ABSTRACT

Introduction: The main objective of this study was to elucidate the importance of the basal ganglia (BG) and insula (INS) for nicotine addiction and smoking behavior.

Methods: We used a lesion study examining the effects of BG and INS damage on changes in smoking behavior and nicotine dependence over time in a prospective manner. We studied whether combined BG and INS damage yields more substantial disruption of smoking and nicotine dependence than damage to the BG alone and compared with damage to other brain regions outside the BG and INS (brain-damaged comparison [BDC] group). We obtained neuroanatomical and behavioral data for 63 neurological patients with stroke at 1 month after onset and at 3-, 6-, and 12-month follow-ups. All patients were smokers at lesion onset.

Results: The BG and BG + INS groups had significantly higher and more sustained rates of smoking cessation than patients with damage elsewhere. By 12 months after onset, only 14.3% of the patients in the BDC group were classified as nonsmokers. In the BG group, 37% were not smoking by the 12-month follow-up, and in the BG + INS group, smoking cessation was even more pronounced, as 75% of this group was not smoking at the 12-month epoch.

Conclusions: The findings show that damage to the BG alone can cause disruption of smoking addiction, and when BG damage is combined with INS damage, the disruption increases. The latter finding is consistent with the proposal that the INS has a key role in smoking addiction.

INTRODUCTION

Neurobiological theories of addiction explain the loss of willpower to resist drugs (including nicotine) in terms of abnormal activity among a network of neural systems involved in (a) implicit associations and (b) affective decisions. Implicit associations and impulsive, automatic, behaviors are dependent on a neural system involving the basal ganglia (BG), especially the mesolimbic dopamine system (Everitt et al., 1999; Everitt & Robbins, 2005), which is critical for the incentive motivational effects of nonnatural rewards (e.g., nicotine) as well as natural rewards (e.g., food) (Balleine & Dickinson, 2000; Di Chiara et al., 1999; Everitt et al., 1999; Koob & Le Moal, 2001; Robbins, Cador, Taylor, & Everitt, 1989; Robinson & Berridge, 1993). This system is also known to exaggerate the incentive value of rewards (Bechara, 2005) and exhibit greater activation in anticipation of immediate relative to delayed rewards (Luo, Ainslie, Giragosian, & Monterosso, 2011) in individuals with substance abuse.

Recent evidence has pointed to the insular cortex as a third neural system critical for smoking addiction (Heffy, Silver, & Silver, 2011; Naqvi, Rudrauf, Damasio, & Bechara, 2007). The insula (INS) is crucial for the representation of bodily states, contributes to conscious emotional feelings (Craig, 2011; Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004; Damasio, 1994), and is indicated in risk prediction (Preuschoff, Quartz, & Bossaerts, 2008). Consistent with these findings, it was proposed that the insular cortex, which is anatomically and physiologically connected to the viscera, may respond to physiological signals generated by homeostatic perturbations during withdrawal, deprivation, stress, and so forth (Paulus, 2007). This insular response may influence the balance between the impulsive and decision-making systems, thereby intensifying activity of the impulsive system and/or disabling the ability of the prefrontal cortex (PFC) to exert self-control (Naqvi & Bechara, 2009; Noel, Brevers, & Bechara, 2013). This hypothesis is consistent with the proposed role of the INS in...
regulating mood, willed action, and behavioral control (Ibanez, Gleichgerrcht, & Manes, 2010), as well as evidence for both differences in insular volumes in drug-dependent individuals (Franklin et al., 2002) and the high density of nicotinic receptors in the INS and anterior cingulate cortex versus other cortical areas (Picard et al., 2013).

In the wake of our 2007 discovery that damage to the INS disrupts addiction to cigarette smoking (Naqvi et al., 2007), one of the most pressing issues was to investigate this finding in a prospective manner. Thus, this was one of the primary goals of this study, and this is the first investigation into the effect of brain damage on smoking behavior in real-time at 1-year follow-up in patients whom we have followed since the onset of their brain damage.

In that earlier study where we reported disruption of smoking addiction after INS damage, we noted near-significant effects in the putamen. On that basis we argued that the key effect relies within the INS, while the BG (specifically the putamen) effect was a “bystander” effect. However, given the small sample size in that study, the role of the BG could not be ruled out. Since isolated INS lesions are rare and most also involve damage to the BG (specifically the putamen), another primary goal of this study was to examine the extent to which smoking would be disrupted by lesions to the BG alone versus lesions to the BG plus INS. As the INS is anatomically adjacent to the BG, comparing the effects of damage to the BG alone versus BG plus INS on smoking addiction would be the best practical approach available to elucidate the contribution of both the INS and BG to addictive behavior. We tested the hypotheses that (a) damage to the BG alone would disrupt smoking addiction and (b) damage involving the BG plus INS would be more effective in disrupting smoking addiction than damage involving the BG alone.

**MATERIALS AND METHODS**

We identified neurological patients who were smoking at the time of lesion onset. In order to observe potential changes in addiction behavior over time, prospectively, we enrolled patients immediately following acute stroke. Examining the effects of lesion location on smoking cessation and smoking experience over the span of 1 year enabled us to correlate disruption of smoking addiction to damage in specific regions of the brain.

**Participants**

The participants were 63 neurological patients who were enrolled prospectively and were blind to the hypotheses of the study. Patients were admitted to the University of Iowa Hospitals and Clinics between October 2009 and July 2011 and were selected based on their history of smoking at lesion onset and number of cigarettes smoked per day (at initial screening and at each subsequent follow-up). Furthermore, patients who reported smoking in the month prior to a given follow-up were classified as “smokers.” Patients who reported not smoking in the past month (point prevalence abstinence) were classified as “past smokers” (e.g., patients who were not smoking in the 30 days prior to their 1-month follow-up were classified as “past smokers” at 1 month; patients who were “past smokers” at 1 month but then had smoked at any point prior to their 3-, 6-, or 12-month follow-up were classified as “smokers” at that follow-up, even if they had episodes of abstinence from smoking during that period). In other words, if patients did not quit at 1 month or 3 months, but quit later and they were found abstinent at 12-month follow-up, we also classified them as “past smokers” only at that timepoint. Single use of a cigarette was not considered a relapse during follow-up. Criteria for relapse included using cigarettes more than 2 times in the month prior to follow-up. For example, one patient reported trying to smoke a cigarette and being disgusted with the experience. This patient was not considered as having relapsed.

**Lesion Analysis**

The neuroanatomical analysis was based on computer-ized axial tomography (CT) or magnetic resonance (MR)
data obtained acutely after stroke. The scans were performed according to the Department of Neurology protocol for admission of suspected stroke. A physician blind to the hypotheses and objectives of the current study performed lesion assessment. We analyzed axial sections of the clinical magnetic resonance imaging (MRI) scans for the presence of ischemic lesion and, when available, utilized diffusion and perfusion scans for more accurate lesion localization. CT scans were used when MRI was contraindicated. Prior to data analysis, we classified the participants as belonging to one of three groups based on the presence of lesions in the BG, INS, or areas outside of the two. This resulted in three groups: (a) “BG” group: patients with damage to the nucleus accumbens, caudate nucleus, putamen, and/or globus pallidus, but not the INS; (b) “BG plus INS (BG + INS)” group: patients with damage that included the INS plus any part of the BG; and (c) “brain-damaged comparison (BDC)” group: patients with damage outside both the BG and INS. Localization of brain damage was further classified into specific cortical lobes, cerebellum, and brainstem. All of the participants were free of damage to the PFC, including the lateral regions of the PFC, as all the cases with middle cerebral artery strokes (which included the INS and BG) did not extend anteriorly to include the lateral PFC regions. The PFC, in general, is thought to be important for guiding higher order behavior and decision making (Bechara, Damasio, Tranel, & Damasio, 1997; Rogers et al., 1999).

RESULTS

Demographic and Neuroanatomical Data

We identified 63 cigarette smokers who had acquired brain damage as a result of a stroke. Nine of these participants had BG damage (without INS involvement), 8 had BG plus INS damage, and 46 had damage outside the BG and INS. Demographic characteristics of the three groups are displayed in Supplementary Table 1. There were no significant differences between the groups in terms of age (p = .30), sex (p = .36), handedness (p = .40), years of education (p = .86), years smoking (p = .79), cigarettes per day (p = .61), or lesion side (p = .47). There were significant differences in lesion etiology (χ²(4, N = 63) = 21.224, p < .001), specifically between the BG + INS and BDC groups (χ²(2, N = 54) = 18.949, p < .001), with the former having a higher percentage of participants with hemorrhagic lesions. There were no significant differences in stroke severity as assessed by the National Institutes of Health Stroke Scale (NIHSS) upon presentation (H = 4.25, p = .12).

Neuroanatomical characteristics of BG, BG + INS, and BDC participants are shown in Supplementary Tables 2–4. Representative brain images, from MR or CT scans, are shown in Figures 1 (BG) and 2 (BG + INS) (the image for one BG patient was not available). In accord with their grouping, the BG participants all had damage confined to the BG, while the BG + INS participants all had damage that included both the BG and INS.

Nicotine Dependence and Behavioral Changes in Smoking Addiction

Behavioral Changes

The BG and BG + INS groups had significantly higher rates and more sustained smoking cessation than participants with damage elsewhere in the brain. At 1 year, our timepoint of interest, we saw between-group differences in smoking status (χ²(2, N = 40) = 7.417, p = .02). This was driven by the differences between the BG + INS and BDC groups, who had nonsmoking rates of 75% and 25%, respectively (χ²(1, N = 30) = 7.549, p = .006). Patients with BG or BG + INS lesions had more profound disruption of smoking addiction at

Figure 1. Acute images from basal ganglia (BG) patients. Images are taken from the magnetic resonance imaging sequence that best represents the lesion. Lesions are indicated by an arrow or a circle (when lesion of interest may be difficult to discern).
BG + INS damage yields disruption of smoking addiction

At each timepoint (Figure 3). At 3 months, the number of smokers was 61.9%; this number rose to 73.7% at 6 months and 85.7% at 12 months. In the BG group, only 22.2% continued to smoke at 1 month, and the number of patients who had returned to or continued to smoke rose and stabilized at around 50%–62.5% at the 3-, 6-, and 12-month follow-ups. In the BG + INS group, smoking cessation was even more pronounced. Only 14.3% of the patients continued to smoke 1 month poststroke, and this figure rose slightly at 3 months (16.7%) and at 6 months (33.3%) as a few patients relapsed along the way, but for at least 6 months prior to the 12-month follow-up, some of these patients quit again, and the number of smokers dropped to 25% at the 12-month follow-up.

In collapsing data from all four follow-up epochs to create an “overall smoking status” variable, we found a significant difference for positive endorsement of smoking between groups ($\chi^2(2, N = 207) = 21.905, p < .001$) (Supplementary Table 5). In the BDC group, participants reported smoking 69.3% of the time, while the BG group reported positive 47.1% and the BG + INS group reported positive only 21.7%. Upon closer examination, both the BG and BG + INS groups had significantly fewer smoking endorsements than the BDC group ($\chi^2(1, N = 184) = 6.602, p = .014$) and ($\chi^2(1, N = 173) = 19.381, p < .001$)) in accord with our first hypothesis. In support of our second hypothesis, the cessation observed in the BG + INS group was even more pronounced than that of the BG group ($\chi^2(1, N = 57) = 3.780, p < .05$).

Participants with BG or BG + INS lesions had a higher probability of quitting and reporting abstinence at 1 year. Using logistic regression analyses, odds ratios for being a past smoker relative to BDC were increased for the BG and BG + INS groups. More specifically, 12 months following the stroke, there was a 3.60-fold increase (95% CI = 0.61–21.35, $n = 8$) for the BG group and an 18-fold increase (95% CI = 1.48–218.95, $n = 4$) for the BG + INS group in the odds of being a past smoker compared with the BDC group. Once again, the odds of quitting after BG + INS damage were higher than after BG damage alone.

Nicotine Dependence

There were no differences between the groups in nicotine dependence (FTND) scores prior to lesion onset ($H = 1.978, p = .372$). At 1 year, our timepoint of interest, we saw between-group differences in FTND scores ($H = 7.23, p = .027$). Both the BG and BG + INS groups had significantly lower FTND scores versus the BDC group ($U = 57, Z = −2.034, p = .046$ and $U = 20, Z = −2.204, p = .046$, respectively). All groups had decreased FTND scores immediately following lesion onset; however, the

![Figure 2](http://example.com/figure2.png)

**Figure 2.** Acute images from basal ganglia plus insula (BG + INS) patients. Images are taken from the magnetic resonance imaging sequence that best represents the lesion. Lesions are indicated by an arrow or a circle (when lesion of interest may be difficult to discern).

![Figure 3](http://example.com/figure3.png)

**Figure 3.** Positive smoking status over 1 year assessed at baseline and each subsequent follow-up.
highest FTND score belonged to the BDC group (Figure 4). Through each follow-up, the BDC group had the highest nicotine dependence score, while both the BG and BG + INS groups showed a stronger disruption of nicotine dependence. The BG + INS group was less nicotine dependent than the BG group. Of note, the BG and BG + INS groups remained in the “very low/ not dependent” category, with FTND scores less than 2. In collapsing data from all four follow-up epochs to create an “overall nicotine dependence” variable, we found a significant difference for nicotine dependence between groups (H = 23.43, p < .001) (Supplementary Table 5). In the BDC group, participants had an overall dependence score of 2.54 (2.59), while the BG group had a score of 1.21 (1.93) and the BG + INS group had a score of 0.29 (0.90). Upon closer examination, both the BG and BG + INS groups had significantly fewer smoking endorsements than the BDC group (U = 1,700, Z = −2.799, p = .005 and U = 703, Z = −4.231, p < .001) in accord with our first hypothesis. In support of our second hypothesis, the nicotine dependence in the BG + INS group was even lower than that of the BG group (U = 251.5, Z = −2.189, p = .029).

**Additional Analyses**

We sought to examine the effect of demographics and neurological characteristics on smoking behavior in univariate modeling. Using correlation analyses, we have observed that lesion severity (assessed by the NIHSS), lesion etiology, lesion laterality, prelesion FTND, and prelesion cigarettes per day were not correlated with nicotine dependence at any follow-up timepoint (p > .05) and thus not added as covariates in data analyses.

We have performed a series of analyses investigating the effects of lesions to various regions of the brain on point-prevalent abstinence at 1 year in the total sample and the BDC, BG, and BG + INS groups (Supplementary Table 6). More specifically, we determined the number of participants with damage to our regions of interest (e.g., frontal lobe, parietal lobe, cerebellum, etc.) and found no statistically significant impact of damage to any of the regions of interest on abstinence from smoking.

**DISCUSSION**

This is the first study to examine the importance of the BG and INS in a long-term prospective manner. The findings confirm the important role played by both the BG and the INS in smoking addiction in a human population, and they support the two key hypotheses in this study that (a) damage to the BG itself (and more specifically the putamen) disrupts smoking addiction and (b) damage to both the INS and the BG has an even more disruptive effect on smoking addiction than damage that involves the BG alone. The fact that the addition of INS damage increases the severity of this disruption of smoking addiction is consistent with our previous conclusion that the INS plays a key role in smoking addiction (Naqvi et al., 2007).

An obvious additional line of investigation is to explore the exclusive contribution of the INS to disruption of smoking addiction. Practically, it is very difficult to obtain isolated INS lesions in human stroke populations (because the strokes are usually small lacunar strokes that tend to fully resolve with recovery in the chronic epoch), but nonetheless obtaining cases of focal and sustained INS damage is possible, and this awaits follow-up studies. Of note, there is evidence from animal literature supporting insular control of nicotine taking and seeking behaviors (Forget, Pushparaj, & Le Foll, 2010; Pushparaj et al., 2013). Regardless of whether isolated INS lesions in human studies yield comparable or different results, the present results clearly show that damage that includes a combination of both the INS and the BG delivers the most reliable, severe, and long-lasting disruption of smoking addiction, thus supporting a conclusion regarding the influential role played by the INS in maintaining smoking addiction.

We note that the BG and BG + INS groups differed in smoking status and nicotine dependence. While there is evidence that those who undergo life-threatening medical events such as stroke, cancer diagnoses, and cardiovascular disease are likely to make at least some effort to quit smoking, the decrease in smoking behavior in the BG and BG + INS groups was much greater than in the BDC group (Bak et al., 2002; Froelicher et al., 2004; Sharp, Johansson, Fagerstrom, & Rutqvist, 2008). Smoking cessation was significantly higher in the BG and BG + INS groups relative to the BDC as seen in the higher overall positive endorsement of smoking throughout the 12 months after lesion onset. More importantly, the overall cessation in the BG + INS group was even stronger than that of the BG group. The stronger effect observed after combined BG + INS damage is rather conservative because several factors may undermine the observation of an even larger difference. First, the sample size is relatively small. In considering the nature of working with acute stroke patients, lesion location distribution and numbers of patients are not factors that can be well

---

**Figure 4.** Nicotine dependence over 1 year assessed at baseline and each subsequent follow-up.
controlled experimentally. Second, the BG damage by itself proved to have an effect and showing a stronger effect with INS damage may be subject to flooring effect. However, we note that this is not the first evidence arguing that the INS plays a role in smoking addiction. Rather, prior lesion studies, as well as several neuroimaging studies, revealed a prominent role for the INS in addiction (Ersche et al., 2011; Hefzy et al., 2011; Naqvi et al., 2007; Surer-Soler et al., 2012; Zhang et al., 2011). Altogether, this provides a strong support for the hypothesis that combined BG + INS damage exerts a more significant disruption of smoking addiction than BG damage alone, and this is primarily due to the important role that INS plays in smoking addiction.

While we have shown support for the role of the BG and INS in point prevalence abstinence, there are other interpretations that can be addressed. For example, perhaps damage to a neighboring region, or dysfunction in a projection target region connected to the INS and/or BG, caused disruption of smoking. The first possibility was addressed by the fact that we looked at the BG (putamen as a neighboring region to the INS), and we found that its damage does indeed play a role. Damage to adjacent areas on the lateral side (e.g., inferior parietal, superior temporal, or posterior frontal) is not likely to account for the findings, as many of the BDC patients had such damage but did not have disruption of smoking behavior. The other possibility in which damage to a functionally connected region may exacerbate or be the cause of the effect also remains feasible; one of our future goals is to determine whether damage in pathways leading to the INS or away from the INS also leads to disruption of smoking behavior.

To document further that point prevalence abstinence was not driven by lesions elsewhere, we performed a series of analyses investigating the effects of lesions to specific regions such as the frontal lobe, parietal lobe, occipital lobe, and brainstem on smoking behavior. There were no statistically significant results (Supplemental Table 6). No damage to brain regions other than the BG and INS had a significant effect on smoking status at the 1-year follow-up. This negative finding replicates similar results reported in earlier studies (Naqvi et al., 2007).

We acknowledge the limitations of self- and collateral reports, and studies examining the reliability of self- and/or collateral reports of smoking behavior are mixed. These reports may be inaccurate for several reasons. First, memory limitations may alter the ability of the participant and/or collateral to accurately report smoking behavior. Second, participants may underestimate smoking behavior due to perceived or actual pressure from family and/or medical professionals, especially in populations whose clinical diagnoses are impacted by their smoking behavior (Lewis et al., 2003; Martinez, Reid, Jiang, Einspahr, & Alberts, 2004; Woodward & Tunstall-Pedoe, 1992). Third, collaterals may not be cognizant of participants’ activities at all times. However, we would emphasize that in our unique population of neurological patients, the self-report measures that we collected on smoking behaviors are sufficiently accurate for the conclusions we reached for several reasons. First, while patients know that they had a stroke, they are entirely naïve about the specific neural region that should (or should not) affect their smoking behavior. More specifically, the patients do not have the insight or knowledge about the specific lesion that could alter their smoking behavior. They are not aware of the hypotheses we are testing or in which group they were placed. Therefore, inaccuracies in self-reported use would be expected to occur equally across all lesion groups, adding some noise to our results but, most importantly, not systematically affecting the self-report of one lesion group more so than any other. Second, this study did not involve a treatment; rather, the results are an incidental finding and the consequence of a stroke, so that there is no incentive for patients to provide inaccurate information after one type of a stroke but not another. Third, many participants reported quitting altogether, so there is no room for inaccuracies in self-reports (since other family members confirm their quitting). In addition, the absolute amount of cigarettes smoked is just one item in the battery of questions asked during each interview (results of which will be reported following subsequent analyses). As such, the likelihood of misreporting information specifically is low and expected to be equal among lesion patients. Finally, there are numerous examples in the literature supporting the accuracy of smoking status self-reports, and this method of collecting data on behavioral changes in neurological patients based on self-reports and on collateral information is a standard method in neuropsychology (Hatzianandrea et al., 1989; Patrick et al., 1994).

The finding that lesions involving the BG disrupt smoking is perhaps not surprising in light of almost three decades of research that has established a role for the striatum (and specifically ventral striatum) in behavioral addiction to many substances, including nicotine (Berridge & Robinson, 1998; Koob & Volkow, 2010; Stewart, de Wit, & Eikelboom, 1984; Wise & Bozarth, 1987). What is intriguing, however, is that although the major focus in addiction research has been on the nucleus accumbens as the key source for the motivation to seek drugs, the current results (Supplementary Table 2) show that damage to the dorsal striatum alone can disrupt the smoking habit. This is consistent with the work of Everitt and colleagues who have demonstrated in animal studies that after drug use becomes chronic, implicit associations and habits are formed, and the neural substrates mediating these automatic and habit behaviors are linked to the dorsal striatum (as opposed to the ventral striatum) (Everitt, Dickinson, & Robbins, 2001; Everitt, Morris, Obrien, & Robbins, 1991; Everitt et al., 1999; Everitt & Robbins, 2005). The other intriguing result is the establishment of the role of the INS in smoking addiction. While the underlying mechanisms of how the INS could participate in the process of addiction remains subject to intense investigations, especially in the neuroimaging field, we have proposed a hypothesis on how this may take place (Noel et al., 2013).

The current study enables us to understand regions of the brain involved in the development and maintenance of smoking cessation in an acute stroke population. Future studies should also determine whether these findings generalize to other addictive behaviors, including food, alcohol, and illicit substances, in light of the fact that research has established that addiction to these different substances is subserved by at least a common neural system linked to the BG and INS (Ersche et al., 2011; George & Koob, 2010; Tomasi et al., 2007; Wise & Bozarth, 1982; Wittmann, Leland, & Paulus, 2007). Interestingly, there were no notable changes in weight for any of the participants in the study. Although the rewards from food and smoking (or other drugs) have overlapping neural systems, when it comes to a behavioral change after
ACKNOWLEDGMENTS

The authors would like to thank Joel Bruss for assistance with the figures. All authors of the paper have fulfilled the criteria for authorship.

REFERENCES


