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Brief Report

BRIEF REPORT

Cigarette Use and Striatal Dopamine D2/3 Receptors: Possible Role in the Link between Smoking and Nicotine Dependence

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Abstract

Background: Cigarette smoking induces dopamine release in the striatum, and smoking- or nicotine-induced ventral striatal dopamine release is correlated with nicotine dependence. Smokers also exhibit lower dopamine D2/3 receptor availability in the dorsal striatum than nonsmokers. Negative correlations of striatal dopamine D2/3 receptor availability with smoking exposure and nicotine dependence, therefore, might be expected but have not been tested.
Methods: Twenty smokers had positron emission tomography scans with [^{18}F]fallypride to measure dopamine D2/3 receptor availability in ventral and dorsal regions of the striatum and provided self-report measures of recent and lifetime smoking and of nicotine dependence.
Results: As reported before, lifetime smoking was correlated with nicotine dependence. New findings were that ventral striatal dopamine D2/3 receptor availability was negatively correlated with recent and lifetime smoking and also with nicotine dependence.
Conclusion: The results suggest an effect of smoking on ventral striatal D2/3 dopamine receptors that may contribute to nicotine dependence.

Keywords: nicotine dependence, dopamine, D2 receptors, positron emission tomography

Introduction

Cigarette smoking is a major contributor to premature death throughout the civilized world through its role in promoting disease, including cancer as well as cardiovascular, pulmonary, and metabolic diseases (National Center for Chronic Disease, 2014). Although smoking cessation reverses many of the negative consequences of cigarette use (Thun et al., 2013), long-term abstinence from smoking is difficult to achieve and relapse rates are high even with treatment (Prochaska and Benowitz, 2016). Thus, new efficacious treatments are needed, and enhanced knowledge of the mechanisms that promote nicotine dependence may facilitate their design.

Like other addictive drugs, nicotine administration acutely increases synaptic dopamine. In human studies, positron emission tomography (PET) has revealed decreases in striatal dopamine D2-type (i.e., D2 and D3, D2/3) receptor availability (binding potential, BP_{ND}), reflecting dopamine release in the ventral

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Significance Statement

This study utilized positron emission tomography to measure striatal dopamine D2/3 receptor availability in cigarette smokers. D2/3 receptor availability in ventral striatum was negatively correlated with measures of recent and lifetime smoking and of nicotine dependence. Additionally, a negative relationship of lifetime smoking with nicotine dependence was not significant when controlling for D2/3 receptor availability in ventral striatum. These results suggest a potential role of smoking-induced D2/3-receptor down regulation in ventral striatum on nicotine dependence.

striatum, following cigarette smoking (Brody et al., 2004; Le Foll et al., 2014). The magnitude of dopamine release in the ventral striatum has been related to relief of cigarette craving and withdrawal symptoms (Brody et al., 2004; Le Foll et al., 2014). These findings suggest a role of ventral striatal dopaminergic signaling in nicotine dependence.

In male smokers, D2/3 BP_{ND} in the putamen was lower than in nonsmokers both immediately after smoking and after 24 hours of abstinence (Fehr et al., 2008). The difference in baseline BP_{ND} in males was replicated in a study that showed a similar difference in the caudate nucleus but no smoking-related group difference in women (Brown et al., 2012). Nicotine dependence has been correlated positively with lifetime cigarette smoking (Lindberg et al., 2015) and negatively with D2/3 BP_{ND} in the ventral striatum and the anterior putamen (Montgomery et al., 2007), but associations of D2/3 BP_{ND} with recent or lifetime cigarette smoking have not been reported. The goal of this study, therefore, was to test for associations of dopamine D2/3 BP_{ND} in the ventral and dorsal striatum with recent and lifetime cigarette use; negative associations were expected. A secondary goal was to determine whether striatal D2/3 BP_{ND} plays a role in the observed relationship between lifetime smoking and nicotine dependence.

Methods

Participants

All procedures were approved by the University of California Los Angeles Office for the Protection of Research Subjects. Twenty participants, 18 to 55 years old, who endorsed daily smoking, were recruited using Internet and local newspaper advertisements. After receiving a complete explanation of the study procedures, the participants provided written, informed consent and were screened for eligibility, and carbon monoxide in expired air was measured to verify recent smoking. Exclusion criteria were use of any psychotropic medications; presence of central nervous system, cardiovascular, pulmonary, or systemic disease; human immunodeficiency virus-seropositive status; hepatic disease; pregnancy; lack of English fluency; magnetic resonance imaging (MRI) contraindications; or current DSM-IV Axis-I diagnoses except for nicotine dependence, measured using the Structured Clinical Interview for DSM-IV.

Demographics and Smoking-Related Ratings

Data collected included age, sex, and recent as well as lifetime smoking history and use of other substances (e.g., alcohol and marijuana) in the month before enrollment. Lifetime smoking was measured in pack-years (i.e., packs per day × years of smoking). In cases where smoking cessation had exceeded 1 year, the time was subtracted from the years of smoking. The Fagerström Test for Nicotine Dependence (FTND) was used to measure dependence.

PET/MRI Scanning and Data Processing

Participants were abstinent from smoking for >2 h before each PET scan, which was performed with [^{18}F]fallypride, a radiotracer for dopamine D2/3 receptors. PET data were acquired using a Siemens ECAT EXACT HR+ scanner, which has an in-plane resolution full-width at half-maximum of 4.6 mm, axial resolution full-width at half-maximum of 3.5 mm, and an axial field of view of 15.52 cm in the 3D mode. Participants were placed in the supine position with the head secured with plastic tape to avoid movement during the scan. After a transmission scan using a rotating ^{68}Ga/^{68}Ge rod source, emission data were collected for 80 minutes after a bolus injection of 185 MBq (±10%; range of 175–203 MBq) [^{18}F]fallypride, which had a specific activity of >1 Ci/μmol; 3.19–21.6 Ci/μmol). Participants were then removed from the scanner for a 20-minute break. They then returned to the scanner and were repositioned, and emission data were collected for 80 minutes.

Reconstructed PET data were combined into 16 frames, each containing data averaged over 10 minutes. FSL MCFLIRT (FMRIB Centre, Department of Clinical Neurology, University of Oxford, Oxford, UK) was used to correct for head motion. Structural MRI scans of the brain were acquired for co-registration with PET images and definition of volumes-of-interest (VOIs). A T1-weighted scan was acquired using a whole-brain magnetization-prepared rapid acquisition with gradient echo (MPRAGE) (TR = 1900 ms, TE = 4.38 ms, flip angle = 15, field of view = 256 × 256 × 160, 160 slices, thickness = 1 mm). PET data were co-registered to the respective MPRAGE images using FSL FLIRT.

A VOI encompassing the whole striatum was first anatomically defined using FSL FIRST on the MPRAGE image of each participant, then a VOI for the ventral striatum was separated according to anatomical landmarks (Mawlawi et al., 2001). The rest of the striatum was defined as dorsal striatum. In addition, for exploratory analyses, VOIs representing extrastriatal regions (i.e., thalamus, globus pallidus, amygdala, and hippocampus) were generated using FSL FIRST. The cerebellum, which has a very low concentration of D2/3 dopamine receptors, was used as a reference region. Cerebellar VOIs, manually drawn on hemispheres while avoiding the vermis in standard space (MNI152 template), were transformed into native space with FSL FNIRT. Time-activity data within VOIs were extracted from motion-corrected, co-registered PET images and imported into PMOD Kinetic Modeling (PMOD Technologies Ltd., Zurich, Switzerland). A volume-weighted average of k2′, the rate constant for the transfer of the radiotracer from the reference-region tissue compartment to the plasma, was estimated from time-activity data for regions of high receptor density (caudate and putamen VOIs as determined by FSL FIRST) using the simplified reference tissue model (Lammertsma and Hume, 1996). The time-activity data for VOIs were refit with the simplified reference tissue model 2 (Wu and Carson, 2002) using PMOD Kinetic Modeling, fixing the computed k2′value. Receptor availability was then calculated as BP_{ND} = R1*k2′/k2a − 1, where R1 = K1/K1′ is the ratio of tracer-delivery parameters from plasma to tissues in the target region and reference region, and k2a is the

single-compartment rate constant for transfer from the target-region tissue compartment to plasma.

Statistical Analyses

Pearson correlation analysis was used to evaluate relationships between cigarettes/day, pack-years, and FTND. Relationships of BPND with cigarettes/day and FTND were evaluated using partial correlation analysis controlling for age and sex. Statistical analyses involving pack-years were performed controlling solely for sex, because age is highly correlated with pack-years. To test potential effects of aging and lifetime smoking on striatal volume, Pearson correlation analysis was conducted to evaluate relationships of striatum volume with age and pack-years. Multiple regression analysis was conducted to assess whether ventral striatal BPND contributes to the relationship of lifetime smoking with nicotine dependence, with FTND score as the dependent variable, and sex, pack-years, and ventral striatal BPND as independent variables. All of the statistical analyses were conducted using SPSS IBM 19 (IBM, Armonk, NY). The criterion for statistical significance was $P < .05$ (2-tailed). P values for correlation analysis involving striatal BPND were corrected for 2 comparisons (i.e., ventral and dorsal striatum), whereas P values for the extrastriatal regions were not corrected, because analyses of data from these regions was exploratory.

Results

Participant Characteristics

There were 20 (11 males and 9 females) participants, 37.8±7.50 (mean ± SD) years of age, in the study. Although all endorsed daily smoking, each met the criterion of a CO level >8ppm in expired air at screening, and mean expired CO at screening was 17.4±7.51ppm; only 12 participants met DSM-IV criteria for current nicotine dependence. On average, the participants started smoking regularly at 19.5±9.14 years of age, with recent daily consumption of 14.1±5.73 cigarettes and a lifetime smoking history of 13.7±6.93 pack-years. The average FTND score was 3.7±1.87, ranging from 0 to 7. Twelve participants reported using alcohol in the month before study, with use on 4.2±2.73 days in the month. Two participants reported recent, light marijuana use, each indicating use on 1 day during the month before enrolling in the study.

Associations of Current and Lifetime Smoking with Nicotine Dependence and D2/3 BPND and of Nicotine Dependence with BPND

Lifetime smoking, measured in pack-years, was correlated with FTND score (r = 0.471, P = .04 [controlled for sex]), whereas recent use, indicated by cigarettes/day, was not (r = 0.301, P = .20 [controlled for sex]). However, both measures of cigarette use were negatively correlated with BPND in the ventral striatum (pack-years: r = -0.640, P = .006 [controlled for sex]); cigarettes/day: r = -0.587, P = .02 [controlled for age and sex]). BPND in dorsal striatum was not significantly correlated with either index (pack-years: r = -0.350, P = .28; cigarettes/day: r = -0.330, P = .36 [controlled for age and sex]). BPND in both striatal regions was significantly negatively correlated (controlled for age and sex) with FTND score (ventral: r = -0.610, P = .01; dorsal: r = -0.552, P = .04) (Figure 1).

Exploratory analyses showed associations of BPND in other subcortical regions with current and lifetime smoking and nicotine-dependence measures. Effects had the same sign as those involving striatal regions, although significance did not survive multiple-comparisons correction: thalamus (pack-years: r = -0.436, P = .06; cigarettes/day: r = -0.440, P = .07; FTND: r = -0.476, P = .05), globus pallidus (pack-years: r = -0.250, P = .30; cigarettes/day: r = -0.348, P = .16; FTND: r = -0.479, P = .04), amygdala (pack-years: r = -0.501, P = .03; cigarettes/day: r = -0.542, P = .02; FTND: r = -0.521, P = .03), and hippocampus (pack-years: r = -0.343, P = .15; cigarettes/day: r = -0.476, P = .05; FTND: r = -0.497, P = .04) (Ps uncorrected for multiple comparisons).

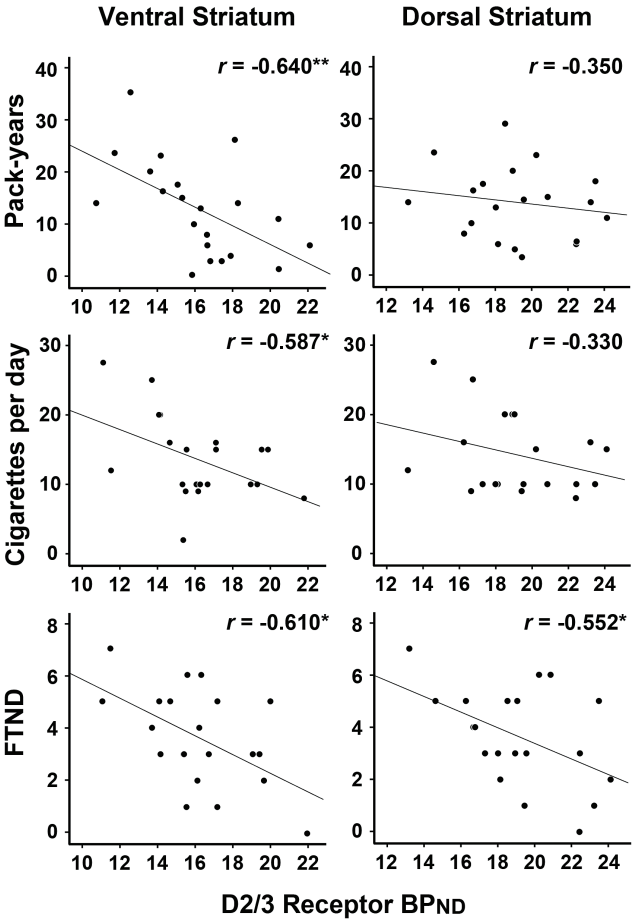

Figure 1. Associations of striatal D2/3 binding potential (BPND) with cigarette use and nicotine dependence. Scatter plots are shown for associations with correlation coefficients. *P < .05, ** P < .01. FTND, Fagerström Test for Nicotine Dependence.

Associations of Age and Lifetime Smoking with Striatum Volume

Whole striatal volume was not correlated with age (r = -0.062, P = .80) or pack-years (r = 0.328, P = .16). These results were minimally affected by controlling for whole-brain volume (age: r = -0.021, P = .93; pack-years: r = 0.335, P = .15).

Role of Ventral Striatal BPND in the Association of Lifetime Smoking with Nicotine Dependence

Regression analyses demonstrated a significant effect of pack-years on FTND score (B = 0.13, SE = 0.06, P = .04), of pack-years on BPND (B = -0.27, SE = 0.08, P = .003), and of BPND on FTND (B = -0.43, SE = 0.11, P = .002). The association of pack-years with FTND did not remain significant after controlling for ventral striatal BPND (B = 0.02, SE = 0.06, P = .78), whereas ventral striatal

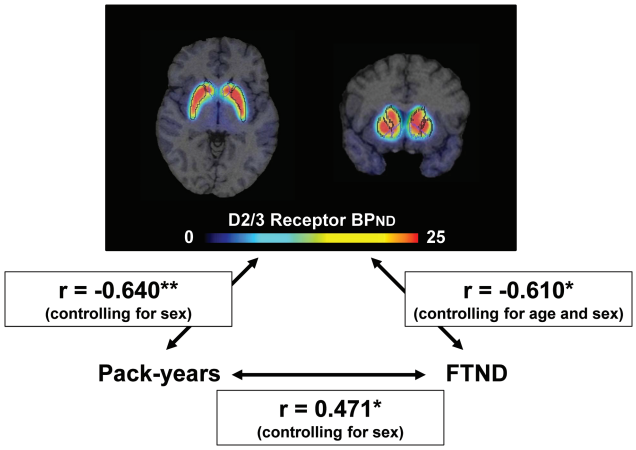

Figure 2. Relationships between D2/3 binding potential (BPND) in ventral striatum and lifetime cigarette use and nicotine dependence. A BPND map with striatal volumes-of-interest (VOIs) (blue: ventral striatum; black: dorsal striatum) superimposed on structural MRI from a representative subject is shown in a black box on top. Each arrow with correlation coefficient represents relationship between pack-years and BPND and Fagerström Test for Nicotine Dependence (FTND). *$P < .05$, **$P < .01$.

BPND remained a significant predictor (B = -0.40, SE = 0.15, $P = .02$) after controlling for pack-years (Figure 2).

Discussion

This study found negative associations of ventral striatal dopamine D2/3 BPND with lifetime and recent cigarette use and with nicotine dependence. In addition, multiple regression analysis, demonstrating that correlation of lifetime smoking with nicotine dependence was no longer significant when controlling for ventral striatal BPND, suggested that low ventral striatal D2/3 receptor signaling may contribute to nicotine dependence. Therefore, enhancing D2/3 receptor availability in ventral striatum may represent a therapeutic approach to reduce nicotine dependence.

The positive association of pack-years with FTND score (Lindberg et al., 2015) is consistent with a previous report and with the fact that the transition from daily smoking to nicotine dependence occurs years after the initiation of daily smoking (Breslau et al., 2001). In rats, chronic nicotine administration reduces D2 receptor density in the basal ganglia, preferentially in ventral striatum, and counteracts lesion-induced upregulation of striatal D2 receptor density (Janson et al., 1992). The observed negative association of lifetime smoking with D2/3 BPND in human subjects is in line with these observations and suggests that cigarette smoking causes D2/3-receptor downregulation in ventral striatum, although the possibility that low D2/3 BPND in ventral striatum promotes smoking behavior cannot be excluded.

A negative association of striatal D2/3 BPND with nicotine dependence was reported before (Montgomery et al., 2007) and may reflect inhibitory control problems. In this regard, striatal D2/3 BPND has been correlated positively with capacity for response inhibition in healthy subjects (Ghahremani et al., 2012) and negatively with impulsivity in methamphetamine users (London, 2016). Notably, impulsivity has been linked to cigarette craving and relapse to tobacco use (Potvin et al., 2015). The overall findings of this study are generally consistent with a model of addiction proposed by Trifilieff and Martinez (2014), whereby reduced signaling through D2/3 receptors accompanies impulsivity and both conditions can be exacerbated by drug exposure. It was proposed that increasing D2/3 receptor signaling is a potential treatment for addiction, which is suggested as well by this study.

One approach to enhance striatal D2/3 BPND is through exercise training, as has been suggested for patients with stimulant use disorder (Robertson et al., 2015). Exercise was proposed as a smoking-cessation aid long ago, and there are some reports of benefits from exercise in reducing tobacco consumption, albeit with limited evidence of long-term benefit (Ussher et al., 2014). In addition, subchronic administration of varenicline, which has efficacy in promoting smoking cessation, produces striatal D2/3 receptor upregulation in rats (Crunelle et al., 2009) as well as dopamine release in striatum, demonstrated by [^{11}C]-(+)-PHNO and PET in smokers (Di Ciano et al., 2015).

This study has limitations. Because it was a cross-sectional study, a causal relationship between smoking and BPND cannot be claimed. Moreover, the fact that [^{18}F]fallypride binds to D2 and D3 receptors, with up to 20% of the striatal signal associated with D3 receptors (Mukherjee et al., 2015), precludes definitive statements regarding either receptor subtype. Notably, D3 receptors are highly expressed in ventral striatum (Diaz et al., 2000). Although participants were abstinent from smoking ≥2 h before PET scans, the time of last smoking was not recorded, but it seems unlikely that recent smoking affected BPND measurements in this study, because D2/3 BPND measured with [^{18}F]fallypride was unchanged immediately after smoking compared with after overnight abstinence (Fehr et al., 2008). Lack of effect on D2/3 BPND measured with [^{18}F]fallypride after dopamine depletion with α-methyltyrosine BPND is further evidence that this measure is minimally affected by differences in tonic intrasynaptic dopamine levels (Cropley et al., 2008). In spite of those limitations, this study demonstrates robust negative associations of ventral striatal dopamine D2/3 BPND with lifetime smoking and suggests a potential role of ventral striatal D2/3 receptors in nicotine dependence.

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Statement of Interest

None

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