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Brain Nicotinic Acetylcholine Receptor Availability and Response to Smoking Cessation Treatment
A Randomized Trial

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IMPORTANCE Cigarette smoking leads to upregulation of nicotinic acetylcholine receptors (nAChRs) in the human brain, including the common α4β2* nAChR subtype. While subjective aspects of tobacco dependence have been extensively examined as predictors of quitting smoking with treatment, no studies to our knowledge have yet reported the relationship between the extent of pretreatment upregulation of nAChRs and smoking cessation.

OBJECTIVE To determine whether the degree of nAChR upregulation in smokers predicts quitting with a standard course of treatment.

DESIGN, SETTING, AND PARTICIPANTS Eighty-one tobacco-dependent cigarette smokers (volunteer sample) underwent positron emission tomographic (PET) scanning of the brain with the radiotracer 2-FA followed by 10 weeks of double-blind, placebo-controlled treatment with nicotine patch (random assignment). Pretreatment specific binding volume of distribution (V_S/f_P) on PET images (a value that is proportional to $α_4β_2$* nAChR availability) was determined for 8 brain regions of interest, and participant-reported ratings of nicotine dependence, craving, and self-efficacy were collected. Relationships between these pretreatment measures, treatment type, and outcome were then determined. The study took place at academic PET and clinical research centers.

MAIN OUTCOMES AND MEASURES Posttreatment quit status after treatment, defined as a participant report of 7 or more days of continuous abstinence and an exhaled carbon monoxide level of 3 ppm or less.

RESULTS Smokers with lower pretreatment V_S/f_P values (a potential marker of less severe nAChR upregulation) across all brain regions studied were more likely to quit smoking (multivariate analysis of covariance, $F_{8,69} = 4.5$; $P < .001$), regardless of treatment group assignment. Furthermore, pretreatment average V_S/f_P values provided additional predictive power for likelihood of quitting beyond the self-report measures (stepwise binary logistic regression, likelihood ratio $\chi_1^2 = 19.8$; $P < .001$).

CONCLUSIONS AND RELEVANCE Smokers with less upregulation of available $α_4β_2$* nAChRs have a greater likelihood of quitting with treatment than smokers with more upregulation. In addition, the biological marker studied here provided additional predictive power beyond subjectively rated measures known to be associated with smoking cessation outcome. While the costly, time-consuming PET procedure used here is not likely to be used clinically, simpler methods for examining $α_4β_2$* nAChR upregulation could be tested and applied in the future to help determine which smokers need more intensive and/or lengthier treatment.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01526005

While the health risks[1,2] and societal costs[3-5] of cigarette smoking are well documented, the prevalence of smoking among adults in the United States remains high at approximately 20%.[6,7] Although most smokers endorse a desire to quit,[8] very few (<5%) will do so in a given year without treatment, and only about 20% to 25% will achieve abstinence even with 6 months or more of gold-standard treatment.[9-14] Therefore, there continues to be a vital need to improve outcomes for cigarette smokers seeking treatment.[15]

Prior research examining prediction of response to smoking cessation treatments has focused primarily on clinical variables, with the most commonly reported predictors of outcome being levels of nicotine dependence,[16-21] craving,[22,23] and self-efficacy.[24-28] Greater severity of nicotine dependence has been associated with poorer treatment outcome for nicotine patch,[16,21] bupropion hydrochloride,[18,19] and group psychotherapy[20] as well as in naturalistic settings with no specific treatment.[17] Similarly, low craving[22,23] and high self-efficacy[24-28] (self-confidence) have been repeatedly demonstrated to be predictors of successful treatment outcome,[27,29,30] especially in situations where smokers are at risk for relapse. Other factors, such as desire to quit,[31] low negative affect,[32] no history of depression,[33] low anger,[34] slow nicotine metabolism,[35] absence of lapses during early treatment,[36] and reduction in smoking over time,[37] have also been found to predict a positive response to treatment. Thus, clinical factors have been extensively examined for their value in predicting response to smoking cessation treatments; however, to our knowledge, there are no published studies examining brain receptor availability as a predictor of smoking cessation outcome.

Upregulation of β_2-containing nicotinic acetylcholine receptors (nAChRs) is one of the most well-established effects of smoking on the brain. Recent studies using single-photon emission computed tomography (CT)[38-40] and positron emission tomography (PET)[41-43] have demonstrated significant upregulation of these receptors in smokers compared with nonsmokers in all brain regions studied other than the thalamus. These in vivo studies were an extension of much prior research, including human postmortem brain tissue studies demonstrating that long-term smokers have increased nAChR density compared with nonsmokers and former smokers.[44,45] Additionally, many studies of laboratory animals have demonstrated upregulation of markers of nAChR density in response to long-term nicotine administration.[46-50]

For this study, we sought to determine whether the degree of pretreatment $\alpha_4\beta_2^*$ nAChR upregulation in cigarette smokers is associated with smoking cessation outcomes with a standard nicotine patch taper. In a smaller prior PET study by our group,[51] we found possible associations that did not reach statistical significance between lower levels of a PET marker for $\alpha_4\beta_2^*$ nAChR availability and improved outcome across 3 smoking cessation treatment groups. Therefore, we hypothesized that smokers with less pretreatment upregulation of available $\alpha_4\beta_2^*$ nAChRs would have a greater likelihood of quitting smoking with the nicotine patch taper than smokers with more upregulation. We also sought to determine whether pretreatment $\alpha_4\beta_2^*$ nAChR availability provided additional predictive power beyond previously reported clinical predictors (severity of nicotine dependence,[16-21] craving,[22,23] and self-efficacy[24-27]).

Methods

Participants and Screening Methods

Eighty-one treatment-seeking adult smokers completed the study and had usable data. These participants underwent a baseline screening visit, rating scale administration, pretreatment PET/CT scanning with the radiotracer 2-FA (for labeling $\alpha_4\beta_2^*$ nAChRs), and double-blind, placebo-controlled treatment with nicotine patch taper (see eFigure in Supplement for details of numbers of screening failures and attrition).

Participants were recruited using the same methods as in prior reports,[41,51] with the central inclusion criteria being tobacco dependence at the time of study initiation, smoking 10 to 40 cigarettes per day, and general good health. Exclusion criteria were pregnancy, use of a medication or presence of a medical condition that might affect the brain at the time of scanning, or any history of an Axis I mental illness or substance abuse or dependence.

During the baseline screening visit, rating scales were administered to verify participant reports and characterize smoking history, which included the Smoker's Profile Form (containing demographic variables and a detailed smoking history), Fagerström Test for Nicotine Dependence (FTND),[52] Hamilton Depression Rating Scale,[53] Hamilton Anxiety Rating Scale,[54] and screening questions from the Structured Clinical Interview for *DSM-IV* Axis I Disorders, Patient Edition, version 2.0.[55] An exhaled carbon monoxide (CO) level was obtained (Micro-Smokerlyzer; Bedfont Scientific Ltd) to verify smoking status (CO ≥8 ppm). A breathalyzer test (AlcoMatePro), urine toxicology screen (Test Country I-Cup Urine Toxicology Kit), and urine pregnancy test (for women of childbearing potential; Test Country Cassette Urine Pregnancy Test) were performed to support the participant's report of no current alcohol or drug dependence and no pregnancy. The study was approved by the institutional review board and radiation safety committee of the VA Greater Los Angeles Healthcare System, and participants provided written informed consent.
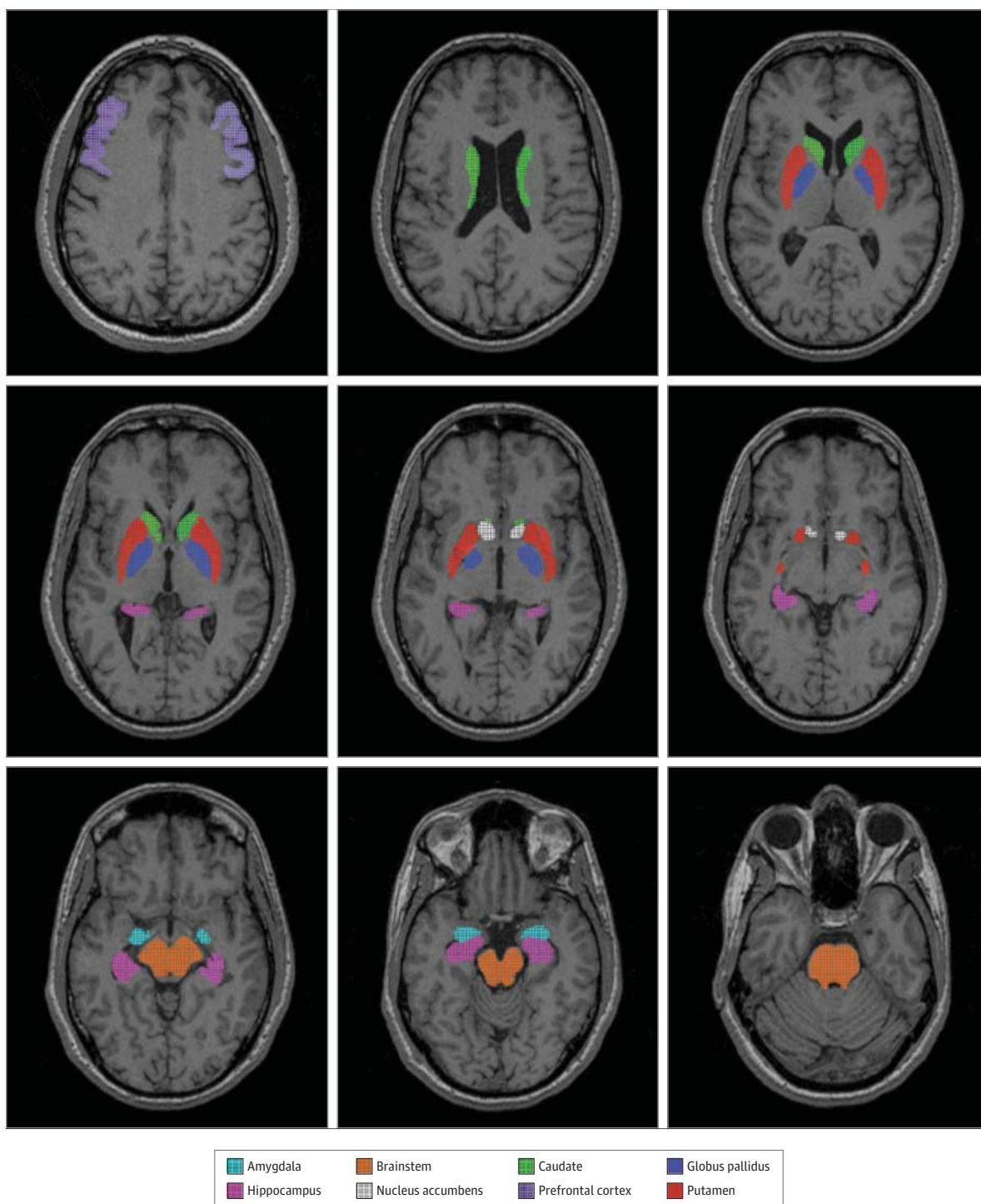
Abstinence Period and PET Protocol

One week after the baseline screening session, participants underwent PET/CT scanning with the same abstinence and 2-FA bolus-plus-continuous-infusion PET/CT protocol as in our recent studies (see eAppendix in Supplement for details).[41,51] Briefly, participants underwent 2 nights of smoking/nicotine abstinence, followed by a bolus-plus-continuous-infusion PET/CT session during which PET/CT data were collected for 3 hours following a 4-hour radiotracer uptake period. During the uptake period, the Urge to Smoke (UTS)[56] craving scale (an analog scale with 10 craving-related questions rated 0-6) and Self-efficacy Rating Scale[57,58] (ratings from 0-100) were administered.

Treatment for Cigarette Smoking

Within a week of PET/CT scanning, participants were randomly assigned[59] to treatment with either active transder-

Figure 1. Study Regions of Interest Shown on a Representative Magnetic Resonance Imaging Scan

	Amygdala		Brainstem		Caudate		Globus pallidus
	Hippocampus		Nucleus accumbens		Prefrontal cortex		Putamen

mal nicotine patches (Nicoderm CQ 24-hour patches; Cardinal Health Pharmaceuticals) or matching placebo patches (Rejuvenation Laboratories, Inc) in a manner similar to that of past research by our group[60,61] and others.[62,63] To maintain the double-blind design, patches were prepared by a research pharmacist and given to participants by a research assistant who was not involved in the participant's treatment.

Participants met with a study physician (M.S.M. or A.L.B.) for an initial visit, were given nicotine or placebo patches, and were told of potential benefits and adverse effects[64-66] of the nicotine patch. They were then seen weekly by a study physician for the remainder of the trial for 15-minute medication management visits, which consisted of assessment of adherence to the medication regimen, monitoring of smoking behavior,[67-69]

and evaluation of adverse effects. Participants assigned to the active patch group received a standard course of treatment beginning with 21-mg/d patches for 4 weeks followed by 14-mg/d patches for 2 weeks and 7-mg/d patches for 2 weeks, while the placebo patch group underwent an identical patch regimen without nicotine. Participants were encouraged to minimize or eliminate cigarette use when they initiated treatment and to choose a quit date 2 weeks after treatment initiation. If participants lapsed into smoking during treatment, they were encouraged to pick another quit date within the following week. After 8 weeks of patch treatment, participants were seen for study visits on 2 consecutive weeks (10 weeks total treatment). Although we recognize that combining medication with psychotherapy would have resulted in an enhanced smoking cessation rate,[8,70,71] no formal psychotherapy was provided so that the relationship between pretreatment brain nAChR availability and nicotine or placebo patch response could be isolated.

At the final study visit, a participant report of 7 or more days of continuous abstinence from any tobacco use and an exhaled CO level of 3 ppm or less were used as criteria for having quit smoking. These criteria are similar to recent recommendations for documenting smoking abstinence[72,73] and are comparable to criteria used in many treatment studies.[9,13,35] Participants who initiated treatment but dropped out of the study were classified as nonquitters in accordance with recent recommendations[72,74] and use[75] of this classification. At the conclusion of the medication or placebo trial, all participants were offered open-label treatment with nicotine patch to assist in smoking cessation and to address (at least partly) ethical concerns[76] about the use of placebo treatment in this study.

PET Image Analysis

After decay and motion correction, each participant's PET/CT scan was coregistered to his or her magnetic resonance imaging scan using PMOD version 3.0 software (http://www.pmod.com/technologies). Regions of interest (ROIs) were drawn on magnetic resonance images using PMOD and transferred to the coregistered PET (**Figure 1**). Most regions were delineated automatically using the Functional Magnetic Resonance Imaging of the Brain Software Library program FIRST, which created automated drawings through model-based segmentation. These automated regions were generated from conditional probabilities based on shape and intensity[77] from each participant's magnetic resonance imaging scans and included the following regions bilaterally: nucleus accumbens, amygdala, caudate, hippocampus, globus pallidus, and putamen. In addition, hand-drawn ROIs consisted of representative slices of the prefrontal cortex (middle frontal gyrus) bilaterally and the whole brainstem. These ROIs were chosen based on having a range of nAChR densities, while the thalamus was specifically excluded from analysis because it is known not to have significant upregulation of $\alpha_4\beta_2$* nAChRs in smokers. To preserve power, mean values of bilateral ROIs were used, so a total of 8 ROI values for each participant were used for statistical analysis. Placement of ROIs was visually inspected for each PET frame to minimize effects of coregistration errors and movement; ROI placement procedures were repeated if there was a noticeable problem.

Specific binding volume of distribution (designated as V_S/f_P based on standard nomenclature[78]) was calculated for each ROI and used for all ROI-based analyses because this value is proportional to $\alpha_4\beta_2$* nAChR availability (see eAppendix in Supplement for details of this calculation).

Statistical Analysis

Means and standard deviations were determined for demographic, rating scale, and smoking-related variables for the entire study sample and subgroups based on treatment type. Baseline data were compared between the nicotine and placebo patch subgroups using t tests for continuous data and Fisher exact tests for categorical data to confirm the success of randomization. For verifying the effect of treatment on smoking-related variables, repeated-measures analyses of variance were performed, with the smoking-related variables (cigarettes per day and exhaled CO levels) as repeated measures and treatment subgroup (nicotine vs placebo patch) as the between-subject factor.

To determine the relationship between $\alpha_4\beta_2$* nAChR availability, treatment type, and quit status, an overall multivariate analysis of covariance (ANCOVA) was performed using V_S/f_P values for the 8 ROIs as the measures of interest, subgroup (placebo or nicotine patch) and quit status as factors, and age as a nuisance covariate (based on prior research indicating that nAChR densities decline with age[41,79,80]). Follow-up ANCOVAS were performed for the ROIs separately with the same variables as in the overall multivariate ANCOVA. For descriptive purposes, mean V_S/f_P values for quitters and nonquitters were compared with available values from nonsmoking control participants in a previous study,[41] and percentage of upregulation for these 2 groups was calculated.

For determining whether PET V_S/f_P data improve the ability to predict treatment response beyond self-report measures, binary logistic regression was used, as in prior studies.[16,18,28,81] For this analysis, quit status was the outcome variable and pretreatment PET V_S/f_P values (mean of all ROIs based on the preceding analysis, which did not reveal regional differences), severity of nicotine dependence (FTND score), subjective UTS craving ratings, and self-efficacy ratings were the independent variables. To specifically determine whether the PET data provided additional predictive power beyond the well-studied measures, a stepwise logistic regression was performed with the 3 self-report measures entered first followed by the PET V_S/f_P data (along with the same analysis in reverse order). Statistical tests were performed using PASW/SPSS Statistics version 21.0 statistical software (SPSS, Inc).

Results

Baseline Demographic and Rating Scale Data

At baseline, the study sample was middle-aged, roughly half female, and approximately half white, with some college education and minimal anxiety and depressive symptoms (**Table 1**). Participants smoked roughly three-quarters of a pack of cigarettes per day and were moderately nicotine dependent. Study subgroups based on randomly assigned treatment type (n = 44 randomized to nicotine patch and n = 41 included in analysis

Table 1. Demographic, Rating Scale, and Smoking-Related Variables for the Study Sample
and Subgroups Randomly Assigned to Placebo or Nicotine Patch Treatment

		Patch-Treated Subgroup[a]	
Variable	Study Sample (N = 81)	Placebo (n = 40)	Nicotine (n = 41)
Age, mean (SD), y	40.7 (12.6)	42.7 (11.9)	38.6 (13.1)
Female, No. (%)	37 (45.7)	18 (45.0)	19 (46.3)
White, No. (%)	39 (48.1)	17 (42.5)	22 (53.7)
Education, mean (SD), y	14.5 (2.2)	14.3 (2.2)	14.8 (2.2)
Hamilton Anxiety Rating Scale score, mean (SD)	2.5 (2.8)	2.2 (2.1)	2.8 (3.4)
Hamilton Depression Rating Scale score, mean (SD)	2.5 (2.9)	2.3 (2.5)	2.7 (3.2)
FTND score, mean (SD)	4.4 (2.1)	4.6 (2.0)	4.3 (2.2)
Longest quit period, mean (SD), y	1.0 (1.6)	0.9 (1.5)	1.1 (1.7)
Cigarettes, No./d			
Pretreatment	15.4 (4.5)	15.4 (4.7)	15.3 (4.3)
Posttreatment	6.8 (8.0)[b]	7.5 (7.1)[b]	6.3 (8.7)[b]
Change in cigarettes/d with treatment, mean (SD), %	−57.8 (43.6)	−52.7 (41.4)	−62.7 (45.6)
Exhaled CO, mean (SD), ppm			
Pretreatment	13.8 (6.3)	14.5 (6.6)	13.1 (6.0)
Posttreatment	8.7 (7.2)[b]	10.5 (7.8)[b]	6.9 (6.2)[b]
Change in exhaled CO with treatment, mean (SD), %	−36.6 (42.7)	−28.7 (38.6)	−44.2 (45.5)
Smokers who quit with treatment, No. (%)	20 (24.7)	6 (15.0)	14 (34.1)[c]

Abbreviations: CO, carbon monoxide; FTND, Fagerström Test for Nicotine Dependence.

[a] No significant differences were found for baseline demographic or rating scale variables between smokers randomly assigned to the placebo vs nicotine patch treatment subgroups (*t* tests for continuous variables and Fisher exact tests for categorical variables).

[b] $P < .001$ for within-group changes in cigarettes per day and exhaled CO from before to after treatment (paired *t* test).

[c] $P = .04$ for difference between placebo and nicotine patch subgroups in percentage of quitters (Fisher exact test).

Table 2. Pretreatment Specific Binding Volume of Distribution for Brain Regions of Interest for Nonquitters and Quitters in the Total Study Group
and the Placebo and Nicotine Patch Subgroups

	V_S/f_P, Mean (SD)[a]					
	Total Group		Placebo Patch		Nicotine Patch	
Brain Region	Nonquitters (n = 61)	Quitters (n = 20)	Nonquitters (n = 34)	Quitters (n = 6)	Nonquitters (n = 27)	Quitters (n = 14)
Amygdala	5.5 (2.7)	2.7 (1.2)	5.9 (2.6)	2.6 (1.2)	5.0 (2.8)	2.8 (1.3)
Brainstem	10.9 (3.4)	6.7 (1.9)	11.5 (3.5)	6.2 (1.7)	10.1 (3.1)	7.0 (2.0)
Caudate	7.1 (2.4)	5.2 (1.5)	7.6 (2.6)	4.7 (1.3)	6.6 (2.1)	5.5 (1.6)
Globus pallidus	10.2 (3.4)	6.0 (1.8)	10.9 (3.4)	5.6 (1.7)	9.5 (3.3)	6.1 (1.8)
Hippocampus	6.7 (3.0)	3.8 (1.3)	7.2 (2.9)	3.5 (1.4)	6.1 (3.1)	3.9 (1.3)
Nucleus accumbens	7.7 (3.6)	4.6 (1.8)	8.1 (3.4)	4.1 (1.3)	7.2 (3.9)	4.8 (2.0)
Putamen	9.7 (3.6)	5.9 (1.7)	10.3 (3.5)	5.4 (1.4)	8.8 (3.6)	6.1 (1.8)
Prefrontal cortex	6.9 (3.3)	4.0 (1.5)	7.5 (3.0)	3.6 (1.5)	6.2 (3.5)	4.2 (1.6)

Abbreviation: V_S/f_P, specific binding volume of distribution.

[a] All values are presented as the mean of left and right regions of interest, where applicable. The overall multivariate analysis of covariance examining the relationship between pretreatment V_S/f_P values, treatment type, and quit status revealed a significant main effect of quit status ($F_{8,69} = 4.5$; $P < .001$), resulting from quitters having lower pretreatment V_S/f_P values than nonquitters. In post hoc analyses of covariance, all of the individual regions of interest had significant associations with quit status ($F_{1,80} = 10.4\text{-}24.9$; $P = .002$ to <.001) but no significant interaction between treatment type and quit status.

in nicotine patch subgroup; n = 44 randomized to placebo patch and n = 40 included in analysis in placebo patch subgroup) (eFigure in Supplement) did not differ on any demographic variables or rating scale scores (Table 1).

Effects of Treatment on Smoking-Related Variables
As expected, treatment was associated with a decrease for the entire study sample in number of cigarettes per day (mean [SD], −57.8 [43.6%]; $F_{1,79} = 106.4$; $P < .001$) and exhaled CO level (mean [SD], −36.6% [42.7%]; $F_{1,79} = 44.0$; $P < .001$). Subgroup × time interactions corresponding to differential change in cigarettes per day and exhaled CO level were not significant ($F_{1,79} = 0.5$, $P = .50$; and $F_{1,79} = 2.2$, $P = .16$, respectively), but the nicotine patch subgroup had greater numerical reduc-

tions in these measures than the placebo patch subgroup (Table 1). Twenty of the 81 participants met criteria for quitting smoking, and active nicotine patch treatment was associated with a higher percentage of quitters than placebo patch treatment (34.1% vs 15.0%, respectively; Fisher exact test, $P = .04$) (Table 1).

Pretreatment $V_S f_P$ Values and Smoking Cessation
The overall multivariate ANCOVA revealed a significant main effect of quit status ($F_{8,69} = 4.5$; $P < .001$), resulting from quitters having lower pretreatment V_S/f_P values than nonquitters (Table 2 and Figure 2). In follow-up ANCOVAs, all ROIs had significant associations with quit status ($F_{1,80} = 10.4\text{-}24.9$; $P = .002$ to <.001), indicating that the relationship between pretreat-

Figure 2. Mean Pretreatment Positron Emission Tomographic Images From the Study Subgroups Demonstrating Higher 2-FA Binding at Baseline in Nonquitters Compared With Quitters
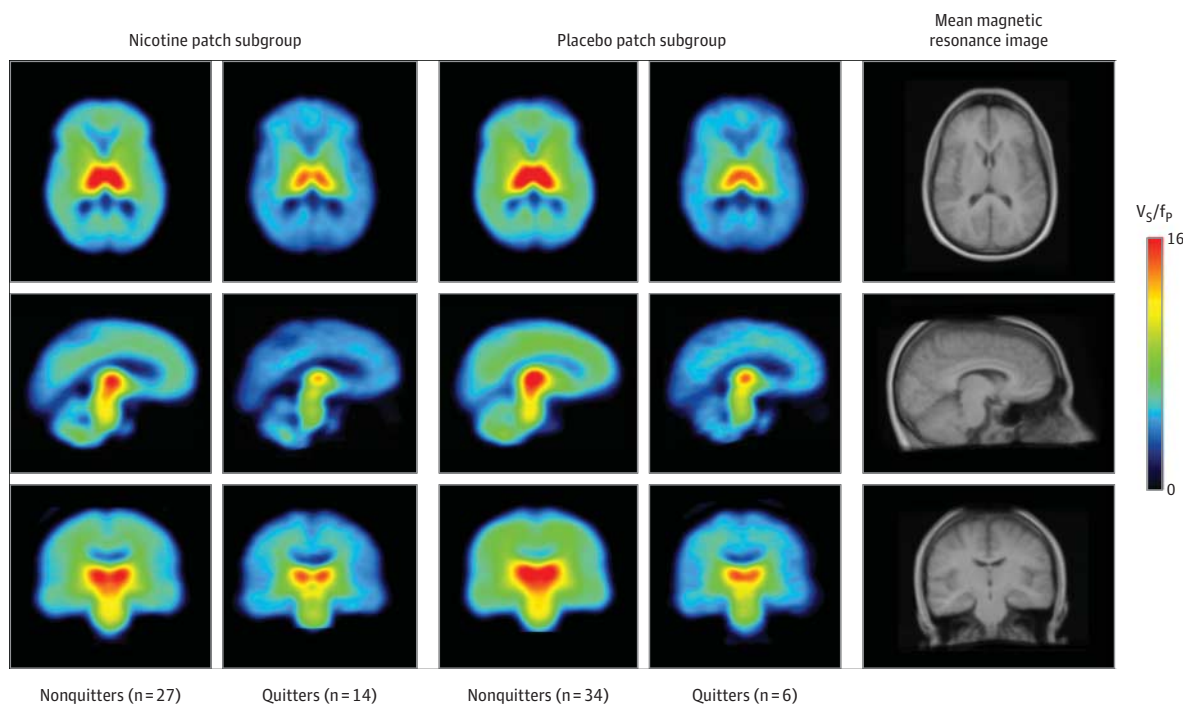
Mean pretreatment positron emission tomographic scans are shown for nonquitters and quitters treated with nicotine patch and for those treated with placebo patch. Positron emission tomographic images were spatially normalized to the group mean magnetic resonance imaging scan. V_S/f_P indicates specific binding volume of distribution.

Table 3. Logistic Regression Analyses of Rating Scale Scores, Specific Binding Volume of Distribution, and the Combined Model of Rating Scale Scores Plus Specific Binding Volume of Distribution for the Prediction of Quit Status With Treatment[a]

Variable	Rating Scale Score		V_S/f_P		Rating Scale Score + V_S/f_P	
	χ^2 (df)	P Value	χ^2 (df)	P Value	χ^2 (df)	P Value
Wald χ^2						
FTND score	0.1 (1)	.77			0.002 (1)	.96
UTS craving scale score	4.9 (1)	.03			2.6 (1)	.11
Self-efficacy	1.6 (1)	.21			0.4 (1)	.51
V_S/f_P			17.1 (1)	<.001	10.5 (1)	.001
Model χ^2	11.0 (3)	.01	26.4 (1)	<.001	30.7 (4)	<.001

Abbreviations: FTND, Fagerström Test for Nicotine Dependence; UTS, Urge to Smoke; V_S/f_P, specific binding volume of distribution.

[a] Logistic regression analyses of quit status as determined by rating scale scores alone, V_S/f_P values alone, and all measures combined. Comparison likelihood ratio χ^2 test results were as follows: for rating scale score + V_S/f_P vs rating scale score, $\chi_1^2 = 19.8$, $P < .001$; for rating scale score + V_S/f_P vs V_S/f_P, $\chi_3^2 = 4.3$, $P = .23$. Likelihood ratio tests show that V_S/f_P significantly increases the predictive power of rating scale scores but that rating scale scores do not significantly supplement the predictive power of V_S/f_P values.

ment nAChR availability and quitting was not region specific. The interaction between treatment type and quit status was not significant ($F_{8,69} = 0.8$; $P = .70$), indicating that the relationship between pretreatment nAChR availability and quit status was not dependent on treatment type. For the brainstem and prefrontal cortex, quitters had means of 20% and 29% upregulation of nAChR availability, respectively, compared with available data from previously scanned nonsmoking control participants,[41] while nonquitters had 66% and 80% upregulation in these respective regions.

Pretreatment Variables and Smoking Cessation

For the logistic regression analysis, the overall test was significant ($\chi_4^2 = 30.7$; $P < .001$), indicating that the combination of PET and clinical factors has high value in predicting treatment outcome (Table 3). For the individual variables, pretreatment PET V_S/f_P values ($P < .001$), UTS craving scores ($P = .003$), and self-efficacy scores ($P = .02$) were all associated with quit status, while FTND score did not reach statistical significance ($P = .25$). In comparing respective mean values of these predictors, quitters compared with nonquitters had lower pretreatment PET

V_S/f_P values (4.9 vs 8.1), lower UTS scores (2.2 vs 3.4), lower FTND scores (4.0 vs 4.6), and higher self-efficacy scores (60 vs 46). Furthermore, in the stepwise logistic regression, pretreatment PET V_S/f_P values provided additional predictive power beyond the self-report measures alone (for comparing the fit of the nested models: likelihood ratio $\chi^2_1 = 19.8$; $P < .001$).

Discussion

Cigarette smokers with less severe upregulation of available brain $\alpha_4\beta_2$* nAChRs have an improved chance of quitting smoking with treatment than smokers with more severe upregulation. This finding was present in smokers treated with nicotine and placebo patch and is consistent with a preliminary indication in a prior report by our group examining smaller groups of smokers treated with cognitive behavioral therapy, bupropion, or pill placebo.[51] Furthermore, the degree of $\alpha_4\beta_2$* nAChR upregulation (a biological phenomenon) was significantly associated with quitting even after adjusting for known associations between subjectively rated symptoms (severity of nicotine dependence, craving, and self-efficacy) and quit status, indicating a very strong association between the biological measure and quitting. Prior research indicates that the level of upregulation of $\alpha_4\beta_2$* nAChR availability may primarily reflect the extent of nicotine exposure[51]; therefore, the biological measure determined here may indicate that markers of brain nicotine exposure may be highly useful in predicting smoking cessation treatment response. This hypothesis is supported by prior research indicating that plasma and salivary markers of greater nicotine exposure are associated with worse treatment response.[82,83] Findings here were also widespread throughout the brain, including all ROIs studied, which is consistent with prior research demonstrating significant upregulation of nAChR densities in all brain regions studied other than the thalamus.[41]

Predictors of response are helpful for treatment planning in smoking cessation programs because smokers with poorer projected outcomes may need more intensive and/or lengthier treatment than smokers with better projected outcomes.[84,85] While the costly, time-consuming PET procedure used here is not likely to be used clinically, simpler PET or single-photon emission CT methods with shorter scanning times (ie, <1 hour, as is common with brain imaging[86-88]) could be tested and applied to help guide treatment for cigarette smoking in the future. Our study indicates that smokers with greater upregulation of nAChRs may require higher medication doses (eg, higher doses of nicotine patch or patch plus another form of nicotine replacement) or more intensive psychotherapy than smokers with less upregulation. In addition, these methods of predicting treatment response could be tested for other medications that affect nAChRs, such as other forms of nicotine replacement or the $\alpha_4\beta_2$* nAChR partial agonist varenicline tartrate,[89,90] or for combination treatment including psychotherapy (as is commonly used in clinical practice[8,91]).

A central limitation of the study was sample size. Although this study was relatively large for a PET experiment of this type, relatively few smokers (15%) quit with placebo patch treatment. While this low quit rate with placebo patch was expected, the small number of quitters in this subgroup precluded a definitive determination of the interaction between nAChR availability, treatment type, and quit status. However, it should be noted that quitters and nonquitters in both treatment subgroups had similar nAChR availabilities (Table 2) and that findings here were consistent with a prior study in which pill placebo was one of the interventions.[51] Another limitation of the study was the absence of follow-up beyond the acute phase of treatment, given that smokers who quit with short-term (several-month) treatment may relapse over longer periods.[92] Because of this limitation, results here should be interpreted with caution regarding long-term smoking cessation outcomes. A third limitation was that participants were not excluded for previous history of nicotine patch use, which could have affected the blinding. Additionally, while our findings have been consistent for otherwise healthy moderate smokers, future studies could include smokers with more complex psychiatric and drug or alcohol dependence histories or lighter (<10 cigarettes/d) or heavier (>40 cigarettes/d) smoking for even greater generalizability.

Conclusions

Cigarette smokers with less upregulation of available brain α4β2* nAChRs have an improved chance of quitting smoking than smokers with more upregulation. This association was significant even after controlling for known associations between subjectively rated symptoms (severity of nicotine dependence, craving, and self-efficacy) and quit status, indicating a very strong association between this biological measure and quitting. Because prior research demonstrates that the extent of α4β2* nAChR upregulation is a marker for brain nicotine exposure, this study indicates that markers for brain nicotine exposure may be highly useful in the future for predicting smoking cessation treatment responses.

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