine depend on dopamine release in the nucleus accumbens.[32] The early stages of nicotine addiction are thought to be initiated by a nicotine-induced increase of dopamine release in the nucleus accumbens, but chronic nicotine exposure leads to glutamatergic-mediated neuroplasticity in prefrontal-nucleus accumbens (ie, corticostriatal) circuitry that in turn mediates cue-induced drug seeking.[33] As addiction becomes more entrenched, the glutamatergic corticostriatal projections become further dysregulated, and morphological changes emerge, such as increased dendritic spine density, synapse size, and dendritic branching.[32,34] Given that the automaticity subscale captures smoking without conscious intention or awareness, a behavioral pattern representative of "end-stage addiction,"[33] and was significantly correlated with pack-years, FTND, and CPD, the positive association between automaticity and nucleus accumbens volume may be attributed to changes in glutamatergic-mediated synaptic plasticity and dendritic arborization in corticostriatal circuitry. Indeed, findings from non-addiction studies suggest that changes in structural complexity via dendritic arborization and synaptic plasticity, independent of changes in neuronal count, may contribute to changes in gray matter volume.[35–37] However, other studies have observed negative associations between nucleus accumbens volume and pack years.[38] More research is needed to better understand how nucleus accumbens volume is associated with automatic or compulsive smoking behavior and cessation outcomes following a quit attempt.[39]

Positive Reinforcement

In contrast to the positive association between the automaticity subscale and nucleus accumbens volume, the positive reinforcement subscale was *negatively* associated with nucleus accumbens volume. The positive reinforcement subscale captures the motivation to experience a positive consequence of smoking, starkly different than the automaticity subscale, which captures smoking compulsively and automatically without consideration of consequences. Indeed, automaticity scores were positively correlated with CPD and pack-years, whereas positive reinforcement scores were not. As addiction progresses, the subjective experience of "rewarding" positive affective states from smoking is confounded with the reversal from a nicotine withdrawal state. Thus, the desire to experience a positive consequence of smoking may be a motive among smokers who have yet to enter end-stage addiction, or among highly dependent smokers, the experience of relief from withdrawal. Future longitudinal studies are needed that conduct a principled examination of a broad range of nicotine and tobacco exposure measures: dose, chronicity, and duration to further disentangle these associations.

FTND and Tolerance

FTND and tolerance were positively associated with caudate volumes. Of all WISDM composites and subscales, tolerance showed the strongest correlation with FTND (r = 0.610), and was significantly correlated with pack-years and CPD. The caudate contains a high density of dopamine receptors and prior research has observed increased dopamine uptake in the caudate of smokers compared to nonsmokers.[40] The caudate plays a functional role in executive function and shows significant functional connectivity with other brain regions implicated in smoking such as the anterior cingulate, insula, thalamus, and inferior frontal and middle frontal gyri.[41] Indeed, an fMRI study by Feng et al.[42] found weaker resting state functional connectivity between the caudate and anterior cingulate in smokers compared to nonsmokers, which was associated with cognitive control. Previous findings regarding smoking and caudate morphometry are limited. However, a study by Li et al.[43] observed larger caudate volumes in smokers compared to nonsmokers. Given that the tolerance subscale captures the need to smoke increasing amounts over time and tolerance scores were strongly correlated with FTND, CPD, and pack-years, the positive associations between caudate volume and FTND and tolerance may be driven by the previously described changes to corticostriatal projections associated with end-stage addiction.

Pack-Years

The present study's finding of a negative association between amygdala volumes and pack-years are similar to the findings reported by Durazzo et al.[38] that observed a negative association between pack-years and amygdala volume in adult smokers. Previous studies have also found smokers to exhibit smaller amygdala volumes in comparison to nonsmokers.[31] The amygdala contains a high density of nicotinic acetylcholine receptors (nAChR)[44] and a previous rodent study by Huang et al.[45] found that chronic nicotine exposure promoted long-lasting synaptic changes in the amygdala. However, it remains unclear if nicotine-associated changes in cholinergic receptors or synapses are related to amygdala morphometry in smokers.

Taste and Sensory Properties

Bilateral nucleus accumbens and left amygdala volumes were negatively associated with taste and sensory properties, whereas bilateral pallidum volumes showed a positive association with taste and sensory properties. The pallidum is a relatively dopamine-rich structure with moderate expression of dopamine receptors and receives dense, efferent γ-aminobutyric acid (GABA) and peptide projections from the nucleus accumbens that are critical for expressing motivation behaviors.[46] A recent study by Zou et al.[47] found that 10-year-old children whose fathers smoked periconceptually had larger pallidum volumes than age-matched children whose parents did not smoke.

The nucleus accumbens, amygdala, and pallidum are structures implicated in gustatory conditioning, associative learning, and taste aversion (for review see ref.[48]). Although nicotine is the primary reinforcer of smoking addiction it is not the only reinforcer, as indicated by previous studies showing the low success rates of nicotine replacement therapy and the minimal enjoyment smokers report when dosed with nicotine infusions.[49] Therefore, non-nicotine components of smoking such as sensory properties (ie, taste, smell, and respiratory tract stimulation) play a significant role in smoking reinforcement. For example, local anesthesia of the airways significantly reduces smoking satisfaction,[50] and attenuation of olfactory or taste cues diminishes enjoyment and behavioral reinforcement effects of cigarette smoke.[51] More research is needed to better understand the neurobiological mechanisms of how taste and sensory properties of smoking are associated with brain morphometry.

Limitations and Future Directions

Provided the lack of genetic, environmental, and longitudinal data for this study, it cannot be conclusively determined if the observed associations between smoking and brain morphometry are caused by smoking-related effects or are because of preexisting genetic or environmental factors that alter brain morphometry. Indeed, previous research has shown that cortical volume is associated with certain genetic polymorphisms.[52,53] In the case that smoking did not impact brain morphometry, one may interpret the results as potential pre-disposed risk factors for developing nicotine dependence (eg, individuals with less right lPFC volume are more likely to develop nicotine dependence). Longitudinal brain imaging studies of smokers are needed to better understand the effects of smoking and nicotine exposure on brain morphometry.

The present study's data were compiled from multiple studies across different sites and included slight variations in scanning protocols. However, all T1s were visually inspected before processing and no observable differences were apparent. Distorted T1s due to motion or artifact were excluded from the study. Additionally, all Freesurfer-generated segmentations and cortical reconstructions were inspected and edited where needed to ensure accurate segmentations. Questionnaires were administered the same across studies, but variation due to different lab environments and personnel across sites may have affected the results.

The present study presents a novel, retrospective analysis of associations between WISDM-68 and brain morphometry. Future prospective studies assessing the relationship between brain morphometry and the WISDM-68 may consider

alternative statistical approaches than the ones used here. For example, Piper et al.'s study[10] describing the latent class and factor analyses for the formulation of PDM and SDM found that after controlling for the variance of PDM, SDM was less or non-predictive of many tobacco dependence measures whereas controlling for the variance of SDM when assessing PDM's predictive value had minimal effect. However, given the novelty of the present study and the lack of clarity regarding the relationship between nicotine dependence and brain morphometry, we chose to only include covariates in our models that have been shown to influence brain morphometry (age, education, sex, and pack-years).

The present study's cohort had a wide age range of participants (20–66 years old), but most were middle-aged adults with extensive smoking histories. A younger cohort of recently dependent smokers may yield better insight into how smoking dependence motives are related to brain morphometry and the development of nicotine addiction.

Conclusions

The present study presents novel findings on associations between regional brain volumes and WISDM-68 smoking dependence motives. Significant associations between cortical volumes and WISDM-68 total, SDM composite, and SDM subscales were localized to the right lPFC. Cortical volumes were not significantly associated with WISDM PDM composite or subscales, FTND, CPD, or pack-years. Analysis of subcortical volumes revealed several significant associations with WISDM-68 subscales. Associations between subcortical volumes and WISDM PDM subscales were positive, whereas associations between subcortical volumes and WISDM SDM subscales were negative. Together, these results suggest that gray matter abnormalities play a significant role in the emotional, cognitive, and sensory processes that reinforce smoking, as opposed to simply anatomical correlates of general exposure to smoking or addiction severity. Longitudinal brain imaging studies of smokers are needed to better understand the relationship between brain morphometry and smoking exposure, addiction severity, and smoking dependence motives.

Supplementary Material

A Contributorship Form detailing each author's specific involvement with this content, as well as any supplementary data, are available online at https://academic.oup.com/ntr.

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Authors Contribution

BF was responsible for the study concept and design. AAB performed the data analysis and drafted the manuscript. BF and RC provided critical revision of the manuscript for important intellectual content. All authors critically reviewed the content and approved the final version of the manuscript submitted for publication.

Declaration of Interest

AAB, RC, and BF reported no biomedical financial interests or potential conflicts of interest.

Data Availability

The data that support the findings of this study may be available from the corresponding author (BF), upon reasonable request. The data are not publicly available due to restrictions related to internal review board policies and informed consent limitations under which the data were originally collected.

Ethics Approval and Patient Consent Statement

The present study was approved by the University of Missouri and Medical University of South Carolina Internal Review Boards and was carried out in accordance with the provisions of the World Medical Association Declaration of Helsinki. Informed consent was obtained for all individuals prior to participation.

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