Original investigation

Immediate and Sustained Decrease in Smoking Urges After Acute Insular Cortex Damage

Amir Abdolahi PhD, MPH^{1,2}, Geoffrey C. Williams MD, PhD³,
Curtis G. Benesch MD, MPH⁴, Henry Z. Wang MD, PhD⁵,
Eric M. Spitzer MD⁶, Bryan E. Scott MD⁶, Robert C. Block MD, MPH¹,
Edwin van Wijngaarden PhD¹

¹Department of Public Health Sciences, University of Rochester Medical Center, Rochester, NY; ²Department of Acute Care Solutions, Philips Research North America, Cambridge, MA; ³Departments of Medicine, Psychiatry, and Clinical and Social Sciences in Psychology, University of Rochester Medical Center, Rochester, NY; ⁴Department of Neurology, University of Rochester Medical Center, Rochester, NY; ⁵Department of Imaging Sciences, University of Rochester Medical Center, Rochester, NY; ⁶Department of Radiology, Rochester General Health System, Rochester, NY

Corresponding Author: Amir Abdolahi, PhD, MPH, Department of Acute Care Solutions, Philips Research North America, 345 Scarborough Rd., Briarcliff Manor, NY 10510, USA. Telephone: 914-261-5504; E-mail: amir.abdolahi@philips.com

Abstract

Introduction: Smoking urges are fundamental aspects of nicotine dependence that contribute significantly to drug use and postquit relapse. Recent evidence has indicated that damage to the insular cortex disrupts smoking behaviors and claims to reduce urges associated with nicotine use, although tools that assess urge have yet to be used to validate these findings. We examined the effect of insular versus non-insular damage on urge using a well-accepted urge scale.

Methods: This 3-month observational prospective cohort study consisted of 156 current smokers hospitalized for acute ischemic stroke (38 with insular infarctions, 118 with non-insular infarctions). During hospitalization, the Questionnaire of Smoking Urges (QSU)-brief was assessed retrospectively based on experiences before the stroke (baseline, T0), prospectively immediately following the stroke (T1) and once more via telephone at 3-month follow-up (T2), with higher scores indicating greater urge. Bivariate statistics and multivariable linear regression were used to evaluate differences in QSU-brief scores, relative to baseline, between exposure groups, controlling for age, baseline dependence, stroke severity, use of nicotine replacement, and damage to other mesocorticolimbic regions.

Results: A greater reduction in QSU-brief score was seen in the insular group compared to the non-insular group from T0 to T1 (covariate-adjusted difference in means of -1.15 , 95% CI: -1.85 , -0.44) and similarly from T0 to T2 (covariate-adjusted difference in means of -0.93 , 95% CI: -1.79 , -0.07).

Conclusions: These findings confirm the potential role of the insula in regulating nicotine-induced urges and support the growing evidence of its novelty as a key target for smoking cessation interventions.

Implications: Human lesioning studies that evaluate the insula's involvement in maintaining nicotine addiction make inferences of the insula's role in decreasing urge, but do not use validated instruments that directly assess urges. This study corroborates prior findings using the continuous Questionnaire of Smoking Urges to quantify changes in urge from before lesion onset to immediate and 3-month follow-up time points.

Introduction

Tobacco dependence is well known globally as the leading preventable cause of morbidity and mortality, yet the prevalence of cigarette smoking—highly variable demographically—remains stable in the United States around 17%¹ and even higher in European (28%) and Western Pacific (26%) countries,² while African and Eastern Mediterranean regions show increasing trends.³ Less known among consumers is that habitual use of cigarettes leads to a chronic condition of brain reward, motivation, memory and related circuitry,⁴ triggering uncontrollable use that is also influenced by genetic susceptibility, physiological response, and environmental cues.⁵ It is these factors that make it difficult for smokers to quit. Annually, an estimated 43% of daily smokers in the United States stop smoking for at least 24 hours without any pharmacologic help, but up to 95% are unsuccessful and relapse by 12 months after their intended quit date.^{6,7} In persons taking pharmacotherapy and/or behavioral therapy to aid in smoking cessation, about 75% relapse within 6 months of the initial quit attempt,⁸ suggesting some part of the reward pathways that are not targeted by these therapies.

Recognized pathways that are involved in drug reward include the mesocorticolimbic regions of the brain—namely the ventral tegmental area, amygdala, nucleus accumbens, prefrontal cortex, and hippocampus—which have consistently shown molecular adaptations when exposed to drugs of abuse in preclinical studies^{9,10} and thus have been the primary target for smoking cessation pharmacotherapies such as bupropion¹¹ and varenicline.¹² More recently, the insular cortex—the cerebral cortex beneath the sylvian fissure between the temporal and frontal lobes—has received attention due to functional neuroimaging studies showing increased insular activity after passive exposure to drugs and drug-related stimuli.¹³ The insula is not part of the mesocorticolimbic pathway but holds dense interconnections with these structures. It is hypothesized that interoceptive information, namely drug-induced stimuli, from thalamocortical structures is received by the insula, which triggers the prefrontal cortex and amygdala to activate dopaminergic response in the ventral tegmental area.^{13,14} In this manner, the insula acts as the link between the conditioned stimuli and physiological states such as urge, which translates to poor decision making and impulsive behaviors.

Clinical evidence of changes in cigarette use and nicotine dependence has been observed in stroke models of neurological deactivation. Several studies have consistently demonstrated that smokers hospitalized for CT- and MRI-verified stroke involving the insular cortex experienced a disruption of smoking addiction,^{9,15,16} observed significantly fewer and less severe withdrawal symptoms during hospitalization,¹⁷ and were less likely to relapse post-discharge^{15,16,18} compared to smokers with stroke involving other regions. Only one study has examined trends from pre-lesion up to 12 months post-lesion and reported a sustained reduction in nicotine dependence, as measured by the Fagerström Test for Nicotine Dependence (FTND),¹⁹ after an acute insular lesion relative to brain-damaged controls.¹⁸ Although these findings are novel and target a key question of the insula's durability to maintain smoking addiction, the items of the FTND were developed to measure smoking behaviors among current smokers (eg, Which cigarette would you hate to give up?) and hence would not be a valid measurement tool for those who stopped smoking during follow-up.

Smoking urges are fundamental aspects of nicotine addiction that contribute significantly to drug use as well as relapse after a quit attempt.²⁰ Urge can arise in both current and former or non-active smokers and thus is a construct that can be reliably measured

even during smoking abstinence.²¹ Recently, treating clinicians have begun to assess urges to smoke before, during, and after a quit attempt as several treatment methods are geared to control urges in the cessation process.²² Furthermore, higher urge scores have been shown to be inversely associated with successful long-term smoking cessation.²³ Prior studies have made implications on reduced smoking urge after stroke-induced lesions to the insula based on satisfying criteria for a disruption of smoking addiction or showing lower FTND scores,^{9,15} yet no study has actually used a validated urge scale to confirm these findings. To address this gap, this study employed the commonly used and validated Questionnaire of Smoking Urges (QSU)-brief to quantify actual level of urge at various time points relative to lesion onset. We hypothesized that among current cigarette smokers hospitalized for acute ischemic stroke, those with damage to their insular cortex would experience a greater reduction in urge from baseline (before the stroke) to acute (during hospitalization) and long-term (3 months post-stroke) follow-up as compared to those with non-insular damage. Three-month follow-up was chosen as a clinically-relevant timeframe in which the neuroadaptations that underlie addiction last after quitting.²⁴

Methods

Study Population

The Measuring the Impact on Nicotine Dependence after Stroke (MINDS) study is a prospective cohort study of adults aged 18 years and older who were admitted to one of three acute care hospitals in Rochester, New York with a diagnosis of acute ischemic stroke (ICD-9 code 434.91) and were active cigarette smokers at the time of stroke onset.^{16,17} 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) were able to understand and speak the English language; (3) has the decisional capacity, as determined by a nurse practitioner, to give autonomous informed consent and respond to the survey questions verbally or on paper; and (4) were willing to respond to the follow-up survey 3 months after hospital admission. Participants were excluded from follow-up evaluation if they had a subsequent stroke of any kind or were maintained in an environment where access to smoking was restricted.

A total of 470 ever smokers with acute ischemic stroke were screened between June 2013 and February 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, 10 were aphasic, nine were discharged before consent, six smoked less than one cigarette per day, four had language barriers and three died in the hospital). Thus, 156 patients provided written informed consent and were enrolled into the study. Due to exclusions and losses to follow-up (nine were unavailable or did not return call, seven died, three were still admitted at facility and three had a subsequent stroke), 134 (85.9%) enrolled participants completed the 3-month follow-up assessment. Participants were paid up to \$25 for study completion in a prorated fashion.

The institutional review boards at all participating institutions approved the study protocols and procedures.

Assessment of Lesion Location

Acute ischemic neurological infarctions were characterized by neuroradiologists (HZW, EMS, BES) using standard of care computed tomography (CT) and diffusion weighted magnetic resonance

imaging (MRI) techniques. Participants with cerebral infarctions involving the insular cortex, whole or partially, were considered exposed; those with non-insular damage were classified as unexposed. Other mesocorticolimbic regions of interest were evaluated and included the prefrontal cortex, nucleus accumbens, amygdala, hippocampus, and the ventral tegmental area. The neuroradiologists were blinded to information other than what is commonly clinically available. The findings from MRI were weighed much more than the CT due to its high sensitivity within hours after stroke onset; however CT imaging was used when MRI was contraindicated. Follow-up fluid attenuated inversion recovery MRI sequence was used to verify initial MRI findings if available. Lesion volume—to quantify the size of the infarction—was not obtained during the exposure assessment. However, severity of stroke as measured by the National Institutes of Health Stroke Scale (NIHSS)²⁵ score is highly correlated with lesion volume in acute ischemic stroke patients ($r = 0.96$, $p < .001$) and was thus used as a surrogate measure for infarction size in this study.²⁶

Exposure data were collected and managed using Research Electronic Data Capture (REDCap)²⁷ tools hosted at the University of Rochester. All participants were confirmed to have acute to subacute neurological infarctions. Lesions in 134 (85.9%) participants were identified using MRI and 22 (14.1%) using only CT. Acute to subacute insular infarctions were detected in 38 (24.4%) participants. Specific lesion characterizations of regions of interest were published in a prior report.¹⁷

Ascertainment of End Points

The primary outcome, the QSU-brief,²⁸ is a 10-item measure designed to assess urges and cravings to smoke using a seven-point Likert scale (1—strongly disagree to 7—strongly agree), with higher scores indicating stronger urges. These items load onto two factors representing (1) the desire and intention to smoke when smoking is thought of as a reward and (2) the anticipation of relief from negative affect that comes with cravings. The QSU-brief exhibits favorable internal consistencies at various stages of cigarette use and is a highly reliable tool for measuring smoking desirability (Cronbach's $\alpha \geq 0.87$).²⁸ The QSU-brief total score is computed by taking the mean of all QSU-brief items.

The QSU-brief was administered twice at bedside after consent (mean = 4.4 days post-admission) in order to quantify level of urge retrospectively based on feelings prior to the stroke (T0, baseline) and cross-sectionally based on current feelings during hospitalization following stroke onset, a period of smoking abstinence (T1). Participants were contacted over the phone approximately 90 days after the date of stroke (T2) to complete the follow-up QSU-brief assessment (mean = 96.5 days post-admission), during which they returned to a less-restrictive living environment. One rater (AA) conducted all the assessments and was naive to insular damage status.

Statistical Analyses

Baseline characteristics of participants were described using relative frequencies for categorical measures and means and SD for continuous measures. Crude mean and SD of QSU-brief scores were computed at T0, T1, and T2. To test for a difference in mean Δ QSU-brief scores from baseline to T1 and T2 between exposure groups, an independent samples Student's t test was used given the normally distributed scores. A two-sided p value of less than .05 was considered a statistically significant result.

Linear regression analyses were performed with Δ QSU-brief as a continuous dependent variable. In addition to crude unadjusted models, fully-adjusted multivariable linear regression models were used to control for covariates that were predictive of outcomes in this particular study (prior intention to quit in the next month with an attempt in the past year (asked retrospectively), NIHSS score, and concurrent acute mesocorticolimbic infarction) as well as all a priori theoretical risk factors for the outcomes, including age, baseline FTND, nicotine replacement therapy (NRT) use during admission (T1), and post-admission NRT/drug use (T2). Crude and adjusted beta (β) coefficients and 95% confidence intervals (CI) were calculated. All statistical procedures were performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC).

Results

The baseline characteristics of study participants, by exposure group, are described in Table 1. The demographic variables were comparable to those of the greater Rochester, New York region and of a smoking population. Overall, the exposure groups were very similar in age, gender, race, socioeconomic and employment status, and prior cigarette use and dependence. Participants with insular damage expressed a greater interest in quitting in the next month prior to hospitalization, had a greater stroke severity as suggested by the higher mean NIHSS score, and were more likely to experience a concurrent mesocorticolimbic infarction as compared to the non-insular group.

Average QSU-brief scores at each time point, by exposure, are illustrated in Figure 1. No difference in urge existed between insular and non-insular damaged groups at T0 before stroke onset ($p = .79$). At T1 and T2, both the insular and non-insular damaged groups had a reduction in urge relative to baseline; however, the levels of urge were significantly lower in the insular damaged group compared to the non-insular damaged group at both time points ($p < .01$). The magnitude of reduction (Δ QSU-brief) was greater in the insular damaged group compared to the non-insular group at both T1 ($p < .01$) and T2 ($p < .01$) (Table 2). The change in mean urge scores from T1 to T2 remained stable in both the insular ($p = .78$) and non-insular ($p = .67$) exposure groups.

Table 3 shows results from the linear regression models examining crude and adjusted magnitude of difference in urge between exposure groups. Q-Q plots for each model showed normal distributions of the residuals, satisfying linear regression assumptions. From baseline to T1 (acute change), participants with any insular damage on average had a 1.41-point larger reduction in QSU-brief score compared to those with non-insular damage (95% CI: $-2.09, -0.74$). After adjusting for covariates, the effect was slightly reduced but remained significant ($\beta = -1.15$, 95% CI: $-1.85, -0.44$). Similarly, from baseline to T2 (long-term change), participants with any insular damage on average had a 1.42-point larger reduction in QSU-brief score compared to those with non-insular damage (95% CI: $-2.19, -0.65$). The effect was again slightly reduced after adjusting for covariates but maintained significance ($\beta = -0.93$, 95% CI: $-1.79, -0.07$). Our interpretation of these findings did not change after conducting a sensitivity analysis in which we matched 1:1 on NIHSS score and concurrent mesocorticolimbic infarct. From baseline to T1, higher baseline dependence scores were associated with a reduction in urge intensity while NRT use during admission was associated with an increase in urge. Higher NIHSS scores appeared to significantly reduce urge from baseline to T2.

Table 1. Baseline Characteristics of Study Participants

	Type of acute infarction		<i>p</i>
	Insula (<i>n</i> = 38)	Non-insula (<i>n</i> = 118)	
Age, mean (<i>SD</i>)	59.7 (12.1)	59.7 (11.3)	.98
Female, <i>n</i> (%)	21 (55.3)	50 (42.4)	.17
White race, <i>n</i> (%)	26 (68.4)	78 (66.1)	.79
Highest education completed, <i>n</i> (%)			.89
<HS	12 (31.6)	33 (28.0)	
HS/GED	21 (55.3)	67 (56.8)	
College graduate or higher	5 (13.1)	18 (15.2)	
Household income, <i>n</i> (%)			.32 ^a
<\$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, <i>n</i> (%)			.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, <i>n</i> (%)			.74
Employed	7 (18.4)	27 (22.9)	
Unemployed	14 (36.9)	46 (39.0)	
Retired	17 (44.7)	45 (38.1)	
FTND, mean (<i>SD</i>)	5.0 (2.1)	5.2 (1.9)	.58
Cigarettes per day, mean (<i>SD</i>)	19.6 (20.7)	18.8 (11.9)	.77
Lifetime smoking years, mean (<i>SD</i>)	37.7 (14.6)	40.1 (13.6)	.35
Intent to quit (prior to stroke) in the next month with attempt in past year, <i>n</i> (%)	12 (31.6)	19 (16.1)	.04
Right handed, <i>n</i> (%)	35 (92.1)	105 (89.0)	.76 ^a
Prior cerebral infarction, <i>n</i> (%)	18 (47.4)	45 (38.1)	.33
NIHSS score, mean (<i>SD</i>)	8.8 (6.4)	5.2 (5.2)	<.001
Length of stay (days), mean (<i>SD</i>)	12.0 (13.1)	10.6 (15.0)	.61
Days hospitalized until baseline survey, mean (<i>SD</i>)	3.8 (0.6)	4.6 (0.6)	.50
Concurrent infarct in mesocorticolimbic structure, <i>n</i> (%)	20 (52.6)	35 (29.7)	.01

FTND = Fagerström Test for Nicotine Dependence; NIHSS = National Institutes of Health Stroke Scale.

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

Figure 1. Average crude Questionnaire of Smoking Urges (QSU)-brief scores (SE bars) at each time point, by exposure group (**p* < .01, relative to non-insula group).

Discussion

Among current cigarette smokers, we examined the longitudinal effect of stroke-induced damage to the insular cortex versus other cerebral regions on smoking urge and found that relative to baseline,

both groups reported a decrease in urge immediately after the stroke that was maintained until 3 months follow-up. The reduction observed in the insular damaged group, however, was greater than that in the non-insular group as hypothesized, supporting the previous claims that the insula is a neurosubstrate involved, at least partially, in the mechanism that controls conscious urges.^{9,29} These findings are also consistent with our prior reports demonstrating fewer and less severe withdrawal symptoms during T1¹⁷ and a lower risk of relapse at T2¹⁶ among participants with insular relative to non-insular damage. This is the first study of its kind to assess smoking urge using a validated scale and taking into consideration several other covariates that may influence the outcome. Controlling for risk factors such as NRT use, acute damage to other regions on the reward pathway, and intention to quit did not materially impact the associations and interpretations. Noteworthy is the strong association between NRT use during admission and an increase in urge score from baseline to T1, which is likely explained by the need for alternative nicotine intake in response to high levels of withdrawal-induced cravings, although insular damage was not strongly associated with NRT use (adjusted odds ratio = 0.82, 95% CI: 0.32, 2.12).¹⁷

Whether the observed differences constitute clinically meaningful differences is difficult to verify as there are no objective cutoffs for determining urge severity. Based on the QSU-brief scale, our findings suggest that both groups slightly to moderately agreed on the urge-related questions prior to stroke. After the stroke, those with

Table 2. Crude Change in Questionnaire on Smoking Urges (QSU)-Brief Scores From Baseline to Hospital Admission (T1) and 3 Months Post-Stroke (T2), by Exposure Group

	Δ QSU at T1			Δ QSU at T2		
	<i>n</i>	Mean (<i>SD</i>)	<i>p</i> ^a	<i>n</i>	Mean (<i>SD</i>)	<i>p</i> ^a
Non-insula	118	-1.97 (1.81)	—	102	-2.08 (1.98)	—
Insula	38	-3.38 (1.87)	<.0001	32	-3.50 (1.69)	.0004

p values are for difference relative to non-insula exposure group.

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

Table 3. Linear Regression Models Assessing Change in QSU-Brief Scores Between Insular Relative to Non-insular Groups From Baseline to Hospital Admission (T1, *n* = 156) and 3 Months Post-Stroke (T2, *n* = 134)

Model	Primary exposure covariates	Δ QSU at T1			Δ QSU at T2		
		β (95% CI)	SE	<i>p</i>	β (95% CI)	SE	<i>p</i>
Crude	Acute insular infarct	-1.41 (-2.09, -0.74)	0.34	<.01	-1.42 (-2.19, -0.65)	0.39	<.01
Full	Acute insular infarct	-1.15 (-1.85, -0.44)	0.36	<.01	-0.93 (-1.79, -0.07)	0.43	.03
	Baseline FTND	-0.22 (-0.37, -0.06)	0.08	.01	-0.01 (-0.19, 0.17)	0.09	.89
	NRT use during admission	1.10 (0.45, 1.76)	0.33	<.01	NA	NA	NA
	Post-admission NRT/ drug use	NA	NA	NA	-0.09 (-0.80, 0.61)	0.36	.80
	NIHSS score	-0.04 (-0.09, 0.02)	0.03	.17	-0.08 (-0.15, -0.02)	0.03	.01
	Age	0.02 (-0.01, 0.04)	0.01	.20	0.00 (-0.03, 0.03)	0.02	.92
	Mesocorticolimbic infarct	0.06 (-0.58, 0.69)	0.32	.86	-0.19 (-0.93, 0.55)	0.37	.61
	Intent to quit	-0.17 (-0.92, 0.58)	0.38	.66	-0.29 (-1.20, 0.62)	0.46	.54

CI = confidence interval; FTND = Fagerström Test for Nicotine Dependence; NA = Not Applicable; NIHSS = National Institute of Health Stroke Scale; NRT = Nicotine Replacement Therapy; QSU = Questionnaire on Smoking Urges; SE = standard error. Bolded line represents the Primary exposure variable of interest. Non-bolded lines represent the covariates that are adjusted for in the model.

non-insular damage on average responded neutrally to the questions, while those with insular damage moderately disagreed. The within-group responses did not change from immediately after stroke (T1) to 3 months post-stroke (T2), suggesting feelings regarding urge in the hospital were maintained even after participants were discharged to their home environment. Considering only participants who quit smoking from discharge through T2 (*n* = 60), those with insular damage experienced significantly less and virtually no urges (*n* = 22, mean QSU = 1.54, *SD* = 1.03) at T2 relative to those with non-insular damage (*n* = 38, mean QSU = 2.22, *SD* = 1.37) (*p* = .05). This suggests the persistence of some withdrawal symptoms beyond 3 months in non-insular damaged abstainers.¹⁷ These findings, although subjective, provide some evidence that insular damage is related to acute and long-term elimination of cravings. In addition, the possibility that feelings obtained in the hospital care setting are predictive of future out-of-hospital behaviors may point to the inpatient setting as a suitable atmosphere for intervention. This is consistent with findings from a systematic review demonstrating the effectiveness of smoking cessation counseling for hospitalized smokers given outpatient support for at least 1 month post-discharge.³⁰

Numerous circumstances may explain the decreases in urge scores in the non-insular damaged group. Acute lesions in the mesocorticolimbic structure, parts of which have been implicated in urge and withdrawal, may disrupt the addiction pathway in mechanisms independent of the insula.^{4,29,31–36} We partially addressed this issue by accounting for mesocorticolimbic infarctions in the adjusted model, which did not alter the effect estimate for insular damage. The possibility that damage to a functionally connected region exacerbates this effect is also feasible. Also, because the non-insular territory is much larger than the insula itself, the likelihood of there being dense interconnections between the known areas of addiction and other

regions is possible. Nonetheless, participants with insular damage still had a greater reduction than those with non-insular damage. Since insular damage was categorized as any versus none, a participant with a tiny insular infarct may have responded differently than someone with a larger area of infarction. The difference between exposure groups may have been more prominent if we would have been able to evaluate only patients with isolated complete insular lesions, as demonstrated in controlled experiments using animal models.^{37,38} This phenomenon, however, is rare given the complex vasculature of the brain, location(s) of occlusion, and timing of therapy.

The mechanism of insular involvement in reducing urge and eliminating cravings remains not fully understood. It is important to note that this study merely demonstrates a correlation of insular activity with urge and does not prove a causal role for the insula in mediating cravings. It is possible that our findings are simply downstream effects of decreased withdrawal symptoms,¹⁷ thus eliminating withdrawal-induced cravings. On the other hand, it may be that the insula suppresses cue-induced cravings (an urge brought on by an environmental trigger), consequently reducing the symptoms of withdrawal. A distinction between cue- and withdrawal-induced urges is warranted to better understand the temporality of the insula's involvement in the neurobiological mechanism responsible for nicotine addiction, which would help scientists map brain regions to certain characteristics of addiction and ultimately be used for targeting interventions.

This prospective cohort study is the largest human study to date examining the relationship between insular cortex lesions and smoking addiction, but some limitations should be mentioned. The QSU-brief is a self-reported subjective measure of smoking urges and no objective corroboration was performed. This continuous measure, unlike other

studies that assess the FTND¹⁸ and dichotomous outcomes,^{9,15,16,39} is sensitive to changes in urge regardless of smoking status and allows for the evaluation of the magnitude of change given the exposure status, which is relevant since urge can range in severity. Retrospective assessments (T0) of the QSU-brief, FTND and intention to quit may have been subject to recall error considering participants recent brain injury or reflective of their current feelings at T1, although we attempted to minimize this bias by assessing this measure soon after the injury rather than waiting for complete recovery. Nevertheless, this investigation filled these gaps from previous studies and controlled for several other influential factors including stroke severity, NRT use and concurrent mesocorticolimbic infarctions. Although NIHSS score was statistically higher in insular damaged participants, the difference may not be clinically meaningful, as scores below 15 are generally considered less severe. The possibility that more severe strokes contributed to changes in the QSU should not be excluded. The higher proportion of concurrent mesocorticolimbic infarctions in the insular damaged group is likely explained by their adjacent positioning, whereas such infarctions in the non-insular damaged group are less likely due to the larger territory. After adjusting for these variables, however, effect estimates remained similar to the unadjusted model, not suggestive of confounding. As the regions affected by the stroke are likely random and unknown to the patient, exposure status should not have mediated one's intention to give false information. The small number of insular damaged patients limited our ability to conduct sub-analyses with adequate power. Identifying partial lesions to specific regions, particularly the insular cortex, would have allowed us to assess exposure-response and potentially identify specific portions of the insula (anterior vs. posterior, medial vs. lateral, right vs. left, granular vs. agranular) that may be driving the observed effect. Finally, results of this study may not be generalizable to all cigarette smokers since those who experience a stroke are likely to be less "healthy" than other smokers.

Our findings of an immediate and sustained reduction in cigarette urges among smokers with insular cortex damage validate the growing literature suggesting the insula as a neurosubstrate involved in the maintenance of cigarette smoking. Future preclinical and clinical studies should employ similar techniques to examine the effect of insular adaptations on other behavioral and physiological changes as well as with other addictions. If such findings support the insula—or a specific insular sub-region—as a safe and effective "switch" for controlling smoking urges, it may be a novel target for effective therapeutic interventions that achieve long-term smoking cessation. Pharmacologically, chemical therapies may target neurotransmitter receptors that are expressed within the insula. Invasively, deep brain stimulation may assist by providing localized stimulation to the insula, delivering a dopamine-like response, and thus a feeling of euphoria without the harms of a cigarette.⁴⁰ Non-invasively, stimulation of the brain using transcranial magnetic stimulation may also be effective by generating a brief, high-intensity electric shock between two electrodes placed on the scalp.^{41,42}

Funding

This study was supported in part by the National Heart, Lung, and Blood Institute Preventive Cardiology Training Grant # T32 HL007937 and by the Clinical and Translational Science Institute Grant # UL1 RR024160 from the National Institutes of Health. The funders had no role in the study design, collection, analysis or interpretation of the data, writing the manuscript, or the decision to submit the article for publication.

Declaration of Interests

None declared.

Acknowledgments

The authors would like to thank Adam Kelly, MD (Department of Neurology, University of Rochester Medical Center) for his input and contributions in the early phases of study design and implementation, and the nurse practitioners and nursing staff at Strong Memorial Hospital, Highland Hospital, and Rochester General Hospital for assisting in the screening and identification of potentially eligible patients.

References

1. Jamal A, Homa DM, O'Connor E, et al. Current cigarette smoking among adults - United States, 2005-2014. *MMWR Morb Mortal Wkly Rep*. 2015;64(44):1233-1240.
2. World Health Organization. Tobacco, Data and Statistics. 2016. www.euro.who.int/en/health-topics/disease-prevention/tobacco/data-and-statistics. Accessed October 18, 2016.
3. World Health Organization. *Global Report on Trends in Tobacco Smoking 2000-2025*. Geneva, Switzerland: WHO; 2015.
4. Benowitz NL. Nicotine addiction. *Prim Care*. 1999;26(3):611-631.
5. US Department of Health and Human Services. *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General*. Atlanta, GA: Department of Health and Human Services/Centers for Disease Control and Prevention/National Center for Chronic Disease Prevention and Health Promotion/Office on Smoking and Health; 2010.
6. National Center for Chronic Disease P, Health Promotion Office on S, Health. Reports of the Surgeon General. *The Health Consequences of Smoking-50 Years of Progress: A Report of the Surgeon General*. Atlanta, GA: Centers for Disease Control and Prevention (US); 2014.
7. Cohen S, Lichtenstein E, Prochaska JO, et al. Debunking myths about self-quitting. Evidence from 10 prospective studies of persons who attempt to quit smoking by themselves. *Am Psychol*. 1989;44(11):1355-1365.
8. Fiore M, Jaen C, Baker T, et al. Treating tobacco use and dependence: 2008 update U.S. Public Health Service Clinical Practice Guideline. *Respir Care*. 2008;53(9):1217-1222.
9. Naqvi NH, Rudrauf D, Damasio H, Bechara A. Damage to the insula disrupts addiction to cigarette smoking. *Science*. 2007;315(5811):531-534.
10. Abdolahi A, Acosta G, Breslin FJ, Hemby SE, Lynch WJ. Incubation of nicotine seeking is associated with enhanced protein kinase A-regulated signaling of dopamine- and cAMP-regulated phosphoprotein of 32 kDa in the insular cortex. *Eur J Neurosci*. 2010;31(4):733-741.
11. Mansvelder HD, Fagen ZM, Chang B, Mitchum R, McGehee DS. Bupropion inhibits the cellular effects of nicotine in the ventral tegmental area. *Biochem Pharmacol*. 2007;74(8):1283-1291.
12. Nocente R, Vitali M, Balducci G, Enea D, Kranzler HR, Ceccanti M. Varenicline and neuronal nicotinic acetylcholine receptors: a new approach to the treatment of co-occurring alcohol and nicotine addiction? *Am J Addict*. 2013;22(5):453-459.
13. Naqvi NH, Bechara A. The insula and drug addiction: an interoceptive view of pleasure, urges, and decision-making. *Brain Struct Funct*. 2010;214(5-6):435-450.
14. Verdejo-Garcia A, Clark L, Dunn BD. The role of interoception in addiction: a critical review. *Neurosci Biobehav Rev*. 2012;36(8):1857-1869.
15. Suñer-Soler R, Grau A, Gras ME, et al. Smoking cessation 1 year post-stroke and damage to the insular cortex. *Stroke*. 2012;43(1):131-136.
16. Abdolahi A, Williams GC, Benesch CG, et al. Smoking cessation behaviors three months following acute insular damage from stroke. *Addict Behav*. 2015;51:24-30.
17. Abdolahi A, Williams GC, Benesch CG, et al. Damage to the insula leads to decreased nicotine withdrawal during abstinence. *Addiction*. 2015;110(12):1994-2003.
18. Gaznick N, Tranel D, McNutt A, Bechara A. Basal ganglia plus insula damage yields stronger disruption of smoking addiction than basal ganglia damage alone. *Nicotine Tob Res*. 2014;16(4):445-453.
19. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. *Br J Addict*. 1991;86(9):1119-1127.

20. Wray JM, Gass JC, Tiffany ST. A systematic review of the relationships between craving and smoking cessation. *Nicotine Tob Res.* 2013;15(7):1167–1182.
21. Doherty K, Kinnunen T, Militello FS, Garvey AJ. Urges to smoke during the first month of abstinence: relationship to relapse and predictors. *Psychopharmacology (Berl)*. 1995;119(2):171–178.
22. Killen JD, Fortmann SP. Craving is associated with smoking relapse: findings from three prospective studies. *Exp Clin Psychopharmacol.* 1997;5(2):137–142.
23. Taggar JS, Lewis S, Docherty G, Bauld L, McEwen A, Coleman T. Do cravings predict smoking cessation in smokers calling a national quit line: secondary analyses from a randomised trial for the utility of ‘urges to smoke’ measures. *Subst Abuse Treat Prev Policy.* 2015;10:15.
24. Dawkins L, Powell JH, Pickering A, Powell J, West R. Patterns of change in withdrawal symptoms, desire to smoke, reward motivation and response inhibition across 3 months of smoking abstinence. *Addiction.* 2009;104(5):850–858.
25. National Institutes of Health. National Institute of Neurological Disorders and Stroke. Stroke Scale. 1989. www.ninds.nih.gov/doctors/NIH_Stroke_Scale.pdf. Accessed May 14, 2014.
26. Tong DC, Yenari MA, Albers GW, O’Brien M, Marks MP, Moseley ME. Correlation of perfusion- and diffusion-weighted MRI with NIHSS score in acute (<6.5 hour) ischemic stroke. *Neurology.* 1998;50(4):864–870.
27. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009;42(2):377–381.
28. Cox LS, Tiffany ST, Christen AG. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. *Nicotine Tob Res.* 2001;3(1):7–16.
29. Naqvi NH, Bechara A. The hidden island of addiction: the insula. *Trends Neurosci.* 2009;32(1):56–67.
30. Rigotti NA, Munafo MR, Stead LF. Smoking cessation interventions for hospitalized smokers: a systematic review. *Arch Intern Med.* 2008;168(18):1950–1960.
31. Dani JA, De Biasi M. Cellular mechanisms of nicotine addiction. *Pharmacol Biochem Behav.* 2001;70(4):439–446.
32. Koob GF, Volkow ND. Neurocircuitry of addiction. *Neuropsychopharmacology.* 2010;35(1):217–238.
33. Volkow ND, Fowler JS. Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex. *Cereb Cortex.* 2000;10(3):318–325.
34. Goldstein RZ, Volkow ND. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *Am J Psychiatry.* 2002;159(10):1642–1652.
35. Cami J, Farré M. Drug addiction. *N Engl J Med.* 2003;349(10):975–986.
36. Berke JD, Hyman SE. Addiction, dopamine, and the molecular mechanisms of memory. *Neuron.* 2000;25(3):515–532.
37. Contreras M, Ceric F, Torrealba F. Inactivation of the interoceptive insula disrupts drug craving and malaise induced by lithium. *Science.* 2007;318(5850):655–658.
38. Forget B, Pushparaj A, Le Foll B. Granular insular cortex inactivation as a novel therapeutic strategy for nicotine addiction. *Biol Psychiatry.* 2010;68(3):265–271.
39. Bienkowski P, Zatorski P, Baranowska A, Ryglewicz D, Sienkiewicz-Jarosz H. Insular lesions and smoking cessation after first-ever ischemic stroke: a 3-month follow-up. *Neurosci Lett.* 2010;478(3):161–164.
40. Ostergard T, Miller JP. Deep brain stimulation: new directions. *J Neurosurg Sci.* 2014;58(4):191–198.
41. Yang LZ, Yang Z, Zhang X. Non-invasive brain stimulation for the treatment of nicotine addiction: potential and challenges. *Neurosci Bull.* 2016;32(6):550–556.
42. Salling MC, Martinez D. Brain stimulation in addiction. *Neuropsychopharmacology.* 2016;41(12):2798–2809.