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Damage to the insula leads to decreased nicotine withdrawal during abstinence

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Abstract

Background and Aims—Current pharmacotherapies for tobacco dependence are generally well tolerated but have relatively high rates of relapse. They primarily target the brains' mesocorticolimbic “reward” pathway. However, recent evidence suggests that the insular cortex, a central cerebral hemispheric region historically overlooked in addiction models, may also play an important role in cognitive and emotional processes that facilitate drug use. We examined whether insular versus non-insular damage from ischemic stroke attenuated acute withdrawal from cigarette smoking and reduced the likelihood of nicotine replacement therapy (NRT) use during hospitalization.

Design—Data were derived from a longitudinal study with 3 months follow-up, beginning June 2013 and ending May 2014.

Setting—Three acute care hospitals in Rochester, NY, USA.

Participants—One-hundred-fifty-six current smokers hospitalized for acute ischemic stroke (38 with insular infarctions and 118 with non-insular infarctions, assessed by 3 neuroradiologists).

Measurements—The Wisconsin Smoking Withdrawal Scale (WSWS) and Minnesota Nicotine Withdrawal Scale (MNWS) were administered during hospitalization (a period of forced abstinence) to assess the frequency and severity of withdrawal symptoms. NRT use was also assessed during hospitalization.

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Findings—On average, smokers with insular damage had a lower WSWs score during admission (mean = 5.89, SD = 4.72) compared with those with non-insular damage (mean = 9.20, SD = 4.71; $p < 0.001$) (covariate-adjusted difference in means of -3.12 , 95% CI: -4.97 , -1.27). A similar difference was also noted when the MNWS was used ($p = 0.02$). Furthermore, participants with insular lesions appeared to be less likely to use NRT during admission compared with those with non-insular lesions (OR = 0.72, 95% CI: 0.32, 1.64).

Conclusions—Current smokers with damage to their insular cortex brain region appear to experience fewer and less severe tobacco withdrawal symptoms, and appear to be less likely to require nicotine replacement therapy during hospitalization, compared with smokers with non-insular damage. These findings support the potential role of the insular cortex in regulating withdrawal during abstinence, a motivator responsible for the maintenance of addictive behaviors.

INTRODUCTION

The prevalence of cigarette smoking has remained stable at 18% since 2005.(1) It is responsible for nearly one in five deaths in the United States(2) and remains a primary cause for several comorbidities.(3) Currently, nicotine replacement therapies (NRT) as well as bupropion and varenicline are FDA-approved first-line treatments for tobacco dependence. These pharmacotherapies are considered highly effective compared to placebo, yet 66.8–81.0% of smokers motivated to quit relapse by six months,(4, 5) suggesting persisting aspects of addiction that remain.(6, 7)

The craving for nicotine has been suggested to originate from long-term adaptations within specific neural systems that promote escalating drug use, difficulty quitting, and relapse.(8) Mesocorticolimbic structures, including the ventral tegmental area (VTA), amygdala, nucleus accumbens (NAc), prefrontal cortex (PFC), and hippocampus, also referred to as the “reward” pathway, exhibit molecular adaptations when exposed to addictive drugs in preclinical studies.(9, 10) Recently, the insular cortex – the cerebral cortex beneath the sylvian fissure surrounded by the temporal, frontal, and parietal opercula – has been of particular interest due to evidence from animal models of addiction(10–13) as well as human studies of functional neuroimaging during drug urges(14–19) and stroke-induced lesions(9, 20, 21). This suggests that the insula is a critical neurosubstrate for the maintenance of addiction by controlling drug desirability, although it has been neglected in neurological mechanisms of drug reward. The theory supporting this specific role of the insula is that the central and peripheral effects of nicotine are implicated in conscious pleasure induced by cigarette smoking. Cues associated with smoking are believed to result in interconnections from the amygdala and orbitofrontal cortex/ventromedial PFC triggering a representation of the euphoria produced by nicotine in the insula and subsequently resulting in insular projections to the NAc core, thus motivating nicotine-taking and nicotine-seeking behavior. (8)

Prior studies that examined the effect of insular damage from stroke on addiction began with Naqvi et al. retrospectively showing that smokers with lesions involving the insula were more likely to satisfy criteria for a disruption of nicotine addiction when assessed on average eight years after lesion onset.(9) Three subsequent prospective studies attempted to replicate

these findings, the first of which found no association between lesion localization and disruption of smoking addiction at three-month follow-up.(22) The two most recent studies, however, demonstrated greater abstinence at one-year post-stroke(20) and a reduction in Fagerström Test for Nicotine Dependence (FTND) score up to one-year post-stroke(21) among smokers with damage to their insula. Such studies acknowledge methodological challenges due to small sample sizes, failure to account for other regions damaged in the reward pathway, and lack of adjustments for important confounding variables such as NRT use. Smoking-related urges, as claimed to be measured in three of the four studies, can be triggered by a variety of stimuli and the insula may be responsible for regulating withdrawal during abstinence, thus leading to a reduction in withdrawal-induced urges which are a major barrier to overcoming nicotine addiction and predicting abstinence. In a sample of current cigarette smokers admitted for acute ischemic stroke, the aims of this study are to 1) examine whether those with damage involving their insular cortex experience fewer and less severe withdrawal symptoms during their hospitalization, a period of forced abstinence, compared to smokers with non-insular damage, and 2) examine whether insular damage would be inversely associated with NRT use during admission.

METHODS

Study Population

The Measuring the Impact on Nicotine Dependence after Stroke (MINDS) study population consisted of adults aged 18 years and older who were admitted to one of three acute care hospitals in Rochester, NY with a diagnosis of acute ischemic stroke (ICD-9 code 434.91) and were active cigarette smokers at the time of stroke onset. Patients were eligible to participate if they met all of the following inclusion criteria: (1) smoked at least one cigarette per day during the month prior to their stroke and at least 100 in their lifetime; (2) understand and speak the English language; (3) stable enough, as determined by a nurse practitioner, to give autonomous informed consent and respond to the survey questions verbally or on paper; and (4) willing to respond to the follow-up survey three months after hospital admission. Exclusion criteria were only applicable for follow-up evaluations and are not relevant for the current study using only admission data.

We needed 125 participants to detect a 2.35-point difference in withdrawal scale scores between groups(23) with 80% power and 0.05 probability of Type I error. A total of 470 ever smokers with acute ischemic stroke were identified between June 2013 and February 2014; data collection ended May 2014. Among the 204 (43.4%) who met the definition of a current smoker, 48 (23.5%) were excluded for not meeting the eligibility criteria (16 declined to participate, 10 were aphasic during admission, 9 were discharged before consent, 6 smoked less than one cigarette per day, 4 had language barriers, and 3 died in the hospital). After these exclusions, 156 patients were enrolled into the study (oversampled by 20%).

All participants signed informed consent forms. The institutional review boards at all participating institutions approved the study protocols and procedures.

Exposure Assessment

Acute infarctions to the insular cortex, the primary region of interest, and the aforementioned mesocorticolimbic structures were characterized by neuroradiologists (H.Z.W., E.M.S., B.E.S.) using standard of care computed tomography (CT) and magnetic resonance imaging (MRI) techniques in all participants (Figure 1). Unexposed participants were those with cerebral infarctions not in the insular cortex. The findings from MRI were weighed more than CT; however CT imaging was used when MRI was contraindicated. On MRI, diffusion weighted imaging was used to evaluate lesion location if done within a few days from the stroke. If follow-up MRI scans were available, the fluid attenuated inversion recovery sequence was used to verify the initial MRI findings. The NAc and VTA were the two most difficult regions to evaluate as they are not routinely evaluated in practice and the standard MRI uses 5mm slices which may be too thick to detect lesions in these areas.(24) Of the 156 participants, acute to subacute infarctions in the insula were detected in 38 (24.4%) participants. Further lesion characterizations of regions of interest are shown in Table 1.

Severity of stroke was measured using the National Institutes of Health Stroke Scale (NIHSS)(25), a 15-item neurologic assessment tool administered by clinicians at bedside to evaluate acuity of patients, guide treatment, and predict outcomes. The scale measures levels of consciousness, speech impairment, neglect, visual perception, extraocular movement, motor function, ataxia, dysarthria, and sensory loss. Lesion volumes from diffusion and perfusion-weighted MRI are highly correlated with NIHSS score in acute ischemic stroke patients ($r = 0.96$, $p < 0.001$) and thus serves as a surrogate measure for infarction size.(26)

Exposure data were collected and managed using Research Electronic Data Capture (REDCap)(27) tools hosted at the University of Rochester. Lesions in 80 (51.3%) participants were identified using only MRI, 22 (14.1%) using only CT, and 54 (34.6%) using both MRI and CT. All participants were confirmed to have acute to subacute infarctions.

Ascertainment of End Points

During hospitalization, patients were not permitted to leave the unit to smoke, signifying a period of smoking abstinence from the time of stroke. Since withdrawal symptoms typically emerge within a few hours following the last smoked cigarette and peak within a few days to one week(28, 29), this period represents an ideal window to assess the presence and intensity of these symptoms.

The Wisconsin Smoking Withdrawal Scale (WSWS)(30) and Minnesota Nicotine Withdrawal Scale (MNWS)(31) were administered at bedside after consent (mean = 4.4 days post-admission) to quantify severity of nicotine withdrawal symptoms in both exposure groups. The primary outcome, the WSWS, is a 28-item scale that uses three to five items to measure seven constructs, including irritability, depression, increased appetite, difficulty concentrating, insomnia, anxiety, and urge. The WSWS has been effectively used in both clinical and research settings and shown to be highly reliable and valid.(30) The total WSWS score was calculated by averaging the items for each withdrawal symptom

(excluding urge since this is not a DMS-IV criteria for withdrawal; we also wanted to differentiate withdrawal from cravings)(32) and summing the means. The MNWS, a secondary measure of withdrawal with less robust psychometrics but more historical value, is an eight-item scale measuring eight constructs, including the seven previously listed plus restlessness.(31) Total MNWS score was calculated by taking the mean of the eight items. Only one rater (A.A.) conducted all the assessments and was blinded to exposure status.

NRT use (yes/no) during hospitalization, including the use of nicotine inhaler, lozenge, patch, gum, and nasal spray, was self-reported by the patient and confirmed in the electronic medical record. Patients were not allowed to use any other forms of tobacco or electronic cigarettes during their hospitalization.

Statistical Analyses

Baseline characteristics of participants were described using relative frequencies for categorical measures and means and standard deviations (SD) for continuous measures. To test for a difference in mean WSWs and MNWS scores during hospitalization between insular and non-insular damaged participants, an independent samples Student t-test was used assuming normally distributed scores while median values and Wilcoxon-Mann-Whitney test were used for non-parametric statistics. To examine effects of individual symptoms, identical analyses were done stratifying the WSWs into its subscale components. A two-sided *p*-value of less than 0.05 was considered statistically significant.

In addition to unadjusted comparisons, multivariable linear regression models were used to control for covariates that were predictive of outcomes in this particular study as well as all *a priori* theoretical risk factors for the outcomes, including age, baseline FTND (asked retrospectively), NRT use during admission (yes/no), NIHSS score, acute mesocorticolimbic infarction (yes/no), and intent to quit (prior to stroke) in the next month with an attempt in the past year (asked retrospectively; yes/no).

To evaluate whether NRT use differed between exposure groups during hospitalization, a logistic regression analysis was performed in which the binary dependent variable was whether or not patients received NRT to cope with their withdrawal symptoms. Crude and adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated, controlling for age, baseline FTND, NIHSS score, acute mesocorticolimbic infarction, and prior intent to quit. All statistical procedures were performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC).

RESULTS

The baseline characteristics of study participants are described in Table 2. Demographic variables were well balanced between exposure groups. When retrospectively asked about their intention to quit immediately prior to hospitalization, participants with insular damage had a greater interest in quitting in the next month with an attempt in the past year compared to those with non-insular damage. Participants with insular damage on average had a higher NIHSS score and experienced a higher proportion of concurrent mesocorticolimbic infarcts compared to the non-insular group.

The distribution of WSWs and MNWS scores were slightly skewed to the right. Log-transformation of these scales did not normalize the distributions more than in their original form. Therefore, we conducted parametric and non-parametric tests to detect crude differences in withdrawal symptom severity between exposure groups (Table 3). On average, participants with insular damage had fewer and less severe withdrawal symptoms than those with non-insular damage as demonstrated by both withdrawal scales. When considering individual constructs of the WSWs (Table 4), participants with insular damage had significantly lower scores for six of the seven components (anger, anxiety, craving, hunger, sadness, and sleep) compared to the non-insular group, suggesting that most of the components that contribute to withdrawal symptom severity may be regulated by the insula. No significant difference was detected in concentration level between groups.

Linear regression modeling findings are shown in Table 5. Participants with insular damage on average had a 3.12-point lower WSWs score and 0.48-point lower MNWS score compared to those with non-insular damage after adjusting for covariates. These effects remained stable when excluding patients who used NRT. Higher baseline dependence scores and NRT use during admission were associated with an increase in withdrawal symptom severity, while concurrent mesocorticolimbic damage and pre-stroke intent to quit were associated with decreased withdrawal symptom severity. A sensitivity analysis including the urge component into the total WSWs score produced larger crude ($\beta = -4.00$, 95% CI: $-6.11, -1.89$) and adjusted ($\beta = -3.64$, 95% CI: $-5.86, -1.42$) associations.

Table 6 shows differences in NRT use during hospitalization for stroke between exposure groups. Participants with any insular damage had a trend toward reduced odds of using NRT during admission compared to participants with non-insular damage, which became slightly attenuated in the fully adjusted model. Higher baseline dependence scores were associated with increased odds of NRT use while mesocorticolimbic infarctions were associated with decreased odds.

Exploratory analyses stratifying by side of insular damage found that on average, the mean withdrawal scores in left insular damaged participants (mean WSWs = 4.66, SD = 3.97) were lower than those with right insular damage (mean WSWs = 6.56, SD = 5.01), both significantly different from those with non-insular damage ($p = 0.01$). Compared to those with non-insular damage, right insular damaged participants had a 2.65-point lower WSWs (95% CI: $-4.75, -0.54$) while left insular damaged participants had a 4.55-point lower WSWs score (95% CI: $-7.06, -2.03$). The stronger effect among left insular damaged patients may be explained by the higher odds of NRT use in that group compared to non-insular damage (OR = 1.35, 95% CI: 0.45, 4.07), whereas those with right insular damage were less likely to use NRT during hospitalization (OR = 0.53, 95% CI: 0.19, 1.53). Given these findings, controlling for handedness (hemispheric dominance) in the main analyses did not change our effect estimates or confidence intervals. The main associations did not vary by gender.

DISCUSSION

We examined the relationship between insular damage and acute withdrawal symptom severity, a major component of addiction responsible for relapse, and found that among current cigarette smokers admitted for acute territorial infarction, those with any damage to their insula experienced significantly fewer and less severe withdrawal symptoms during their hospitalization compared to participants with damage in any other region. These results were consistent between withdrawal scales and changed little when adjusting for covariates.

Although no human studies exist relating the insula specifically to withdrawal scores, our findings coincide with evidence found in human imaging studies and animal models of withdrawal. Previous fMRI studies have shown the insula to be activated during periods of forced withdrawal.(14, 15) Subjects who were anxiety-prone, a component of withdrawal, had greater bilateral insular activation compared to an anxiety-normative group.(33) Self-generated feelings of anger(34) and sadness(35, 36) were also associated with insular activation. Similar techniques have demonstrated the insula to be one of several brain regions involved in the regulation of eating behaviors and hunger via decreased activity following satiation.(37) In addition, the insula has been shown to be activated during sleep deprivation(38) and deactivated during sleep(39, 40), although a study in patients with multiple sclerosis demonstrated six of 10 patients with insular lesions had sleep complaints.(41) Such lesions, however, are pathophysiologically different than ischemia from stroke. In a self-administration animal model of nicotine addiction, rats demonstrated increased nicotine seeking behaviors (measured via lever presses previously associated with drug delivery) during prolonged forced abstinence, which was correlated with higher levels of dopamine- and cAMP-regulated phosphoprotein 32 k in the insula, suggesting the insula's role in withdrawal and cravings.(10)

We note that, among the seven withdrawal components, all but level of concentration were significantly less common in subjects with insular damage. Attention deficits are not uncommon in patients after acute stroke.(42) The insula, however, has been implicated in cognitive functions and awareness(43), which may explain why there was no difference in concentration between groups. Future studies may also benefit by examining more objective physical signs of withdrawal such as decreased heart rate, diaphoresis, sleep awakenings, and increased caloric intake relative to a baseline.(44) While our findings suggest subjective aversive withdrawal symptoms are reduced from a disruption of interoceptive signals with insular damage, knowing how the expression of physical withdrawal measures change are also of high clinical importance.

These findings suggest a potential role for the insula in moderating cravings and urge. When smoking becomes regular, nicotine binds to nicotinic acetylcholine receptors causing an excess release of dopamine in the brain. To compensate for the oversaturation of neurotransmitters, the amount of naturally released dopamine is reduced. When smoking stops, there is an inadequate supply of dopamine neurotransmitters being released to control and maintain homeostasis, thus resulting in withdrawal symptoms, including dysphoria and a desire to smoke.(45, 46) Withdrawal-induced urges might be seen as a subjective need to alleviate the dysphoria.(47) The insula may function to translate the physiological state of

withdrawal into subjective dysphoria. (48) If such symptoms can be eliminated after a quit attempt, this may result in a subsequent lack of withdrawal-related urges. Given our findings that damage to the insula reduced acute withdrawal, this may be a plausible mechanism by which insular damage lead to cessation(9, 20, 21), decreased dependence(21), and a disruption of addiction(9) in previous observational studies.

Patients who experience withdrawal from nicotine in an environment where smoking is prohibited (i.e., the hospital) are usually given NRT to cope with symptoms. We found no clear relationship between insular damage and NRT use during hospitalization, which was somewhat unexpected given our finding of fewer withdrawal symptoms in the insular damaged group. One possible explanation may be that some patients were given NRT due to their history of tobacco use to avoid withdrawal or cravings before they started. There were some instances where patients felt they did not need NRT but used it “just in case.” The 2008 National Guidelines for Treating Tobacco Use and Dependence suggests that 90% of smokers would benefit from NRT during withdrawal,(5) however the prevalence of hospital NRT use in our study was only 31.4%, suggesting potential underutilization. In some cases, patients were unaware or afraid of the side effects of NRT and elected not to use it or felt they could deal with the cravings without pharmacological assistance, consistent with prior qualitative reports.(49, 50)

This study has strengths and limitations. Data were derived from a prospective cohort study, the largest human study to date to assess the relationship between insular cortex lesions and nicotine addiction. Withdrawal outcomes were measured on a continuous scale, allowing for a better understanding of the magnitude of change given the wide range of severity. These measures, however, were based on self-report with no objective corroboration. Because the location of the stroke was uncontrollable and “random”, exposure status should not have mediated one’s intention to give false information. Unlike the previous studies which did not report information about smoking-related cravings before stroke onset, we retrospectively assessed these measures by asking participants about their cigarette dependency prior to their stroke and controlled for this in the statistical model, as dependent smokers are more likely to experience more severe withdrawal syndrome during abstinence compared to non-dependent smokers.(51) Retrospective assessments, however, may have been subject to recall error considering their recent brain injury. Also, the possibility that patient responses to the questions regarding behaviors at baseline were more reflective of their feelings during admission should not be excluded. This could similarly explain the higher prevalence of pre-stroke intention to quit among those with insular damage. The risk for exposure misclassification also exists. If the quality of imaging was poor, there may have been some ambiguity as to the involvement of the insula for infarctions deep within the midbrain. With more refined techniques for lesion characterization, the observed associations may have been even stronger. Some clinical differences in stroke characteristics were present between exposure groups. Participants with insular damage on average had a higher NIHSS score than those with non-insular damage. Although this difference was statistically significant, whether this signifies a meaningful difference is less likely, as stroke severity scores between 5 and 15 are considered less severe (moderate) strokes. Patients with severe strokes were likely to be excluded from the study due to their aphasia. The proportion of participants experiencing a concurrent infarction in a mesocorticolimbic structure was also

higher in the insula group. Because the insula is adjacent to this structure, the chance of an infarction in both regions is higher, whereas a non-insular infarction could have occurred anywhere else in the cerebrum and its involvement with the mesocorticolimbic structure is less likely. Although this study is the largest of its kind, the acquired sample size limited the number of subgroup analyses we could perform with adequate power; thus, such calculations were considered exploratory. Future studies may also consider examining the effect of anterior versus posterior lesions. Finally, results of this study may not be generalizable to all cigarette smokers. The target population, smokers who experience a stroke, could be less “healthy” than other smokers, and it is unclear whether quitting patterns are different between these “healthy” versus “unhealthy” smokers. Also, administration of tissue plasminogen activator in stroke patients may manifest post-treatment neurotoxicity which has the potential to influence the outcomes, although proportions exposed from two hospitals ($n = 80$) was similar between groups ($p = 0.24$) and thus not likely to influence the association in our sample.

Our findings indicate that insular damage from stroke resulted in fewer and less severe withdrawal symptoms during abstinence. Additional controlled experimental studies using animal models, molecular-level studies, as well as observational studies should examine whether damage in pathways leading to the insula or away from the insula also results in disruption of smoking behavior. If additional evidence supports the insular cortex as a primary neurosubstrate for regulating withdrawal, it may be a novel target for therapeutic interventions that prove effective in long-term smoking cessation.

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Figure 1. Subset of participants with axial plane diffusion weighted (A) and computed tomography (B) images revealing acute insular cortex infarctions.

Table 1

Exposure regions of interest (n = 156)

	Type of damage ^a			Any abnormality
	Acute/subacute infarct	Chronic infarct	Other abnormality ^b	
Insular cortex (any)	38 (24.4)	5 (3.2)	19 (12.2)	54 (34.6)
Right insula	23 (14.7)	1 (0.6)	7 (4.5)	23 (14.7)
Left insula	14 (9.0)	3 (1.9)	6 (3.8)	15 (9.6)
Bilateral	1 (0.6)	1 (0.6)	6 (3.8)	16 (10.3)
<i>Acute insular infarct (n = 38)</i>				
Mesocorticolimbic structure	20 (52.6)	6 (15.8)	14 (36.8)	32 (84.2)
Prefrontal cortex	18 (47.4)	5 (13.2)	7 (18.4)	30 (78.9)
Nucleus accumbens	0 (0.0)	0 (0.0)	4 (10.5)	4 (10.5)
Ventral tegmental area	0 (0.0)	0 (0.0)	6 (15.8)	6 (15.8)
Amygdala	0 (0.0)	0 (0.0)	5 (13.2)	5 (13.2)
Hippocampus	2 (5.3)	1 (2.6)	8 (21.1)	11 (28.9)
<i>Acute non-insular infarct (n = 118)</i>				
Mesocorticolimbic structure	35 (29.7)	14 (11.9)	34 (28.8)	67 (56.8)
Prefrontal cortex	26 (22.0)	12 (10.2)	20 (17.0)	58 (49.2)
Nucleus accumbens	1 (0.9)	0 (0.0)	7 (5.3)	8 (6.8)
Ventral tegmental area	0 (0.0)	0 (0.0)	13 (11.0)	13 (11.0)
Amygdala	1 (0.9)	1 (0.9)	5 (4.2)	7 (5.3)
Hippocampus	9 (7.6)	1 (0.9)	9 (7.6)	19 (16.1)

Values expressed as n (%).

^aParticipants may have more than one type in a given region.^bIncludes gliosis and other lesions not stroke related.

Table 2

Baseline characteristics of study participant's

	Type of acute infarction		P
	Insula (n = 38)	Non-insula (n = 118)	
Age, mean (SD)	59.7 (12.1)	59.7 (11.3)	0.98
Female, n (%)	21 (55.3)	50 (42.4)	0.17
White race, n (%)	26 (68.4)	78 (66.1)	0.79
Highest education completed, n (%)			0.89
< HS	12 (31.6)	33 (28.0)	
HS/GED	21 (55.3)	67 (56.8)	
College or higher	5 (13.1)	18 (15.2)	
Household income, n (%)			0.32*
< \$40,000	23 (60.5)	89 (75.4)	
\$40,000 or higher	5 (13.2)	10 (8.5)	
Missing	10 (26.3)	19 (16.1)	
Marital status, n (%)			0.41
Married or living with partner	10 (26.3)	37 (31.3)	
Not married	15 (39.5)	33 (28.0)	
Divorced, separated, widowed	13 (34.2)	48 (40.7)	
Employment status, n (%)			0.74
Employed	7 (18.4)	27 (22.9)	
Unemployed	14 (36.9)	46 (39.0)	
Retired	17 (44.7)	45 (38.1)	
FTND, mean (SD)	5.0 (2.1)	5.2 (1.9)	0.58
Cigarettes per day, mean (SD)	19.6 (20.7)	18.8 (11.9)	0.77
Lifetime smoking years, mean (SD)	37.7 (14.6)	40.1 (13.6)	0.35
Intent to quit (prior to stroke) in the next month with attempt in past year, n (%)	12 (31.6)	19 (16.1)	0.04
Right handed, n (%)	35 (92.1)	105 (89.0)	0.76*
Prior cerebral infarction, n (%)	18 (47.4)	45 (38.1)	0.33
NIHSS score, mean (SD)	8.8 (6.4)	5.2 (5.2)	<0.001
Length of stay (days), mean (SD)	12.0 (13.1)	10.6 (15.0)	0.61
Days until consent, mean (SD)	3.8 (0.6)	4.6 (0.6)	0.50
Concurrent infarct in mesocorticolimbic structure, n (%)	20 (52.6)	35 (29.7)	0.01

SD, Standard Deviation; FTND, Fagerström Test for Nicotine Dependence; NIHSS, National Institutes of Health Stroke Scale.

* Fisher's Exact test p-value used (not including missing subjects); >20% of cells have expected counts less than 5

Table 3
Crude withdrawal symptom severity between exposure groups during hospitalization

	Insula (n = 38)				Non-insula (n = 118)				p ^d	p ^b
	Mean (95% CI)	SD	Median (IQR)		Mean (95% CI)	SD	Median (IQR)			
WSWS	5.89 (4.34, 7.44)	4.72	4.13 (2.90, 6.82)		9.20 (8.35, 10.06)	4.71	9.34 (5.05, 12.97)		<0.001	<0.001
MNWS	0.61 (0.29, 0.93)	0.98	0.13 (0.00, 0.50)		1.22 (1.03, 1.41)	1.04	0.94 (0.38, 1.88)		0.002	<0.001

WSWS, Wisconsin Smoking Withdrawal Scale; MNWS, Minnesota Nicotine Withdrawal Scale; SD, Standard Deviation; CI, Confidence Interval; IQR, Interquartile Range.

^dIndependent samples t-test (pooled method for equal variances)

^bWilcoxon-Mann-Whitney test for non-parametric data

Table 4

Breakdown of the WSWs components by subscale between exposure groups during hospitalization

	Insula (n = 38)				Non-insula (n = 118)				<i>p^d</i>	<i>p^b</i>
	Mean (95% CI)	SD	Median (IQR)		Mean (95% CI)	SD	Median (IQR)			
Anger	0.81 (0.35, 1.27)	1.39	0.00 (0.00, 0.67)		1.45 (1.20, 1.71)	1.38	1.00 (0.00, 2.67)	0.01	0.002	
Anxiety	0.80 (0.43, 1.16)	1.12	0.25 (0.00, 1.00)		1.42 (1.21, 1.62)	1.12	1.25 (0.50, 2.25)	0.003	0.001	
Concentration	1.00 (0.63, 1.37)	1.14	0.33 (0.00, 1.67)		1.22 (1.03, 1.42)	1.07	1.00 (0.33, 2.00)	0.27	0.17	
Craving ^c	0.92 (0.50, 1.34)	1.27	0.25 (0.00, 1.50)		1.61 (1.35, 1.86)	1.41	1.25 (0.25, 3.00)	0.009	0.003	
Hunger	1.55 (1.21, 1.89)	1.03	1.30 (0.80, 2.40)		2.08 (1.91, 2.24)	0.90	2.00 (1.40, 2.80)	0.003	0.002	
Sadness	0.95 (0.61, 1.28)	1.03	0.50 (0.25, 1.25)		1.67 (1.49, 1.86)	1.00	1.75 (0.75, 2.50)	<0.001	<0.001	
Sleep	0.79 (0.50, 1.07)	0.87	0.60 (0.00, 1.40)		1.36 (1.16, 1.55)	1.07	1.20 (0.40, 2.20)	0.003	0.003	

WSWS, Wisconsin Smoking Withdrawal Scale; SD, Standard Deviation; CI, Confidence Interval; IQR, Interquartile Range.

^aIndependent samples t-test (pooled method for equal variances)

^bWilcoxon-Mann-Whitney test for non-parametric data

^cCraving excluded from total WSWS score as this is not a criteria for withdrawal

Linear regression models assessing withdrawal symptom severity in the insular relative to non-insular group during hospitalization (n = 156)

Table 5

Model	Primary exposure	WSWS			MNWS		
		β (95% CI)	SE	P	β (95% CI)	SE	P
Crude	Acute insular infarct	-3.31 (-5.05, -1.58)	0.88	<0.001	-0.61 (-0.99, -0.23)	0.19	<0.001
Adjusted	Acute insular infarct	-3.12 (-4.97, -1.27)	0.94	<0.001	-0.48 (-0.86, -0.09)	0.20	0.02
	Baseline FTND	0.34 (-0.06, 0.74)	0.20	0.09	0.08 (0.00, 0.17)	0.04	0.05
	NRT use during admission	1.81 (0.09, 3.53)	0.87	0.04	0.63 (0.27, 0.99)	0.18	<0.001
	Age	-0.01 (-0.08, 0.05)	0.03	0.67	0.00 (-0.01, 0.02)	0.01	0.93
	NIHSS score	0.06 (-0.08, 0.20)	0.07	0.38	0.00 (-0.03, 0.03)	0.01	0.83
	Mesocorticolimbic infarct	-0.68 (-2.33, 0.98)	0.84	0.42	-0.11 (-0.46, 0.24)	0.18	0.52
	Intent to quit	-0.30 (-2.26, 1.67)	0.99	0.77	-0.14 (-0.55, 0.27)	0.21	0.50

WSWS, Wisconsin Smoking Withdrawal Scale; MNWS, Minnesota Nicotine Withdrawal Scale; CI, Confidence Interval; SE, Standard Error; FTND, Fagerström Test for Nicotine Dependence; NIHSS, National Institute of Health Stroke Scale; NRT, Nicotine Replacement Therapy.

Table 6

Logistic regression modeling the risk of NRT use during hospitalization associated with an insular relative to non-insular infarct (n = 156)

Primary exposure				
Model	Covariates	OR	95% CI	P
Crude	Acute insular infarct	0.72	0.32 – 1.64	0.44
Full	Acute insula infarct	0.82	0.32 – 2.12	0.68
	Baseline FTND	1.31	1.06 – 1.61	0.01
	Mesocorticolimbic infarct	0.35	0.15 – 0.84	0.02
	Age	0.99	0.96 – 1.03	0.69
	NIHSS score	1.04	0.98 – 1.12	0.22
	Intent to quit	1.01	0.38 – 2.73	0.98

OR, Odds Ratio; CI, Confidence Interval; FTND, Fagerström Test for Nicotine Dependence; NIHSS, National Institutes of Health Stroke Scale.