Received: 8 October 2018 | Revised: 24 February 2019 | Accepted: 2 March 2019
DOI: 10.1111/adb.12750

ORIGINAL ARTICLE

WILEY Addiction Biology SSA

Double jeopardy: Comorbid obesity and cigarette smoking are linked to neurobiological alterations in inhibitory control during smoking cue exposure

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Funding information
National Institute on Alcohol Abuse and Alcoholism, Grant/Award Number: K23AA023894; National Institute on Drug Abuse, Grant/Award Numbers: R01DA029845 and R01DA030394; National Institutes of Health, Grant/Award Numbers: K23AA023894, R01DA029845 and R01DA030394

Abstract
Obesity and cigarette smoking are two of the leading preventable causes of death in the United States. Research suggests that overlapping pathophysiology may contribute to obesity and nicotine use disorder (NUD), yet no studies have investigated the effect of obesity on neural response to reward stimuli in NUD. This study used arterial spin-labeled perfusion functional magnetic resonance imaging (fMRI) to examine neural responses during exposure to smoking versus nonsmoking cues in 79 treatment-seeking participants with NUD, 26 with normal weight, 28 with overweight, and 25 with obesity. Given that deficits in behavioral inhibitory control have been associated with both obesity and NUD, participants completed an affect-congruent Go/NoGo task to assess the effect of body mass index (BMI) on this construct in NUD. Analyses revealed that BMI was negatively associated with activation in the right dorsolateral prefrontal cortex (dlPFC) in response to smoking cues, with significantly reduced response in smokers with overweight and smokers with obesity compared with normal-weight smokers. In addition, greater commission errors on the Go/NoGo task were correlated with reduced neural response to smoking cues in the right dlPFC only among those with obesity. Together, these findings provide evidence that obesity in treatment-seeking NUDs is related to neurobiological alterations in inhibitory control over cue-potentiated behaviors, suggesting that smoking cessation may be more difficult in individuals with comorbid NUD and obesity than in those without, requiring treatment strategies tailored to meet their unique needs.

KEYWORDS
fMRI, inhibitory control, nicotine, obesity, smoking

1 | INTRODUCTION

Obesity and cigarette smoking are the two leading causes of preventable death in the United States.[1] Both cigarette smoking[2] and obesity (National Institutes of Health, 1998)[3] are linked to increased risk of cardiovascular diseases, cancers, and other chronic health conditions.[4] The negative health effects of cigarette smoking and obesity can shorten life by more than 10 years[5] and substantially impact productivity and public health costs.[6] Alarmingly, cigarette smoking and obesity lead to 10 times more deaths per year than the opioid epidemic ([5,7]; Services 2014). Comorbid cigarette smoking and high weight increase risk of all-cause mortality by more than four times that of lean individuals who have never smoked.[8] Despite these significant negative health effects of nicotine use disorder (NUD) and obesity, there is a paucity of neurobehavioral research on the influence of obesity in individuals who smoke cigarettes. Neuroimaging provides a unique opportunity to identify neurobiological mechanisms underlying comorbid NUD and obesity and may help target and tailor therapeutic strategies for this unique population.

Both frequent nicotine use and consumption of foods that are high in fat and sugar sensitize dopaminergic mesocorticolimbic neurocircuitry.[9,10] Through classical conditioning, internal (eg, craving and hunger) and external (eg, advertisements) cues that predict smoking or eating acquire reward properties, while receipt of the reward becomes less evocative.[11,12] This phenomenon, known as incentive sensitization,[13] is hypothesized to drive craving, thereby motivating continued drug use and/or relapse[14] and impulsive overconsumption of food, leading to excessive weight gain.[15]

Individuals with NUD demonstrate elevated activation in response to visual smoking stimuli in reward-related brain regions, including the striatum, amygdala, orbitofrontal cortex (OFC), insula, and rostral anterior cingulate cortex,[16-18] as well as increases in activation correlated with craving in brain regions associated with executive control, specifically the dorsolateral prefrontal cortex (dlPFC) and dorsal cingulate.[16,18] Neuroadaptations in corticolimbic circuitry may perpetuate craving and compulsive reward-seeking behavior, subsequently overriding homeostatic processes and cognitive control, and this phenomenon may be similar in obesity.[19,20]

Research suggests that bodyweight may be linked to neural responses to nonnatural rewards, pointing to a possible global interaction of chronic overeating and reward processing. Specifically, individuals with overweight[21] or obesity[22,23] show increased neural response to monetary reward in the ventral striatum, amygdala, and medial frontal cortex. It has also been shown that individuals with excess weight have greater frontal functional connectivity with parietal and striatal regions in response to monetary rewards than do individuals with normal weight.[24] Further, reduced activation in inferior, middle, and superior frontal gyri in response to monetary reward-based decision making has been shown to predict weight gain in participants with obesity.[25] Individuals prone to weight gain have also been shown to have differential neural responses to nonfood stimuli,[26] suggesting that this alteration in neurobiological reward processing may predate significant weight gain or potentially predispose an individual to obesity. Together, these findings suggest that obesity is related to alterations in neural response to reward beyond food, with elevated activation in reward-related brain circuitry and reduced activation in cortical regions linked to inhibitory control.

Sensitization of reward-related networks has been posited to impact inhibition, such that prolonged consumption of appetitive rewards leads to dysfunction in the prefrontal neurocircuitry involved in executive control and decision making.[19,27] Functional magnetic resonance imaging (fMRI) studies in both obesity and smoking show hypoactivation in frontal regions, including the superior frontal gyrus, middle frontal gyrus, and ventrolateral and medial PFC, during inhibitory control tasks,[28,29] but the influence of obesity on neural correlates of reward in the NUD population remains unknown.

Prior research from our lab has demonstrated the importance of the dlPFC and insula in response to smoking cues[18,30,31] and in resting state paradigms in individuals with NUD,[32] in addition to extant literature described above. fMRI studies of inhibitory control, such as the Go/NoGo task, have demonstrated that individuals who successfully abstained from cigarette smoking show increased dlPFC activation during inhibitory control than do those who currently smoked.[29] The insula has also been implicated in smokers' ability to quit; however, findings are conflicted. Specifically, one study showed that difficulty abstaining from smoking is associated with elevated insula activation in response to smoking cues,[33] yet other studies indicate that reduced insula activation during a smoking-related inhibition-related Go/NoGo task[34] is associated with difficulty in abstaining from smoking. Additional research of the role of these regions is clearly warranted. In an initial study to examine whether BMI was related to neural response to smoking cues, we conducted a pilot study of 30 individuals with NUD: 13 normal weight and 17 with obesity.[35] We conducted a whole-brain analysis and found that individuals with comorbid NUD and obesity exhibited reduced response to audio/visual smoking cues in the dlPFC than did their normal-weight counterparts, suggesting diminished inhibitory control. The current study extends these findings in a larger sample that includes an intermediate overweight group, enabling us to determine whether reduced response to audio/visual smoking cues in the dlPFC is associated with increasing weight or if it is a distinctive feature of obesity. We hypothesize that our previous findings will be replicated, such that individuals with comorbid NUD and obesity will show reduced dlPFC response to smoking cues. Further, we hypothesize that brain response in the dlPFC will correlate with behavioral performance on a Go/NoGo task designed to measure the ability to inhibit prepotent behavioral responses.

2 | MATERIALS AND METHODS

2.1 | Participants

Participants were recruited from the local community via advertisements, online LISTSERVEs, and word of mouth. All eligible and interested participants provided informed consent prior to participation. Telephone screens and an in-person screening visit included medical and psychiatric evaluations assessing eligibility. All participants met the criteria for *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) NUD and smoked at least six cigarettes per day for at least 6 months prior to study start. Exclusion criteria included current unmanaged Axis I *DSM-IV* psychiatric diagnosis (including eating disorders, psychotic disorders, and bipolar disorder), substance use disorder other than NUD, pregnancy, history of head trauma or injury causing loss of consciousness greater than 3 minutes or associated with skull fracture or inter-cranial bleeding, or irremovable ferromagnetic objects on or within their body. Uncontrolled medical diagnoses (eg, uncontrolled diabetes) and use of psychoactive medication also rendered potential participants ineligible.

A total of 216 individuals were screened as part of two treatment studies of which 79 (39 male and 40 female) met criteria for participation. The two studies had identical criteria for participation and baseline scanning visit procedures. Demographics and variables of interest did not differ between studies. Participants were separated into three groups depending on their body mass index (BMI). Participants with normal weight (n = 26, 13 male) were defined as those with BMIs less than 25.0, participants classified as overweight (n = 28, 11 male) had BMIs of 25.01 to 29.99, and participants classified as having obesity had BMIs of 30 or greater (n = 25, 15 male). The study was approved by the University of Pennsylvania Institutional Review Board and adhered to the Declaration of Helsinki.

2.2 | Procedures

Procedures are similar to those described elsewhere.[18,30,31,36] Prior to the scanning session, participants completed self-report measures and a computerized neurobehavioral battery, including an affect-congruent Go/NoGo task (described below). Approximately 25 minutes prior to the scan session, participants smoked one of their own cigarettes to satiety to maintain individual and characteristic pharmacological, physiological, and psychological states and standardize time since last cigarette. Participants were scanned in the sated state in order to investigate craving independent of withdrawal. Participants were also offered a light snack (ie, granola bar) prior to scanning. During the scanning session, participants passively viewed two 9-minute audiovisual clips, depicting individuals differing in race, age, and sex relating short stories or anecdotes. Prior to the video comprising smoking cues, participants were given a cigarette to hold while a technician lit and blew out a match and placed it in an ashtray within the participant's line of vision to enhance neurophysiological and subjective cue reactivity. During the smoking cue video, actors smoked cigarettes and used language designed to induce appetitive desire for a cigarette. The nonsmoking cue video was similar in content; however, the video did not portray cigarette smoking or smoking reminders. For the nonsmoking cue video, a freshly sharpened pencil was placed in the participant's hand. Both videos were intentionally devoid of other appetitive stimuli (eg, sex, food, alcohol, and caffeine). Neural activation generated by drug cues may persist via carryover effects,[37-39] thereby obscuring the activation in response to nondrug cues. Therefore, presentation of smoking cue and nonsmoking cue videos was not counterbalanced.

2.3 | Measures

2.3.1 | Demographics

Demographic characteristics were obtained using a comprehensive background questionnaire.

2.3.2 | Mini International Neuropsychiatric Interview[39]

The Mini International Neuropsychiatric Interview (MINI) is a structured diagnostic measure administered to determine diagnosis of other substance dependence or severe psychiatric symptoms (eg, psychosis, dementia, acute suicidal or homicidal ideation, mania, or depression). The MINI was administered by a doctoral- or masters-level clinician. Current diagnoses of severe psychiatric illness were exclusionary.

2.3.3 | Smoking History Questionnaire

Severity and duration of nicotine dependence were determined from a laboratory-developed questionnaire that included the Fagerström Test for Nicotine Dependence (FTND[41];).

2.3.4 | Craving and Withdrawal Questionnaire

The Craving and Withdrawal Questionnaire (CWQ) is a nine-item measure[18] that measures cigarette craving and subjective withdrawal symptoms. Ratings are acquired while participants are in the scanner, both immediately prior to and following the smoking and nonsmoking stimulus presentations. Change in craving (postsmoking minus presmoking cues) is calculated to determine the extent to which smoking cues evoke craving.

2.3.5 | Affect-congruent Go/NoGo task

The Go/NoGo task is a computer-based task measuring the ability to inhibit prepotent motor responses. The version developed by our group is described in prior work[42] and is novel in that it uses visual stimuli with inherent ecological validity to reduce the confounding effects of vigilance and memory. For example, Go stimuli are pictures of evolutionarily pleasant/appetitive stimuli such as baby animals or flowers, and NoGo stimuli are pictures of universally aversive scorpions, snakes, and spiders. The task was administered prior to the scanning session using E-Prime[43] and consisted of three levels of difficulty: easy, in which 33% of stimuli are NoGo stimuli (with 20 NoGo trials and 40 Go trials); medium, in which 25% are NoGo stimuli (with 20 NoGo trials and 60 Go trials); and hard, with 12.5% NoGo stimuli (with 20 NoGo trials and 140 Go trials). Maintaining the same number of NoGo trials (20) allowed for direct comparison of error rates across the three conditions. To optimize the prepotency load, the Go and NoGo trials were randomly presented with the constraint that one NoGo trial would occur within each block of eight trials in the 12.5% condition, within each block of four trials for the 25% condition, and within each block of three trials for the 33% condition. In the current study, commission errors (incorrect “Go” responses to “NoGo” stimuli) were used as the metric of interest as they reflect difficulty in inhibiting behavioral responses.

2.4 | Arterial spin-labeled perfusion MRI and data acquisition

Pseudo-continuous arterial spin-labeled (*p*CASL) perfusion MRI was used to characterize regional brain activation during cue exposure.[18,31,36] *p*CASL perfusion data were acquired on a Siemens 3Tesla Trio whole body scanner (Siemens Medical Systems, Erlangen, Germany) using the standard eight-channel head coil receiver array. Head motion was limited by carefully positioning the head coil and foam pads securely around the head. To measure cerebral blood flow (CBF), perfusion fMRI was performed using a previously described *p*CASL sequence.[44] Acquisition parameters were as follows: field of view (FOV) = 220 mm, 64 × 64 × 18 matrix, TR/TE = 4000/17 milliseconds, postdelay time = 1 milliseconds, labeling time = 1.6 seconds, bandwidth = 100 kHz, slice thickness = 6 mm with a 7.2-mm gap. For registration to Montreal Neurological Institute (MNI) standard space, high-resolution anatomical images were acquired using a three-D magnetization prepared rapid gradient echo (MPRAGE) T1-weighted sequence (192 × 256 matrix size; 1 × 1 × 1 mm of in-plane resolution; TR/TE = 1620/3.09 ms; flip angle = 8°).

2.4.1 | *p*CASL data processing

The *p*CASL data were preprocessed using SPM8 package (Wellcome Department of Cognitive Neurology, UK) and ASL toolbox[44] implemented in a MATLAB 2015[45] environment. For both smoking cue and nonsmoking cue scans, 34 pairs of label and control images were acquired repeatedly in an interleaved manner. All images are reoriented to the anterior commissure-posterior commissure (AC-PC) line and corrected for head motion not exceeding 2 mm or rotation 2.0° during scanning. The mean volume of the perfusion images was coregistered to the structural image and subsequently smoothed with a full-width at half maximum (FWHM) Gaussian kernel of 9 mm. CBF image series were calculated by taking the difference of control-tag perfusion signal using a two-compartment model. The deformation field, obtained from the segmentation step, was applied to CBF images to spatially normalize to the standard MNI space (voxel size of 2 mm^3). Each within-subject contrast map of smoking cue versus nonsmoking cue response was defined in the generalized linear model (GLM) to assess the voxel-by-voxel CBF difference. The resulting contrast maps were entered into group level analysis. Age and sex were included as nuisance covariates.

2.5 | Statistical analyses

Following whole-brain analysis, significant clusters within a priori regions of interest (ROIs) including dlPFC, postcentral gyrus, and insula were identified. To control for multiple comparisons, we utilized small volume correction (SVC), with a cluster defining initial height threshold of $P < 0.005$ using a 10-mm sphere and a cluster-wise significance threshold of $P < 0.05$, family-wise error (FWE) corrected. The center of each sphere was located at the peak coordinates of the significant clusters falling within the ROIs. For post hoc analysis, the average activation values were extracted from the significant ROI clusters, and a three-group (normal weight, overweight, and obesity) analysis of variance (ANOVA) was conducted to compare group differences in activation. Tukey honestly significant difference (HSD) was used to correct for multiple comparisons. To determine if the relationship differed depending on BMI status, the average value from significant findings was used in linear regression analyses to examine the relationship between brain activation and Go/NoGo commission errors in easy, medium, and hard trials within those with normal weight, overweight, and obesity.

ANOVAs were used to compare individuals with NUD with normal weight, with overweight, and with obesity on demographic data, pack years, self-reported craving during scans, FTND scores, and commission errors on the Go/NoGo task, with post hoc Tukey HSD analyses to compare groups. Bivariate Pearson correlations were used to determine relationships between descriptive and behavioral variables.

3 | RESULTS

3.1 | Demographic and descriptive data

Participant characteristics are reported in Table 1. Participants with NUD with normal weight, overweight, or obesity did not differ on age, education, pack years, number of cigarettes per day, change in reported craving from before to after viewing smoking cues, or nicotine dependence. BMI was significantly different across groups ($F_{2,76} = 135.197$, $P < 0.001$). As a whole, the sample was identified as 34.2% white, 50.6% African American, 6.3% Asian, 6.3% multiracial, and 2.5% other or unknown; 8.9% of participants identified as of Hispanic ethnicity and 91.1% as non-Hispanic. Weight groups did not significantly differ in racial or ethnic makeup.

3.2 | Neuroimaging results

With age and sex controlled, BMI was negatively associated with activation in response to smoking cues compared with nonsmoking cues in two clusters of the right dlPFC (Table 2; Figure 1) but not the insula. Greater response to smoking cues was observed (cluster 1: $F_{2,78} = 5.46$; cluster 2: $F_{2,78} = 8.20$) in those with normal weight compared with those with overweight (cluster 1: $P = 0.027$; cluster 2: $P = 0.001$) and obesity (cluster 1: $P = 0.009$; cluster 2: $P = 0.010$) in the right dlPFC (Table 2). In other words, as BMI increased, dlPFC activation decreased.

3.3 | Go/NoGo performance and correlation with smoking cue response

Behaviorally, groups did not differ in their ability to inhibit responses on the Go/NoGo task, as measured by commission errors (an incorrect "Go" response on a "NoGo" trial) on easy ($F_{2,73} = 2.74$, $P = 0.071$),

TABLE 1 Participant characteristics and differences by body mass index group

	Full Sample (n = 79)		Normal Weight (n = 26)		Overweight (n = 28)		Obese (n = 25)		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*P* Value
BMI	27.8	5.7	21.8	2.3	27.5	1.2	34.3	4.1	<0.001
Age	38.5	11.6	36.9	13.2	39.7	10.7	38.8	11.0	0.67
Education	14.0	2.3	13.8	2.1	13.8	2.2	14.3	2.7	0.74
Pack years	15.0	13.1	15.5	15.0	14.6	10.9	14.9	13.8	0.97
Cigarettes per day	7.1	5.3	6.9	4.5	7.9	5.7	6.5	5.8	0.63
Change in craving[a]	0.84	1.3	0.8	1.3	0.8	1.1	1.0	1.4	0.83
FTND score	4.8	1.6	4.9	1.5	4.6	1.9	4.9	1.6	0.68

Abbreviations: BMI, body mass index; FTND, Fagerström Test for Nicotine Dependence.

[a]Change in craving reflects postscan minus pre-scan craving scores.

TABLE 2 Regions of interest showing greater cerebral blood flow to smoking cues compared with nonsmoking cues and inverse correlation with body mass index[a]

									Post Hoc Comparisons (Tukey HSD)	
Area	R/L	Volume (Voxels)	*x*	*y*	*z*	*F*	*P*	η^2	Contrast	*P* Values
Dorsolateral prefrontal cortex	R	19	49	17	39	5.46	0.01	0.126	OB < NW	0.01
									OW < NW	0.03
	R	35	33	37	39	8.20	0.001	0.177	OB < NW	0.01
									OW < NW	0.001

Abbreviations: NW, normal weight; OB, obesity; OW, overweight; R, right.

[a]Tukey honestly significant difference (HSD) post hoc comparisons.

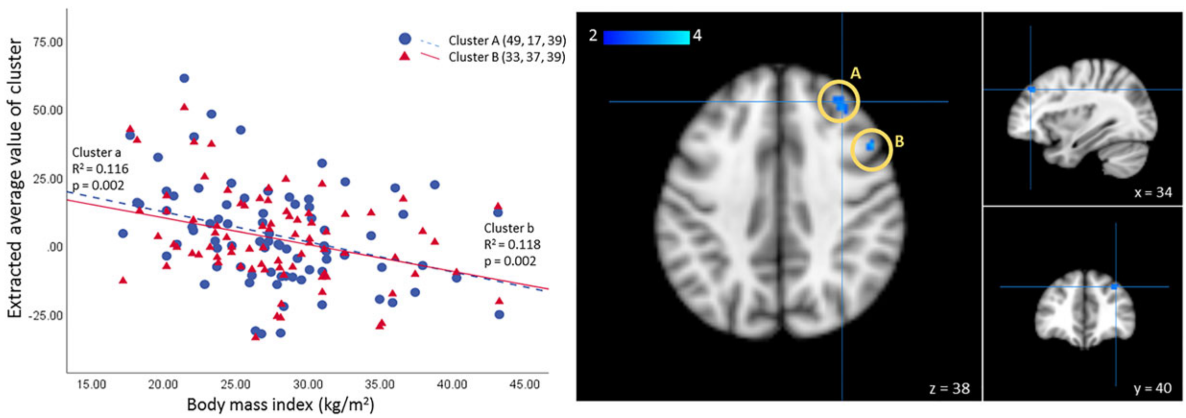

FIGURE 1 Individuals with nicotine use disorder (NUD) and obesity show reduced perfusion in two clusters in the right dorsolateral prefrontal cortex (dlPFC) in response to viewing smoking vs nonsmoking cues. There were no regions in which individuals with NUD and obesity demonstrated elevated perfusion. Peak coordinates: cluster A, $x = 33$, $y = 37$, $z = 39$; cluster B, $x = 49$, $y = 17$, $z = 39$. Data are displayed neurologically (right is right). The magnitude of perfusion in these regions is associated with body mass index (BMI). Shown on the *y*-axis is the extracted value of activation in dlPFC clusters A and B. Shown on the *x*-axis is BMI. The higher an individual's BMI, the less activation in both clusters

medium ($F_{2,73} = 1.95$, $P = 0.150$), or hard trials ($F_{2,73} = 2.82$, $P = 0.066$). Commission errors were also not significantly related to age, BMI, craving, pack years, or scores on the FTND. Among NUD individuals with normal weight and those with overweight, response to smoking cues was not related to Go/NoGo performance. Among NUD individuals with obesity, more commission errors were significantly associated with reduced activation in response to smoking cues in the right dlPFC on both medium ($R^2 = 0.243$, $\beta = -0.109$, $P = 0.017$) and hard trials ($R^2 = 0.200$, $\beta = -0.089$, $P = 0.032$). That is, the less activation there was in the dlPFC, the worse participants performed the task, but only among those with obesity (Figure 2).

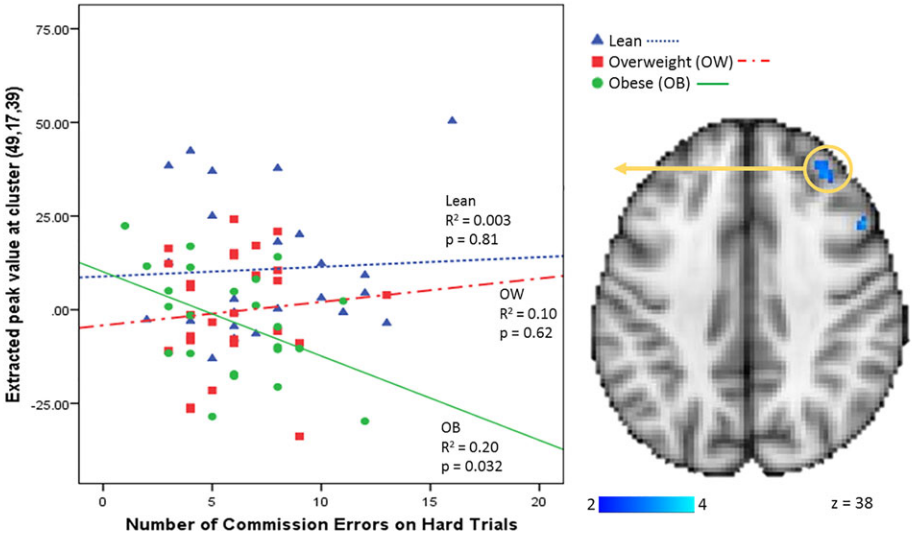

FIGURE 2 The magnitude of perfusion in the right dorsolateral prefrontal cortex (dlPFC) in response to viewing smoking versus nonsmoking cues is associated with the number of commission errors (incorrect "Go" responses) on the Go/NoGo task only among participants with obesity. Shown on the *y*-axis is the extracted value of activation in the dlPFC cluster circled at right (49, 17, 39). Shown on the *x*-axis is the number of commission errors at the hardest level of difficulty of the task. Among participants with obesity, the less activation in this region, the greater the number of inhibitory errors they committed

4 | DISCUSSION

NUDs with obesity, compared with their overweight and normal-weight counterparts, demonstrated hypoactivation in the right dlPFC, a region known to be involved in inhibitory control, when viewing smoking cues. Further, activation in the right dlPFC correlated with Go/NoGo performance among individuals with comorbid NUD and obesity, but not in those with overweight or normal weight. Together, these findings suggest that individuals with comorbid NUD and obesity show diminished responses in the dlPFC during smoking cue exposure, and a unique association between dlPFC brain response to smoking cues and performance during inhibitory processing, such that the lower the brain response in the dlPFC, the greater the number of inhibitory errors. In other words, in individuals with comorbid NUD and obesity, neural response to smoking cues in frontal regions is more related to their ability to stop a conditioned behavior than in individuals with overweight or normal weight. To illustrate, an individual with comorbid NUD and obesity may have more difficulty inhibiting reward-motivated behaviors when presented with rewarding stimuli, leading to increased smoking and/or overeating in general.

These findings are consistent with prior studies demonstrating that obesity is related to hypoactivation of the PFC associated with self-control during inhibitory tasks.[28,29,46] Results are also in alignment with a study showing an association between reduced glucose metabolism in the PFC and increased BMI and poorer performance on tests of executive function.[47] Given participants' similarities in smoking history, nicotine dependence, and craving, our findings raise the possibility that BMI is specifically linked to dysfunction in the dlPFC. Additional research is clearly warranted.

Among NUDs with obesity, inhibitory control performance correlated with dlPFC response to smoking cues, such that those with greater activation in the dlPFC performed better. Notably, in individuals with NUD with overweight or normal weight, the number of commission errors was not linked to dlPFC response to evocative smoking stimuli. Prior research suggests that the dlPFC may play a role in successful response inhibition.[48-51] However, the dlPFC's role in modulating dopaminergic response may be particularly important in regulating the expectation of reward.[52] Blunted right dlPFC activation with obesity may contribute to greater difficulty regulating the motivation to smoke provoked by conditioned cues. This raises the possibility that dysfunction of dlPFC response in individuals with obesity may lead to greater difficulty with smoking cessation in such a way that may not affect individuals with NUD who are overweight or normal weight. Indeed, a recent fMRI study of Go/NoGo-related activation[29] showed enhanced response in the dlPFC in individuals who successfully abstained from smoking as compared with those who currently smoked. As such, NUDs with obesity may have greater difficulty in quitting smoking than those who are normal weight or overweight, or may be more likely to need supplemental therapies.[53,54] For example, treatments focused on improving inhibitory control (eg, mindfulness)[55] or specifically modulating right frontal activation (eg, transcranial magnetic stimulation)[56] may provide supplemental support for patients with obesity making a quit attempt.

4.1 | Limitations and strengths

This study, the first of its kind, examined the effects of obesity on brain and behavioral responses to reward stimuli in NUD. It was not a prospective examination, and as such, we were unable to analyze additional variables of interest that might specifically be relevant to a population with obesity, such as hunger ratings, weight loss, dieting, weight stability/suppression, or dietary intake. Hunger state has been shown to differentially influence response to food reward in lean participants[57] and those with obesity[58] and, thus, may have had a differential effect on response to smoking cues. Unfortunately, we lacked adequate measures to control for hormonal status among female participants. However, lack of control over hormonal variability would, if anything, increase error variance, theoretically reducing the ability to detect differences. Given the resulting increase in unaccounted variance due to hormonal variability, this suggests a robust effect; however, additional prospective research in larger samples is warranted. Participants were scanned in a sated state with respect to nicotine, and as such, this study cannot describe differences related to withdrawal; however, the design allows us to explore brain response to cues independent of the withdrawal state. Future studies of the impact of obesity would benefit from comparing neural activation to smoking cues in both abstinent and sated states. We were not able to explore prior number of quit attempts in these analyses due to missing data. This would be important to examine in future studies to explore the hypothesis that those with higher BMI will have more difficulty quitting smoking. Finally, sex affects responses to smoking reward,[36,59-61] which we were unable to examine with the limited sample size of the current study. An interaction between BMI status and sex is conceivable and should be considered as a future area of study. Finally, it is possible that there is a nonlinear relationship between BMI and response to rewards that was not fully captured by our analyses. Reward-related research suggests that individuals with overweight may be distinct from those with obesity,[62,63] and as such, this would be an interesting approach for further study. Despite these limitations, our findings suggest that individuals with comorbid NUD and obesity may experience greater difficulty when attempting to quit smoking, and future research should test this by prospectively following NUDs with and without obesity during quit attempts to determine if obesity does, in fact, confer greater difficulty with smoking cessation.

5 | CONCLUSIONS

In summary, obesity and cigarette smoking are two of the leading preventable causes of death in the United States and have overlapping pathophysiology, yet no studies have investigated the effect of obesity on neural response to reward stimuli in NUD. The current study is the first neuroimaging study to examine whether individuals with comorbid NUD and obesity, compared with their lean and overweight counterparts, show a different pattern of neural activation to smoking cues. Specifically, findings revealed individuals with comorbid NUD and obesity show blunted activation in a brain region commonly associated with cognitive control, the right dlPFC, and this blunted activation was associated with the inability to inhibit behavioral responses to external affective cues. As such, individuals with comorbid NUD and obesity may experience greater difficulty with quitting smoking. Additional research is needed in order to tailor treatment to this population of individuals at greater risk for experiencing significant negative health-related outcomes.

ACKNOWLEDGEMENTS

This research was supported by funds from the National Institutes of Health (R01DA030394 and R01DA029845 to T.R.F.; K23AA023894 to R.R.W.). The authors would like to thank the MRI technical staff at the Hospital of the University of Pennsylvania and the clinical staff (MDs, nurses, psychologists) and support staff (reception, clerical, administration) at the Center for the Studies of Addiction, with special thanks to M. Maron (Lab Manager). The authors wish to acknowledge Sarah Sivilich, the webmaster for franklinbrainimaging.com.

DISCLOSURE/CONFLICT OF INTEREST

All authors report no biomedical financial interests or potential conflicts of interest.

AUTHORS CONTRIBUTION

AVE, TRF, and RRW were responsible for the study concept and design. NH, TRF, and RRW acquired the data. AVE, KJ, and RRW conducted the data analyses. AVE, AK, TRF, and RRW interpreted the findings. AVE, KJ, AK, TRF, and RRW drafted the manuscript. All authors provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved the final version for publication.

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How to cite this article: Ely AV, Jagannathan K, Hager N, Ketcherside A, Franklin TR, Wetherill RR. Double jeopardy: Comorbid obesity and cigarette smoking are linked to neurobiological alterations in inhibitory control during smoking cue exposure. *Addiction Biology*. 2019;e12750. https://doi.org/10.1111/adb.12750