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Short communication

Implications of insular cortex laterality for treatment of nicotine addiction

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ABSTRACT

Background: Damage to the insula disrupts nicotine-induced cravings and is associated with greater odds of cessation. The role of laterality in regulating these changes is unclear. Neuroimaging studies in cigarette smokers show left hemispheric activation during a period of forced withdrawal and right hemispheric activation after having just smoked. Among current smokers hospitalized for stroke involving their insula, we compared left versus right insular damage and its effect on smoking outcomes.

Methods: A total of 37 smokers hospitalized with unilateral insular strokes (14 right, 23 left) were administered questionnaires to assess urge (Questionnaire on Smoking Urges) before (retrospectively) and during hospitalization and 3 months post-stroke, withdrawal during hospitalization (Wisconsin Smoking Withdrawal Scale), and prolonged abstinence at 3 months post-stroke. Crude and adjusted linear regression models were performed controlling for baseline covariates.

Results: Right and left insular-damaged smokers experienced a significant decrease in urge from baseline to hospitalization and three-month follow-up ($p < 0.01$). Smokers with left-sided insular infarcts relative to right-sided experienced a larger decrease in acute urge (adjusted $\beta = -1.16$, 95% CI: −2.59, 0.27, $p = 0.11$) but not chronically (adjusted $\beta = -0.06$, 95% CI: −1.53, 1.40, $p = 0.93$). Left-sided insular damage was also associated with significantly fewer and less severe withdrawal symptoms during hospitalization (adjusted $\beta = -3.52$, 95% CI: −7.01, −0.04, $p = 0.05$). No differences were noted between groups for prolonged abstinence ($p = 0.50$).

Conclusions: Left insular adaptations are suggestive to have an impact on acute changes in urge and withdrawal more so than the right insula, however lateral asymmetries did not exist for long-term changes.

1. Introduction

Chronic users of drugs of abuse are often susceptible to misuse because of a desensitized dopaminergic reward system. Consequently, higher doses are required to achieve the euphoric rewarding effects. These neuroadaptations to brain reward and circuitry result in progressive, uncontrollable drug-taking behavior known as addiction (Benowitz, 1999). While nearly 70% of adult smokers want to quit, attempts are often unsuccessful due in part to the physiological withdrawal symptoms and environmental cues associated with smoking. Even among smokers taking pharmacotherapy to aid in smoking cessation, only about 25% achieve six-month abstinence (Fiore et al., 2008). Thus, a deeper understanding of the brain regions responsible for regulating the key features of addiction – namely urge and withdrawal (APA, 2013) – is necessary to help guide targeted therapies.

Studies on addiction and consequently therapeutic areas have historically focused on regions within the mesocorticolimbic reward pathway. The insular cortex, a region located deep within the sylvian fissure between the temporal and frontal lobes, has received increased attention for its involvement in addictive behaviors yet is not in this critical pathway. Known for receiving interoceptive signals and its involvement in self-awareness (Craig, 2010), recent animal (Forget et al., 2010) and human studies (Naqvi et al., 2007; Suner-Soler et al., 2012; Abdolahi et al., 2015a) have shown controlled insular inactivation and stroke-induced damage, respectively, to influence drug use and its characteristics. For example, in a study comparing current smokers hospitalized for acute ischemic stroke with and without insular involvement and followed for three months, we found that smokers with insular lesions had significantly lower withdrawal scores during hospitalization (Abdolahi et al., 2015b) and a greater decrease in urge

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scores from pre-stroke to hospitalization and three months post-stroke relative to smokers with non-insular lesions (Abdolahi et al., 2017). Thus, it appears that insular damage to some extent reverses addictive behaviors related to smoking and addiction, suggesting drug-induced sensitization of the interoceptive insula system (Droutman et al., 2015; Sutherland et al., 2013). In this manner we theorize that the insula serves as a link between the conditioned stimuli and physiological states such as urge, translating into progressive and impulsive drug-taking behaviors.

Although behavioral and neuroimaging studies have demonstrated consistent associations between insular activity and drug dependence, few have differentiated between the right and left insula on regulating addictive behaviors. Brain lateralization is the propensity for certain cognitive processes to be localized or more dominant in one hemisphere over the other, a concept that is important for understanding disease mechanisms and therapeutic strategies. A recent review of published reports examining brain activation using functional magnetic resonance imaging (MRI) showed consistent left hemispheric activation during cue-induced drug craving for alcohol and cocaine. For nicotine, interestingly, laterality was dependent on state of withdrawal, such that smokers who had some amount of withdrawal before testing showed left hemisphere activation while those who were satiated (having just smoked) exhibited right hemisphere activation (Gordon, 2016). Specific to the insula, active cigarette smoking has been associated with enhanced reactivity in the right insula (Janes et al., 2017) while showing convergent structural decreases in the left insula (Sutherland et al., 2016). We sought to expand on these findings by investigating whether damage to the left versus right insular cortex resulted in a greater reduction in subjective levels of urge and withdrawal in a cohort of cigarette smokers hospitalized for acute ischemic stroke involving the insular cortex.

2. Materials and methods

2.1. Study population

Data were derived from a three-month prospective cohort study of 156 adult active cigarette smokers hospitalized for acute ischemic stroke (Abdolahi et al., 2015a). A subset of participants with cerebral infarctions involving the insular cortex (n = 38) were eligible for the current analysis. The unit Nurse Practitioner evaluated and confirmed decisional and mental capacity for each participant. This study was approved by each medical center's institutional review board.

2.2. Laterality exposure assessment

Acute ischemic strokes involving the insula were characterized by laterality (right or left) by neuroradiologists using standard of care computed tomography and diffusion weighted MRI (Supplemental Fig. 1). If available, follow-up fluid attenuated inversion recovery MRI sequence was used to verify initial MRI findings. One participant with a bilateral insular stroke was excluded to avoid exposure misclassification, resulting in a final sample size of n = 37. Size of the infarction was quantified by severity of stroke using the National Institutes of Health Stroke Scale (NIHSS) score (National Institutes of Health, 2003), a surrogate measure for lesion volume in acute ischemic stroke patients ($r = 0.96$, $p < 0.001$) (Tong et al., 1998).

2.3. Ascertainment of end points

Study procedures to ascertain endpoints have been described previously (Abdolahi et al., 2015b, 2017). In summary, subjective levels of urge and withdrawal were assessed at various time points throughout the study. The Questionnaire of Smoking Urges (QSU)-brief (Cox et al., 2001) was administered during index hospitalization to retrospectively quantify level of urge based on feelings *before* the stroke (T0, baseline), during index hospitalization to measure *current* level of urge following the stroke (T1, hospitalization), and approximately 90 days after the date of stroke (T2, follow-up). The Wisconsin Smoking Withdrawal Scale (WSWS) (Welsch et al., 1999) was administered during hospitalization (T1), a period of forced abstinence. We did not investigate cessation outcomes since it is a behavior (not a feeling) that can be influenced by social, situational, and environmental factors that were not accounted for in our model.

2.4. Statistical analysis

Baseline characteristics of participants were described using relative frequencies for categorical measures and means and standard deviations (SD) for continuous measures. One-way ANOVA tests compared mean QSU scores between time points within groups. Linear regression analyses were performed with ΔQSU-brief (from T0 to T1 and T2) and WSWS as continuous dependent variables. Variables that have been previously associated with insular damage (Abdolahi et al., 2015b, 2017) and are theoretical risk factors for the outcome were controlled for in multivariable analyses, including baseline cigarettes per day, NIHSS score (NIH), concurrent acute mesocorticolimbic infarction, and intention to quit (prior to stroke) in the next month with an attempt in the past year (asked retrospectively). Crude and adjusted beta (β) coefficients and 95% confidence intervals (CI) were calculated. Due to the modest sample size of this subset, inferences were made based on magnitude of effect estimates (β) more so than statistical significance. Prolonged abstinence from hospital discharge to three-month follow-up was also compared between groups. All statistical procedures were performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC).

3. Results

Of the 37 unilateral insular stroke patients, 14 (37.8%) were classified as having left insular infarcts and 23 (62.2%) with right insular infarcts. Sample characteristics, described in Supplemental Table 1, were well balanced between exposure groups with respect to demographics, baseline nicotine dependence, stroke attributes, and intention to quit prior to the stroke ($p > 0.05$). The difference in baseline number of cigarettes per day between groups is explained by one very heavy smoker in the left insular damaged group (removing this individual, $p = 0.06$). There was also a notably higher prevalence of concurrent mesocorticolimbic infarctions in the right insular-damaged group, although not statistically significant. Six participants were excluded from follow-up evaluation due to death (n = 3), losses to follow-up (n = 2), and subsequent stroke (n = 1).

No difference existed in average QSU-brief scores between groups at baseline ($p = 0.68$) (Fig. 1). At T1 and T2, both groups had a reduction in urge relative to baseline but more so for the left insular damaged group at T1. At T2, urge scores increased on average in the left group and decreased slightly in the right. One-way ANOVA tests showed significant differences between time points for left ($F = 31.9$, $p < 0.01$) and right ($F = 24.7$, $p < 0.01$) insular damaged groups. Taken together, single-sided insular stroke patients with left insular infarcts had on average a 1.20-point greater reduction in QSU-brief score acutely from baseline to T1 relative to those with right insular infarcts (95% CI: −2.46, 0.06) (Table 1). This association did not change after adjusting for covariates, including additional adjustments for age and sex. Chronic change from baseline to T2 did not reveal any differences between left and right insular damage. For withdrawal, measured at T1 during abstinence at the hospital (Table 1), participants with left sided insular damage had an average WSWS score that was 1.94 points lower than right sided insular damaged participants (95% CI: −5.20, 1.32). The association became significantly larger after adjusting for covariates ($\beta = -3.52$, 95% CI: −7.01, −0.04). Q-Q plots for all models showed normal distributions of the residuals, satisfying linear regression assumptions. Prolonged abstinence at T2 was achieved

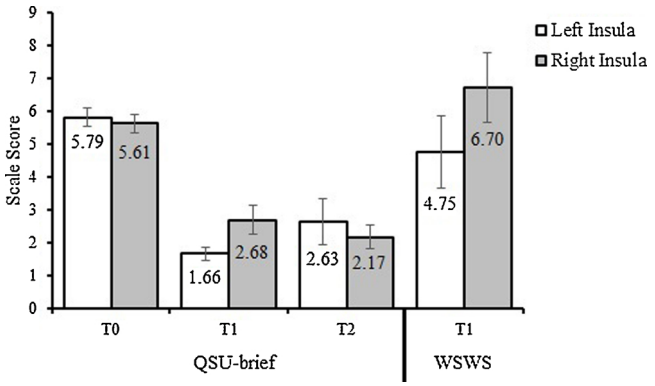

Fig. 1. Distribution of urge and withdrawal scores over time. Average crude Questionnaire of Smoking Urges (QSU)-brief and Wisconsin Smoking Withdrawal Scale (WSWS) scores (with standard error bars) at each time point, by exposure group.

Table 1
Linear regression models assessing change in QSU-brief scores and withdrawal symptom severity between left vs. right (control) insular infarcts during course of study.

	ΔQSU from Baseline				WSWS	
	T1 (n = 37)		T2 (n = 31)		T1 (n = 37)	
Model	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
Crude	−1.20 (−2.46, 0.06)	0.06	0.34 (−0.97, 1.65)	0.60	−1.94 (−5.20, 1.32)	0.23
Adjusted*	−1.16 (−2.59, 0.27)	0.11	−0.06 (−1.53, 1.40)	0.93	−3.52 (−7.01, −0.04)	0.05

QSU, Questionnaire on Smoking Urges; WSWS, Wisconsin Smoking Withdrawal Scale; CI, Confidence Interval.

* Adjusted for baseline cigs/day, National Institute of Health Stroke Scale score, mesocorticolimbic infarct, and baseline intent to quit.

in 63.6% of the left insular damaged group and 75.0% of the right insular damaged group (p = 0.50).

4. Discussion

This secondary analysis of prospective observational data examined the influence of insular laterality on smoking urge and withdrawal, as these are contributors to relapse vulnerability. We found that among current cigarette smokers with unilateral insular damage from stroke, both right and left insular damaged groups experienced a significant decrease in urge from baseline to hospitalization. Those with left sided infarcts experienced a larger decrease in acute but not chronic urge and had significantly fewer and less severe withdrawal symptoms during hospitalization compared to participants with right sided infarcts. No differences were noted between groups for prolonged smoking abstinence at three months follow-up. Although findings for acute changes in urge were not statistically significant at the 0.05 alpha level, the magnitude and direction of effect estimates produced from linear regression models are noteworthy given the shortcoming of small sample size.

Examining laterality, our findings suggest that the left hemispheric insula drives acute changes in urge and withdrawal more than the right but no differences were observed for long-term changes, including cessation. While evidence from functional MRI studies contradictorily shows both reduced (Sutherland et al., 2016; Fritz et al., 2014) and increased (Zhang et al., 2011) gray matter density in the left insula, these appeared to be dependent on timing of the study relative to last cigarette smoked. Testing done after a period of abstinence was associated with left insular activation, potentially explaining the higher sensitivity to decreases in urge and withdrawal after a stroke in the left insula in our sample of deprived smokers. The lack of an observed association from baseline to T2 may arise from the fact that participants were now in an environment with unrestricted access to nicotine, aligning with previous findings of reduced left insular gray matter density (Fritz et al., 2014) and non-left hemisphere activation among satiated smokers (Gordon, 2016). Using a similar stroke model retrospectively comparing smokers with right and left insular damage to those with non-insular damage, Naqvi et al. (2007) found significant associations between both right and left insular damage and having “a disruption of smoking addiction” measured several years later, suggesting laterality to have little or no impact on long-term drug desirability. Findings from that study cannot make inferences on short-term lateral asymmetries.

As handedness may be associated with hemispheric dominance for certain behaviors, we conducted a sensitivity analysis removing the three left handed subjects from the analysis, all in the right insular damaged group, and observed nearly identical effect sizes for acute change in urge (adjusted β = −1.16, 95% CI: −2.65, 0.34), chronic change in urge (adjusted β = −0.10, 95% CI: −1.47, 1.28), and withdrawal symptom severity (adjusted β = −3.86, 95% CI: −7.52, −0.19). A heterogeneous sample with more left-handed participants would be needed to more accurately assess the impact of handedness or territorial dominance as effect modifiers for regulating acute attributes of smoking.

Our findings provide new insights on insular laterality for smoking addiction but come with some limitations. The small number of participants with insular damage limited our study power for multivariate analyses and would not allow for meaningful conclusions to examine dichotomous outcomes. Since the extent of insular damage was not classified, a participant with a small infarct may have responded differently than someone with a larger area of infarction. Observed differences, however, may have been more prominent if we were able to evaluate patients with isolated insular lesions, as done in animal models (Forget et al., 2010) but rare to find in a human stroke model. The study endpoints were self-reported measures with no objective corroboration. Retrospective assessments (T0) may have been subject to recall error given participants recent brain injury or reflective of their current feelings at T1; this was minimized by assessing measures soon after the injury to avoid further mix of feelings later on.

5. Conclusions

The ability of the insula to reduce urge and eliminate cravings has been established, and our findings further suggest that the left insula may play a stronger role in driving acute desire of drug use than the right insula. It may be that damage or functional changes to the left insula suppresses cravings brought on by environmental triggers, consequently reducing withdrawal symptoms, or it could work by directly eliminating withdrawal-induced cravings. The reason for left asymmetries noted in this study and others are not well understood and should be studied in future investigations. For example, preclinical and clinical research may want to consider the integrity of the corpus callosum, the structure that facilitates communication between the two hemispheres, as a mediator of observed hemispheric differences. This deeper understanding of the mechanism through which the brain wires addiction could lead to pharmacological therapies that target neurotransmitter receptors expressed in the insula or techniques such as deep brain stimulation (Ostergard and Miller, 2014) and transcranial magnetic stimulation (Salling and Martinez, 2016).

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Contributors

Dr. Abdolahi contributed to the design, acquisition of data, analysis and interpretation of data, and drafting of the manuscript. Dr. Williams contributed to the critical review and editing of the addiction components of the manuscript. Dr. van Wijngaarden contributed to the critical review and editing of the methodology and statistical analysis of the manuscript. All authors have approved the final version of the article.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2019.04.017.

References

Abdolahi, A., Williams, G.C., Benesch, C.G., Wang, H.Z., Spitzer, E.M., Scott, B.E., Block, R.C., van Wijngaarden, E., 2015a. Smoking cessation behaviors three months following acute insular damage from stroke. Addict. Behav. 51, 24–30.

Abdolahi, A., Williams, G.C., Benesch, C.G., Wang, H.Z., Spitzer, E.M., Scott, B.E., Block, R.C., van Wijngaarden, E., 2015b. Damage to the insula leads to decreased nicotine withdrawal during abstinence. Addiction 110, 1994–2003.

Abdolahi, A., Williams, G.C., Benesch, C.G., Wang, H.Z., Spitzer, E.M., Scott, B.E., Block, R.C., van Wijngaarden, E., 2017. Immediate and sustained decrease in smoking urges after acute insular cortex damage. Nicotine Tob. Res. 19, 756–762.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, fifth ed. DSM-5®), Arlington, Virginia.

Benowitz, N.L., 1999. Nicotine addiction. Prim. Care 26, 611–631.

Cox, L.S., Tiffany, S.T., Christen, A.G., 2001. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. Nicotine Tob. Res. 3, 7–16.

Craig, A.D., 2010. The sentient self. Brain Struct. Funct. 214, 563–577.

Droutman, V., Read, S.J., Bechara, A., 2015. Revisiting the role of the insula in addiction. Trends Cogn. Sci. 19, 414–420.

Fiore, M.C., Jaén, C.R., Baker, T.B., Bailey, W.C., Benowitz, N.L., Curry, S.J., Dorfman, S.F., Froelicher, E.S., Goldstein, M.G., Healton, C.G., Henderson, P.N., Heyman, R.B., Koh, H.K., Kottke, T.E., Lando, H.A., Mecklenburg, R.E., Mermelstein, R.J., Mullen, P.D., Orleans, C.T., Robinson, L., Stitzer, M.L., Tommasello, A.C., Villejo, L., Wewers, M.E., Murray, E.W., Bennett, G., Heishman, S., Husten, C., Morgan, G., Williams, C., Christiansen, B.A., Piper, M.E., Hasselblad, V., Fraser, D., Theobald, W., Connell, M., Leitzke, C., 2008. Treating Tobacco Use and Dependence: 2008 Update U.S. Public Health Service Clinical Practice Guideline. US Department of Health and Human Services, Public Health Service, Rockville, Maryland.

Forget, B., Pushparaj, A., Le Foll, B., 2010. Granular insular cortex inactivation as a novel therapeutic strategy for nicotine addiction. Biol. Psychiatry 68, 265–271.

Fritz, H.C., Wittfeld, K., Schmidt, C.O., Domin, M., Grabe, H.J., Hegenscheid, K., Hosten, N., Lotze, M., 2014. Current smoking and reduced gray matter volume-a voxel-based morphometry study. Neuropsychopharmacology 39, 2594–2600.

Gordon, H.W., 2016. Laterality of brain activation for risk factors of addiction. Curr. Drug Abuse Rev. 9, 1–18.

Janes, A.C., Gilman, J.M., Radoman, M., Pachas, G., Fava, M., Evins, A.E., 2017. Revisiting the role of the insula and smoking cue-reactivity in relapse: a replication and extension of neuroimaging findings. Drug Alcohol Depend. 179, 8–12.

Naqvi, N.H., Rudrauf, D., Damasio, H., Bechara, A., 2007. Damage to the insula disrupts addiction to cigarette smoking. Science 315, 531–534.

National Institutes of Health, 2003. National Institute of Neurological Disorders and Stroke. Stroke Scale. https://www.stroke.nih.gov/documents/NIH_Stroke_Scale_508.

Ostergard, T., Miller, J.P., 2014. Deep brain stimulation: new directions. J. Neurosurg. Sci. 58, 191–198.

Salling, M.C., Martinez, D., 2016. Brain stimulation in addiction. Neuropsychopharmacology 41, 2798–2809.

Suner-Soler, R., Grau, A., Gras, M.E., Font-Mayolas, S., Silva, Y., Dávalos, A., Cruz, V., Rodrigo, J., Serena, J., 2012. Smoking cessation 1 year poststroke and damage to the insular cortex. Stroke 43, 131–136.

Sutherland, M.T., Carroll, A.J., Salmeron, B.J., Ross, T.J., Hong, L.E., Stein, E.A., 2013. Down-regulation of amygdala and insula functional circuits by varenicline and nicotine in abstinent cigarette smokers. Biol. Psychiatry 74, 538–546.

Sutherland, M.T., Riedel, M.C., Flannery, J.S., Yanes, J.A., Fox, P.T., Stein, E.A., Laird, A.R., 2016. Chronic cigarette smoking is linked with structural alterations in brain regions showing acute nicotine drug-induced functional modulations. Behav. Brain Funct. 12, 16.

Tong, D.C., Yenari, M.A., Albers, G.W., O'Brien, M., Marks, M.P., Moseley, M.E., 1998. Correlation of perfusion- and diffusion-weighted MRI with NIHSS score in acute (< 6.5 hour) ischemic stroke. Neurology 50, 864–870.

Welsch, S.K., Smith, S.S., Wetter, D.W., Jorenby, D.E., Fiore, M.C., Baker, T.B., 1999. Development and validation of the wisconsin smoking withdrawal scale. Exp. Clin. Psychopharmacol. 7, 354–361.

Zhang, X., Salmeron, B.J., Ross, T.J., Geng, X., Yang, Y., Stein, E.A., 2011. Factors underlying prefrontal and insula structural alterations in smokers. Neuroimage 54, 42–48.