ONLINE FIRST

Effect of Bupropion Treatment on Brain Activation Induced by Cigarette-Related Cues in Smokers

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Context: Nicotine-dependent smokers exhibit craving and brain activation in the prefrontal and limbic regions when presented with cigarette-related cues. Bupropion hydrochloride treatment reduces cue-induced craving in cigarette smokers; however, the mechanism by which bupropion exerts this effect has not yet been described.

Objective: To assess changes in regional brain activation in response to cigarette-related cues from before to after treatment with bupropion (vs placebo).

Design: Randomized, double-blind, before-after controlled trial.

Setting: Academic brain imaging center.

Participants: Thirty nicotine-dependent smokers (paid volunteers).

Interventions: Participants were randomly assigned to receive 8 weeks of treatment with either bupropion or a matching placebo pill (double-blind).

Main Outcome Measures: Subjective cigarette craving ratings and regional brain activations (blood oxygen level-dependent response) in response to viewing cue videos.

Results: Bupropion-treated participants reported less craving and exhibited reduced activation in the left ventral striatum, right medial orbitofrontal cortex, and bilateral anterior cingulate cortex from before to after treatment when actively resisting craving compared with placebo-treated participants. When resisting craving, reduction in self-reported craving correlated with reduced regional brain activation in the bilateral medial orbitofrontal and left anterior cingulate cortices in all participants.

Conclusions: Treatment with bupropion is associated with improved ability to resist cue-induced craving and a reduction in cue-induced activation of limbic and prefrontal brain regions, while a reduction in craving, regardless of treatment type, is associated with reduced activation in prefrontal brain regions.

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ORIGINALLY MARKETED AS an atypical antidepressant, bupropion hydrochloride was found to enhance smoking cessation in patients with depression and is now the most commonly recommended nonnicotinic pharmacotherapy for smoking cessation in the world.[1] Bupropion improves quit rates[2-4] and prolongs abstinence in nicotine-dependent smokers.[5,6] Standard 8-week treatment with bupropion (administered with brief counseling) results in approximately 40% short-term abstinence (7 weeks)[3] and 20% to 30% long-term abstinence (12 months).[4,7,8] Smokers treated with bupropion describe a reduction in nicotine withdrawal symptoms including negative affect, urge to smoke, difficulty concentrating, and irritability.[9,10] Numerous studies encompassing a wide spectrum of clinical populations have replicated the success of treatment with bupropion,[11-15] suggesting a common mechanism by which this medication facilitates smoking cessation.

Bupropion and its metabolites appear to modulate smoking-induced dopamine release by increasing extracellular dopamine and norepinephrine levels in subcortical regions (striatum and locus coeruleus, respectively) through the inhibition of dopamine and norepinephrine reuptake transporters.[16-24] Enhancing subcortical dopamine and norepinephrine may facilitate smoking cessation by mitigating the effects of nicotine-evoked dopamine transmission from the ventral tegmental area to

the ventral striatum, thereby reducing nicotine reward and withdrawal.[25,26] Bupropion also acts as an antagonist at nicotinic acetylcholine receptors, decreasing the probability of their activation and desensitization.[27-32] Therefore, bupropion may also block nicotinic receptors and reduce the reinforcing value of smoking.[33]

Environmental cues associated with nicotine reinforcement induce cigarette craving, which propagates smoking habits in smokers and relapse in abstinent individuals.[34-39] Human brain imaging studies using functional magnetic resonance imaging (fMRI) and positron emission tomography scanning have provided insight into brain regions associated with cue-induced cigarette craving. Nicotine-dependent smokers exhibit activation in brain regions related to attention (prefrontal cortex), emotion (amygdala), reward (ventral tegmental area), and motivation (striatum) while viewing cigarette-related cues.[40-45] A number of factors including level of nicotine dependence,[46-48] length of abstinence and/or severity of withdrawal,[49-51] expectancy to smoke,[52,53] and genotype[54] may affect cue-induced neural activation.

Although brain regions mediating cue-induced craving have been closely examined,[55] little research has focused on understanding how smoking cessation treatments alter this well-characterized phenomenon. Animal studies of bupropion and nicotine self-administration, discrimination of nicotinelike effects, and reinforcement have provided conflicting evidence regarding the neural mechanisms by which bupropion aids smoking cessation in humans.[56,57] Human studies using positron emission tomography have shown that bupropion treatment attenuates cue-induced increases in glucose metabolism in the anterior and posterior cingulate gyri.[58,59] Furthermore, recently abstinent smokers treated with bupropion and group therapy display lower levels of craving and less increase in glucose metabolism in the striatum, thalamus, and midbrain while viewing smoking-related cues compared with identically treated nonabstinent smokers.[60] Taken together, these studies establish that smoking cessation treatments not only attenuate self-reported cue-induced craving but also attenuate cue-induced neural activation within the limbic system and associated prefrontal brain regions.

This study aimed to assess the effect of standardized treatment with bupropion on regional brain activation in response to smoking-related cues while participants either passively allowed or actively resisted craving. Based on previous research, we hypothesized that participants treated with bupropion would show a greater treatment-induced reduction in activation of limbic and prefrontal regions associated with cue-induced craving compared with participants treated with placebo. We hypothesized that this effect would be accentuated while participants resisted craving.

METHODS

PARTICIPANTS

Healthy, treatment-seeking cigarette smokers (≥10 cigarettes per day) who met *DSM-IV* criteria for nicotine dependence were recruited through local newspaper and internet advertisements. Potential participants underwent telephone and in-person screenings. For the telephone screening, a research assistant obtained medical, psychiatric, and substance-abuse histories without personal identifiers. Two study investigators (R.E.O. and A.L.B.) performed the in-person screenings, which included screening questions from the Structured Clinical Interview for *DSM-IV*[61] and administration of the Smoker's Profile, Fagerström Test for Nicotine Dependence (FTND),[62,63] Urge to Smoke Scale,[40,64] and Hamilton Depression[65] and Anxiety[66] rating scales. Potential participants provided breath samples for a carbon monoxide assay, using a MicroSmokerlyzer (Bedfont Scientific Ltd, Kent, England) at the time of initial screening to verify recent smoking. Breath carbon monoxide level (at a cutoff of >5 ppm) is highly associated with self-reported smoking, correlates negatively with time since last cigarette, and correlates positively with carboxyhemoglobin levels.[67,68] All participants received a detailed verbal and written description of the study procedures before giving informed consent, as approved by the Greater Los Angeles Veterans Affairs Healthcare System Institutional Review Board.

Exclusion criteria included (1) history of any Axis I psychiatric diagnosis other than nicotine dependence, (2) medical conditions that might affect brain function, (3) current use of medications that could alter brain function, (4) pregnancy, and (5) current illicit drug use other than occasional use of marijuana. All potential participants were required to have a negative result on a urine test for drug use during the in-person screening session and immediately prior to each scanning session. Participants who reported recreational alcohol (≤1 drink per day), marijuana (≤1 use per week), or caffeine (≤2 cups of coffee per day or the equivalent) use who did not meet the criteria for abuse/dependence were allowed to participate but were instructed to abstain for at least 24 hours before scanning.

fMRI PROCEDURE

Thirty-four participants underwent the first fMRI scan within 1 week of the in-person screening. They were instructed to smoke their usual morning cigarette(s) prior to scanning. A research assistant interviewed the participants and measured exhaled carbon monoxide breath samples at the start of each session (7:00 AM) to ensure that they had smoked prior to the fMRI session. The structural MRI image began at 7:15 AM followed by an fMRI scan including neutral and smoking cue videos at 7:25 AM. This procedure standardized the time since the last cigarette (25 minutes) and allowed for moderate craving[69] while avoiding the possibility of a ceiling effect caused by prolonged abstinence. Thirty participants underwent an identical post-treatment scan (4 dropouts) while taking the study medication at the end of the 8-week treatment period.

Functional imaging was performed with a 1.5-T Magnetom Sonata scanner (Siemens AG, Erlangen, Germany) using a gradient-echo, echo-planar acquisition sequence in which the repetition time was 2.5 seconds; echo time, 45 milliseconds; flip angle, 80°; image matrix, 128 × 64; field of view, 40 × 20 cm; and in-plane resolution, 3 mm. Sixteen slices, each 4 mm thick, with a 1-mm gap between slices were obtained every 2.5 seconds for 45 seconds while participants were exposed to cigarette-related and neutral cues and during control periods (resting state with neutral visual stimulus: flashing white boxes on black background). High-resolution spin-echo echo-planar scans (128 × 256 matrix; in-plane resolution, 1.5 mm; repetition time, 4000 milliseconds; echo time, 54 milliseconds; 4 excitations) obtained in the same plane as the functional scans were acquired with bandwidth matched to that of the functional studies. The spatial distortions of the functional and high-resolution spin-echo echo-

planar imaging scans were held in common to facilitate the subsequent spatial normalization procedure.

CUE PRESENTATION AND CRAVING MONITORING

Our group and a collaborator developed and validated 18 cigarette-related and 9 neutral cue videos used in this study.[70,71] The cigarette-related videos include professional actors and actresses smoking in a variety of generic settings (eg, writing a letter, standing outside of a building, driving). The neutral cue videos were similar but included no smoking-related behaviors. Cue videos were 45 seconds in length and were seen from the first-person viewpoint.

Participants viewed the cue videos through MRI-compatible goggles with an attached headphone/microphone headset (MRVision 2000 Ultra; Resonance Technology, Northridge, California). Before scanning, participants received instructions on how to provide craving ratings using an optically isolated universal serial bus interface consisting of a 5-button response box (Rowland Institute at Harvard, Cambridge, Massachusetts). Participants were instructed to respond from 1 (definitely not) to 5 (definitely) on the question, "I crave a cigarette right now" (taken from the Urge to Smoke scale[64]) immediately following each cue presentation. Owing to the repetitive nature of measuring acute craving and time constraints inherent in the fMRI scanning procedure, a single-item craving questionnaire was substituted for a more comprehensive multidimensional craving survey.[72]

Each scanning session consisted of 3 runs, with each run including 3 cue conditions. During each run, participants viewed 1 neutral cue video, 1 crave-allow cigarette-related cue video, and 1 crave-resist cigarette-related cue video. Prior to initiation, participants were instructed to allow themselves to crave cigarettes during the cigarette-related cue videos unless explicitly instructed to resist craving (eg, "during the next video clip, try to resist any feelings of craving for cigarettes"). The cue videos were presented in a randomized fashion (Latin square design).

SMOKING CESSATION TREATMENT PROCEDURE

Following the first fMRI scan, participants met with a research physician and were randomly assigned to smoking cessation treatment with either bupropion sustained release (n=17) or a matching pill placebo (n=17) in a double-blind fashion. Participants were instructed to start taking 1 pill (150 mg of bupropion or 1 placebo pill) daily for the first 3 days of treatment, followed by titration up to 2 pills daily, separated by 8 hours, for the remaining 8 weeks of treatment. Participants met with the physician weekly to monitor treatment adherence and adverse effects. The physician instructed participants to set a smoking quit date of 2 weeks after the initiation of treatment and continued to encourage participants to quit throughout the study. Participants continued to take bupropion or the pill placebo through the completion of the second fMRI scan. Participants who quit smoking during the study (confirmed by self-reports and exhaled carbon monoxide $\leq$3 ppm) were not required to smoke prior to the second fMRI scan. Three bupropion-treated participants stopped taking the study medication owing to relocation (n=1), vocational constraints (n=1), and self-reported lack of efficacy (n=1). One placebo-treated participant also stopped taking the study medication owing to self-reported lack of efficacy. All of these participants were withdrawn from the study because they did not have both the before-treatment and after-treatment data needed for the primary study analyses, leaving a final sample size of 30. No participants included in the study described significant adverse effects of study medication requiring a reduction in dosage or discontinuation of administration.

DEMOGRAPHIC AND TREATMENT VARIABLES ANALYSIS

Mean (SD) values of demographic and treatment variables were determined independently for each treatment group. To ensure that the randomly assigned study groups were similar at baseline, *t* tests and a χ^2 test (for sex) were performed on the demographic variables. To evaluate treatment outcomes, the treatment groups were compared together and independently using unpaired and paired *t* tests, respectively, on the primary smoking outcome measures (cigarettes per day, FTND scores, and exhaled carbon monoxide levels).

SELF-REPORTED CRAVING ANALYSIS

A within-subject repeated-measures analysis of variance including a between-group variable (treatment type), was used to test for interactions and/or effects of treatment type (bupropion and placebo), cue condition (crave-allow, crave-resist, and neutral), time (before to after treatment), and run on self-reported craving. Secondarily, craving scores were averaged across the 3 runs for each cue condition and an unpaired *t* test was used to assess group differences in the self-reported craving for each condition before treatment, after treatment and in the change from before to after treatment. A paired *t* test was also used to assess within-group differences in self-reported craving for each condition from before to after treatment.

fMRI STATISTICAL ANALYSIS

Preprocessing

Images were preprocessed using FEAT (FMRI Expert Analysis Tool) Version 5.4.2 from the FMRIB Software Library (http://www.fmrib.ox.ac.uk/fsl) and the following steps: motion correction using the Linear Registration Tool (MCFLIRT)[73]; exclusion of nonbrain areas using the Brain Extraction Tool[74]; spatial smoothing with a Gaussian kernel of 5 mm full-width at half maximum; mean-based intensity normalization to remove linear trends; and nonlinear, high-pass temporal filtering to exclude low-frequency confounds such as breathing (Gaussian-weighted least squares straight line fit, with σ=25.0 seconds). Time series statistical analysis was carried out using Improved Linear Model with local autocorrelation correction.[75]

Level 1: Within-Participant, Within-Run

Voxelwise general linear model analyses of the 3 cue conditions (crave-allow, crave-resist, and neutral) were modeled as explanatory variables in the first-level analysis. Each scan was registered to a high-resolution T1-weighted structural image using FMIRB's Linear Registration Tool (FLIRT)[76] and coregistered to MNI152 (Montreal Neurological Institute, Montreal, Quebec, Canada) standard space. Contrasts at this level compared parameter estimates of the hemodynamic response with the 3 cue conditions vs each of the other cue conditions and rest.

Level 2: Within-Participant, Within-Session

The second-level, within-participant analysis used FMRIB's fixed effects model. This analysis was conducted individually for each participant to determine the relative activation between cue conditions during before-treatment and after-treatment sessions

Table 1. Demographic and Smoking Characteristics

Characteristic	Mean (SEM) by Treatment	
	Bupropion	Placebo
Age, y	40.4 (2.8)	42.9 (3.1)
Sex, %		
Male	64	75
Female	36	25
Smoking duration, y	20.3 (3.9)	22.5 (3.4)
Quit rates, %	21.4	5.3
Cigarettes per day, No.		
Before treatment	24.4 (2.6)[a]	22.8 (2.5)[a]
After treatment	8.5 (2.5)[a]	13.0 (2.8)[a]
Change	−15.9 (3.2)	−9.8 (2.1)
Exhaled carbon monoxide		
Before treatment	24.5 (3.9)[a]	20.3 (2.5)
After treatment	13.8 (3.0)[a]	18.7 (2.7)
Change	−10.7 (3.5)[b]	−1.6 (1.7)[b]
FTND score		
Before treatment	6.1 (0.4)[a]	6.2 (0.5)[a]
After treatment	2.5 (0.6)[a,b]	4.3 (0.6)[a,b]
Change	−3.6 (0.6)[b]	−1.9 (0.6)[b]

Abbreviations: FTND, Fagerström Test for Nicotine Dependence; SEM, standard error of the mean.
[a] $P < .01$ within group.
[b] $P < .05$ between group.

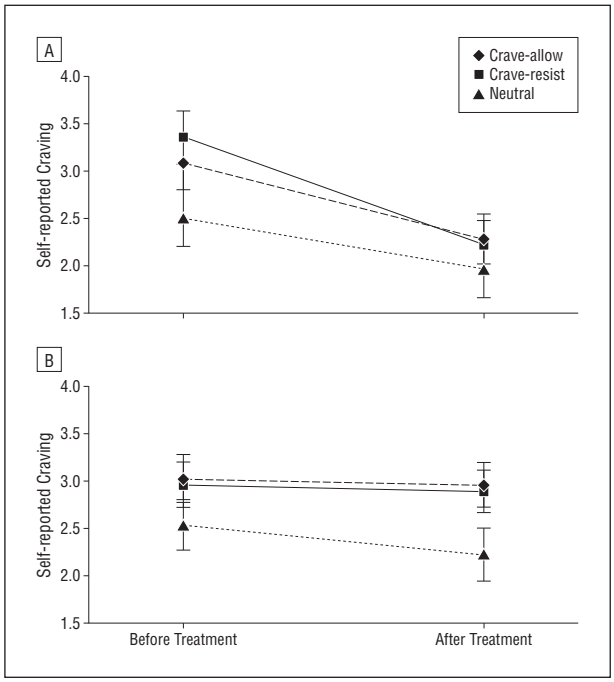

Figure 1. Average self-reported craving (on a scale of 1-5) for each cue condition before and after treatment for patients treated with bupropion (A) or placebo (B).

(crave-allow vs neutral; crave-resist vs neutral; crave-allow vs crave-resist).

Level 3: Between-Group, Before and After Treatment

The third level of analysis assessed between-group differences (bupropion vs placebo) in activation between cue conditions before and after treatment separately using FMRIB's Local Analysis of Mixed Effects (FLAME 1).[77-79] Participant's self-reported cigarettes per day was measured prior to each fMRI scan, then de-meaned and included as a covariate in the analysis to control for the effect of cigarette use on regional brain activation.

Level 4: Within- and Between-Group, Before to After Treatment

The fourth and primary level of analysis examined pretreatment to posttreatment activation changes within each group and between the 2 groups relative to cue condition using FLAME 1.[77-79] Participants' change in reported cigarettes smoked per day from before to after treatment was de-meaned and included as covariate in this analysis to control for the effect of reduced cigarette use on regional brain activation. A region-of-interest analysis was applied to the regions where significant group differences were observed using FMRIB's featquery to assess correlations (Pearson) between mean percentage of signal change and change in craving from before to after treatment. (For thoroughness, group differences were also assessed in regions where significant activation/deactivation differences were observed between the crave-resist and crave-allow vs neutral conditions in all participants before treatment.)

Level 5: fMRI and Self-reported Craving

The fifth-level analysis examined the relationship between changes in self-reported craving and fMRI activation from before to after treatment in all participants and each treatment group separately using FLAME 1. Participants' change in self-reported craving from before to after treatment was de-meaned and applied as a covariate of interest in this analysis. A region-of-interest analysis was applied to the regions where significant associations were observed using FMRIB's featquery to assess group differences (unpaired *t* test) in mean percentage of signal change from before to after treatment.

STATISTICAL PARAMETERS

z Statistic images were thresholded using clusters determined by $z > 2.3$, with an adjusted corrected cluster significance threshold of $P = .05$ for the first, second, third, and fourth level of analysis.[80] The fifth level of analysis used clusters determined by $z > 2.1$, with an adjusted corrected cluster significance threshold of $P = .05$.

RESULTS

DEMOGRAPHIC AND SMOKING CHARACTERISTICS

No differences were observed between the bupropion-treated participants (n = 14) and the placebo-treated participants (n = 16) on demographic measures or number of years smoking. At the initiation of treatment, no differences were observed between the treatment groups on reported cigarettes per day, exhaled carbon dioxide, or FTND scores. At the completion of treatment, bupropion-treated participants reported significantly lower FTND scores compared with placebo-treated participants ($P = .04$, 2-tailed *t* test). Bupropion-treated participants also exhibited greater reductions in FTND scores ($P = .04$, 2-tailed *t* test) and exhaled carbon dioxide ($P = .02$, 2-tailed *t* test) from before to after treatment than placebo-treated participants. No difference was observed in the

number of participants who quit smoking in each treatment group during the study. Within-group analyses revealed that bupropion-treated participants exhibited significant decreases in reported cigarettes per day ($P=.001$, 2-tailed t test), exhaled carbon dioxide, and FTND scores ($P=.001$, 2-tailed t test), while placebo-treated participants exhibited significant decreases in reported cigarettes per day ($P=.001$, 2-tailed t test) and FTND scores ($P=.006$, 2-tailed t test) but not exhaled carbon dioxide (**Table 1**).

SELF-REPORTED CRAVING

A within-subject repeated-measures analysis of variance revealed a significant 3-way interaction between treatment group (bupropion and placebo), cue condition (crave-allow, crave-resist, neutral), and time (before to after treatment) ($F_{2,24}=3.60$; $P=.04$) on self-reported craving (scale, 1-5) measured immediately following each cue condition (**Figure 1**), indicating that bupropion-treated smokers displayed a significantly different craving response pattern to the cue conditions from before to after treatment compared with placebo-treated participants. Significant effects of cue condition ($F_{2,24}=14.88$; $P<.001$), time ($F_{1,25}=7.66$; $P=.01$), and run ($F_{2,24}=5.86$; $P=.005$) were also observed on self-reported craving, indicating that the smoking-related cues elicited more craving than neutral cues, craving decreased from before to after treatment, and craving increased across runs in all participants.

No significant group differences were observed in craving during any of the cue conditions at baseline (before treatment). An unpaired t test demonstrated that, on average, the bupropion-treated participants reported significantly less craving after treatment ($P=.04$) and significantly greater reduction in craving from before to after treatment ($P=.02$) during the crave-resist condition compared with placebo-treated participants. No group differences were observed during the crave-allow or neutral cue conditions before treatment, after treatment, or in the change from before to after treatment (**Table 2**).

Table 2. Average Self-reported Craving

Treatment Condition	Mean (SEM) by Treatment	
	Bupropion	Placebo
Crave-resist		
Before treatment	3.28 (0.17)[b]	2.92 (0.28)
After treatment	2.17 (0.25)[a,b]	2.93 (0.19)[a]
Change	–1.10 (0.31)[a]	0.01 (0.26)[a]
Crave-allow		
Before treatment	3.03 (0.23)	3.06 (0.26)
After treatment	2.48 (0.29)	2.99 (0.24)
Change	–0.54 (0.37)	–0.07 (0.26)
Neutral		
Before treatment	2.41 (0.22)	2.44 (0.31)
After treatment	2.12 (0.30)	2.21 (0.25)
Change	–0.36 (0.32)	–0.23 (0.24)

Abbreviation: SEM, standard error of the mean.
[a] $P<.05$ between groups.
[b] $P<.05$ within group.

fMRI: EFFECTS OF TREATMENT

Between-Group: Before to After Treatment

In the contrast of crave-resist vs neutral from before to after treatment, participants treated with bupropion exhibited significantly greater treatment-induced reductions in activation in the left ventral striatum, right medial orbitofrontal cortex, and bilateral anterior cingulate cortex compared with participants who received placebo (**Figure 2**; **Table 3**). No treatment-induced increases in activation were observed in this comparison. The groups showed no difference in activation changes

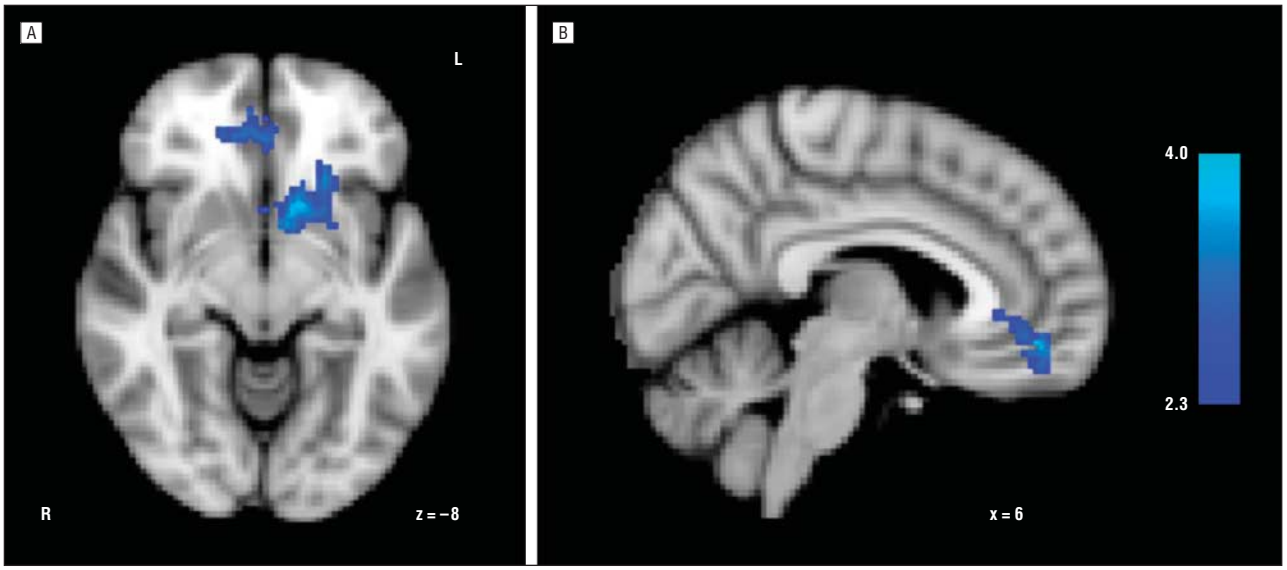

Figure 2. Significant between treatment group differences in change in regional brain activation from before to after treatment during the crave resist vs neutral cue condition. Bupropion-treated participants exhibited significantly greater treatment-induced reductions in activation in the left ventral striatum (A), bilateral anterior cingulate cortex (A and B), and right medial orbitofrontal cortex (B) compared with placebo-treated participants (z threshold >2.3; cluster threshold, $P<.05$). Z-axis values correspond to MNI152 standard space coordinates.

from before to after treatment in comparisons of crave-allow vs neutral or crave-allow vs crave-resist.

Within-Group: Before to After Treatment

When assessed independently, bupropion-treated participants exhibited significantly reduced activation during the crave-resist vs neutral condition in the bilateral anterior cingulate cortex, precuneus, and lateral occipital cortex from before to after treatment (**Figure 3**; Table 3). These participants showed no treatment-induced increases in activation in this comparison and no activation changes during comparisons of crave-allow and neutral or crave-allow and crave-resist. The placebo-treated participants showed no significant changes in activation from before to after treatment for any of the cue condition comparisons.

Table 3. Local Maxima for Significant Within- and Between-Group Activations

Region (Contrast)	*z* Score	x, y, and z Coordinates[a]
Between groups: before to after treatment (bupropion > placebo)		
Ventral striatum, left	4.10	−14, 14, −10
	3.65	−12, 6, −12
Medial orbitofrontal cortex, left	3.58	6, 46, −10
Anterior cingulate cortex, bilateral	3.48	0, 36, −4
Within bupropion: before to after treatment (pretreatment > posttreatment)		
Precuneus, bilateral	3.80	2, −68, 56
	3.42	0, −76, 44
	3.04	−2, −64, 48
Lateral occipital cortex, bilateral	3.25	−12, −80, 50
	3.12	48, −74, 24
	2.98	40, −78, 34
Anterior cingulate cortex, bilateral	2.91	8, 40, −8
	2.88	2, 40, 10
	2.83	−4, 40, 22
Between groups: after treatment (placebo > bupropion)		
Anterior cingulate cortex, left	3.90	−4, 34, 0
Ventral striatum, left	3.67	−18, 14, −10
	3.59	−14, 14, −10
	3.56	−10, 14, −8

[a] Coordinates in MNI152 standard space; x, y, and z refer to right/left (x: positive = right), anterior/posterior (y: positive = anterior), and dorsal/ventral (y: positive = dorsal).

Between Groups: Before and After Treatment

Prior to treatment, the 2 groups displayed no differences in activation to any of the cue condition comparisons. After treatment, bupropion-treated participants exhibited significantly less activation in the left ventral striatum and left anterior cingulate cortex than placebo-treated participants when comparing crave-resist vs neutral (**Figure 4**; Table 3). The bupropion-treated participants exhibited no regions of greater activation in this comparison. The groups did not differ significantly following treatment when comparing crave-allow and neutral or crave-allow and crave-resist.

Region-of-Interest Analysis

In regions where significant between-group differences were observed from before to after treatment (Figure 2; Table 3), bupropion-treated participants who reported a reduction in craving following treatment demonstrated a positive correlation between reduction in craving and reduced mean percentage of signal change ($r=0.695$; $P=.02$). This correlation was also observed when placebo-treated participants were included in the analysis ($r=0.488$; $P=.01$), but not when placebo-treated participants were assessed alone. Two bupropion-treated participants were excluded owing to lack of treatment response and 1 was excluded for

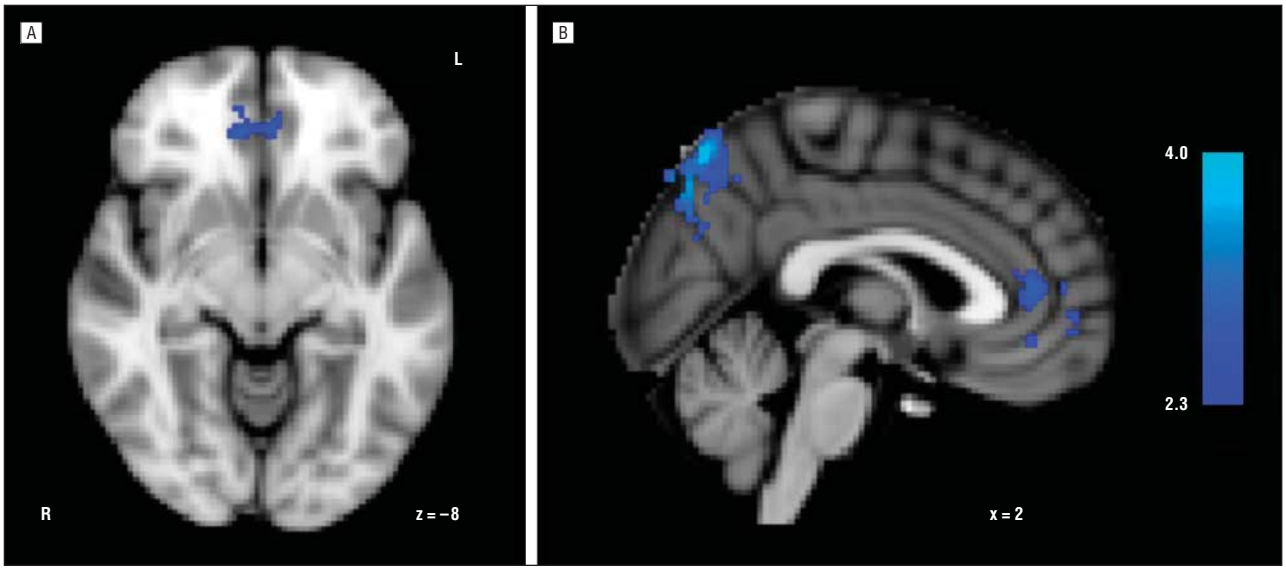

Figure 3. Significant within-treatment group (bupropion-treated) differences in regional brain activation from before to after treatment during the crave-resist vs neutral cue condition. Bupropion-treated participants exhibited significant treatment-induced reductions in activation in the bilateral anterior cingulate (A and B), bilateral precuneus (B), and lateral occipital cortex following treatment (*z* threshold, >2.3; cluster threshold, $P<.05$). Z-axis values correspond to MNI152 standard space coordinates.

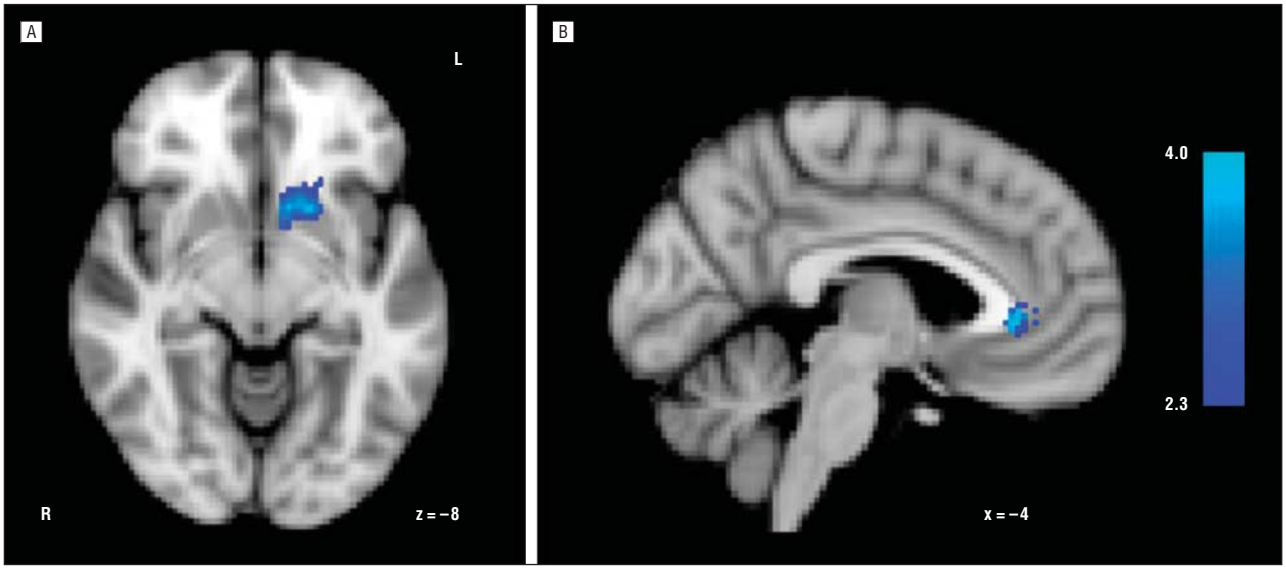

Figure 4. Significant between-treatment group differences in regional brain activation following treatment during the crave-resist vs neutral cue condition. Bupropion-treated participants exhibited significantly less activation in the left ventral striatum (A) and left anterior cingulate cortex (B) compared with placebo-treated participants (*z* threshold, >2.3; cluster threshold, $P<.05$). Z-axis values correspond to MNI152 standard space coordinates.

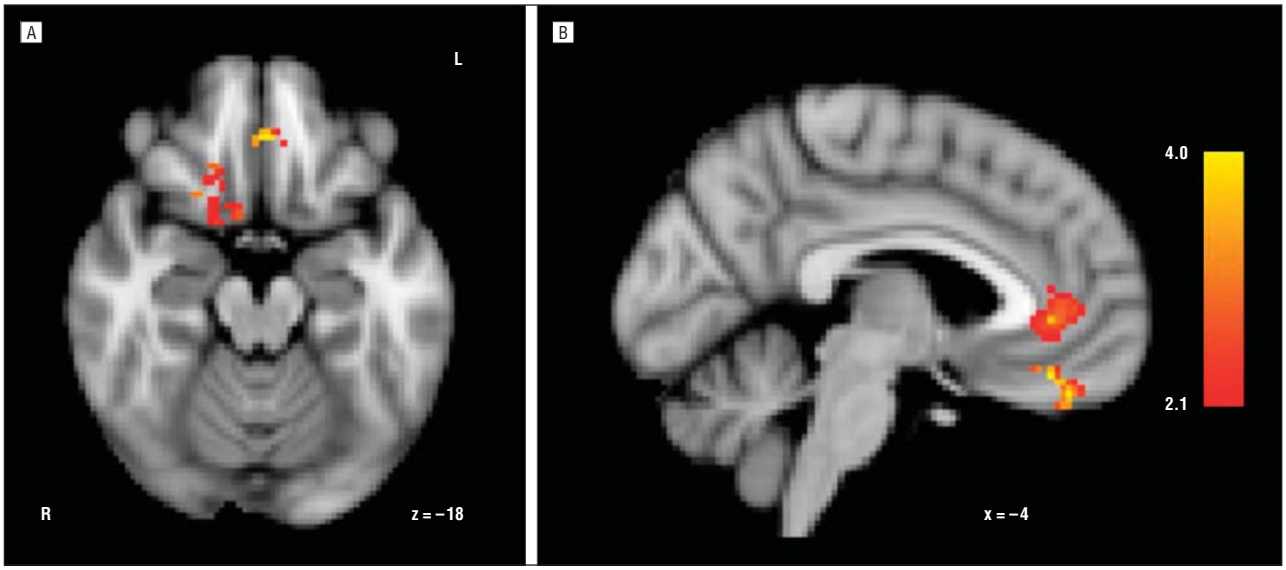

Figure 5. Brain regions correlated between changes in self-reported craving and changes in activation from before to after treatment during the crave-resist vs neutral cue conditions. A significant association was observed between reduction in self-reported craving and reduced activation in the bilateral medial orbitofrontal cortex (A) and left anterior cingulate cortex (B) in all participants (*z* threshold, >2.1; cluster threshold, $P<.05$). Z-axis values correspond to MNI152 standard space coordinates.

not completing posttreatment craving responses. (No group differences were observed in brain regions that differed significantly between cue conditions in all participants before treatment.)

fMRI and Self-reported Craving

A positive association was observed between changes in self-reported craving and activation changes from before to after treatment in the bilateral medial orbitofrontal cortex and left anterior cingulate cortex in all participants during the crave-resist vs rest comparison (**Figure 5**, **Table 4**). The treatment subgroups did not demonstrate this association when assessed independently. A positive association was also observed in all participants between craving and activation changes in the bilateral precentral gyrus during the crave-allow vs rest comparison. In this same comparison, placebo-treated participants demonstrated a positive association in the right precentral gyrus, postcentral gyrus, precuneus, posterior cingulate cortex, frontal pole, central opercular cortex, inferior frontal gyrus, and transverse temporal gyrus. The bupropion-treated participants demonstrated no association in this comparison (Table 4). In regions where an association was observed between changes in craving and activation during the crave-resist condition (Figure 5, Table 4), bupropion-treated participants exhibited significantly greater reductions in mean percent

Table 4. Local Maxima for Significant Associations Between Reduced Craving and Reduction in Activation From Before to After Treatment

Cue Condition, Association, and Region	*z* Score	x, y, z Coordinates[a]
Crave-resist: all subjects		
Medial orbitofrontal cortex, bilateral	4.06	0, 38, –18
	3.87	–4, 44, –24
	3.86	–6, 40, –22
Anterior cingulate cortex, left	3.67	–8, 42, 2
	3.58	–4, 38, 0
Crave-allow: all subjects		
Precentral gyrus, bilateral	3.31	2, –22, 60
	3.25	8, –30, 68
	3.23	–6, –14, 60
	3.09	10, –22, 62
	2.99	28, –26, 50
Crave-allow: placebo-treated subjects		
Precuneus, right	3.85	18, –54, 10
	3.65	12, –52, 12
	3.10	10, –60, 46
	2.85	10, –52, 40
Precentral gyrus, bilateral	3.46	8, –30, 68
	3.22	12, –26, 44
	3.17	–6, –14, 60
Postcentral gyrus, right	3.25	42, –32, 52
	3.21	40, –30, 58
	3.24	12, –44, 70
Posterior cingulate cortex, right	3.98	8, –48, 30
	2.93	12, –42, 40
Frontal pole, right	3.78	24, 68, 16
	3.72	28, 62, 12
	3.30	32, 56, 10
	3.18	42, 56, 10
	3.08	30, 54, 22
Central opercular cortex	3.36	50, –2, 2
	3.12	48, 6, 2
Inferior frontal gyrus	3.07	62, 16, 16
Transverse temporal gyrus	3.20	46, –24, 6
Superior temporal gyrus	3.10	62, –14, 8

[a] Coordinates in MNI152 standard space; x, y, z refer to right/left (x: positive = right), anterior/posterior (y: positive = anterior), dorsal/ventral (y: positive = dorsal).

signal change from before to after treatment (t_{28}= 2.301; *P*= .03) compared with placebo-treated participants.

COMMENT

Nicotine-dependent smokers treated with bupropion report significantly greater reductions in craving and exhibited reduced activation in the ventral striatum, medial orbitofrontal cortex, and anterior cingulate cortex when resisting craving compared with smokers treated with placebo. When assessing these specific regions, activation changes correlated positively with changes in craving from before to after treatment. The bupropion-treated group alone exhibited reduced activation in the anterior cingulate cortex and in secondary visual processing centers while resisting craving. While no craving or activation differences were observed between treatment groups before treatment, bupropion-treated participants reported significantly less craving and exhibited less ventral striatum and anterior cingulate cortex activation than placebo-treated participants when resisting craving after treatment. These results demonstrate that treatment with bupropion is associated with an improved ability to resist cue-induced craving and a reduction in cue-induced activation of limbic and prefrontal brain regions.

Our findings complement previous research demonstrating that nicotine-dependent smokers exhibit activation in the anterior cingulate cortex and ventral striatum as well as other brain regions that integrate information regarding executive function (prefrontal cortex), prior experience (hippocampus), emotion (amygdala), and reward (ventral tegmental area) while viewing smoking-related cues.[40-45] Bupropion treatment attenuates cue-induced metabolism in the anterior cingulate cortex[58] and, as demonstrated here, cue-induced activation of this region and other brain regions (ventral striatum and medial orbitofrontal cortex) known to be involved in drug craving and addiction.[81,82] Activation changes in these brain regions correlated with a reduction in craving, suggesting that modulation of limbic and prefrontal function associated with bupropion treatment may directly influence subjective craving.

The association between craving and brain activation observed during the crave-resist condition, irrespective of treatment, parallels previous research demonstrating a relationship between drug craving and activation of brain regions that are responsible for emotional and cognitive appraisal (anterior cingulate cortex) and conditioned reinforcement (medial orbitofrontal cortex).[40,70,82] Bupropion-treated participants exhibited reduced activation in these specific regions while resisting craving compared with placebo-treated participants. These findings further support the role of prefrontal regions in mediating cue-induced craving and support the primary finding of this study that bupropion treatment modulates activation in the anterior cingulate and medial orbitofrontal cortices.

Bupropion is reported to enhance smoking cessation by altering basal levels of dopamine though inhibition of dopamine reuptake while simultaneously modulating phasic dopamine release in the ventral striatum in response to smoking or smoking-related cues.[9,16,17,21,33,83-85] Although fMRI data remain difficult to interpret in the context of specific neurotransmitters, our results demonstrate that bupropion treatment induced changes in the dopamine-rich ventral striatum and functionally related anterior cingulate cortex[86] and medial orbitofrontal cortex. The anterior cingulate cortex collects information from limbic and prefrontal regions to assess the salience of emotional and motivational information, while the ventral striatum works in concert to mediate reward, particularly for drugs,[87,88] as well as predict and act on the presence of reward.[25,89] Research combining positron emission tomography and fMRI imaging has verified this functional association and revealed a positive correlation between dopamine synthesis capacity in the ventral striatum and blood oxygen level–dependent signal increases in the anterior cingulate cortex elicited by rewarding stimuli.[90] Hence, modulation of dopamine signaling in the ventral striatum via bupropion may alter reward signaling to the anterior cingulate cortex and associated prefrontal regions, attenuating affective ap-

praisal of smoking cues and relative reward salience, thereby leading to a reduction in craving.

Although no treatment-induced changes were seen in regions previously shown to differ when untreated smokers allow or resist craving,[70] the associations between craving and brain activation observed under these 2 conditions varied considerably. During the crave-allow condition, placebo-treated participants exhibited an association between changes in craving and activation in default mode networks (posterior cingulate cortex, precuneus)[91] and brain regions associated with imitation (frontal lobe, premotor cortex, superior parietal lobe, inferior frontal cortex[92]). This finding suggests that placebo-treated participants who reported less craving during the crave-allow condition were less engaged by the smoking-related cues. This effect was not observed in the bupropion-treated smokers or the combined sample (both treatment groups). Considering these findings, instructing smokers to allow cue-induced craving elicits brain activation associated with mentally mimicking or imagining smoking behavior while encouraging them to resisting craving influences brain regions that relate to conditioned reward and affective appraisal, providing a more relevant state for assessing smoking cessation therapies.

While published articles demonstrate roughly 35% to 40% short-term abstinence rates with bupropion treatment,[3,4] we expected a quit rate of approximately 20% in our bupropion-treated smokers because we did not provide concomitant behavioral intervention along with the medication administration as in prior studies. We did not include behavioral intervention in order to isolate the effects of bupropion treatment on regional brain activation. Although the bupropion-treated participants exhibited significantly greater reductions in FTND scores and exhaled carbon monoxide from before to after treatment and lower FTND scores after treatment (Table 1), no significant between-group difference was observed in cigarettes per day (though bupropion-treated smokers did, on average, have a greater reduction in this measure). The discrepancies between objective (exhaled carbon monoxide) and self-reported (cigarettes per day) smoking measures reported in placebo-treated smokers may reflect the desire of research participants to please study researchers. In addition to controlling for nicotine consumption in our primary analysis, we also replicated the primary finding of this study, excluding participants who quit smoking during treatment (bupropion, n=3; placebo, n=1) to ensure that the unbalanced number of quitters in each group did not unintentionally influence our findings (eFigure; http://www.archgenpsychiatry.com).

In summary, a standard course of treatment with bupropion enhances the ability of smokers to resist cue-induced craving, measured as reductions in self-reported craving and reduced activation in the ventral striatum, anterior cingulate, and medial orbitofrontal cortex.

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