Balanced Modulation of Striatal Activation from D₂/D₃ Receptors in Caudate and Ventral Striatum: Disruption in Cannabis Abusers

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Abstract: Proper communication between dorsal caudate (CD) and ventral striatum (VS) is likely to be crucial for on-time responses and its disruption might result in impulsivity. Here, we used functional magnetic resonance imaging (fMRI) with a sensorimotor reaction time task and positron emission tomography (PET) with [¹¹C]raclopride in 14 healthy controls and 18 cannabis abusers to contrast the modulation of striatal fMRI responses by dopamine receptors (D₂/D₃R) in CD and VS. In controls, we show that the fMRI signals in VS that occurs concomitantly with on-time responses showed opposite modulation from D₂/D₃R in CD (inhibitory) and D₂/D₃R in VS (stimulatory). In contrast, this modulation was not significant in cannabis abusers. Findings suggest that action speed requires balanced VS-inhibition from D₂/D₃R in CD and VS-facilitation from D₂/D₃R in VS. *Hum Brain Mapp* 36:3154–3166, 2015. © 2015 Wiley Periodicals, Inc.

Key words: raclopride; reward; dopamine; sensorimotor; reaction time; functional magnetic resonance imaging; positron emission tomography

INTRODUCTION

The striatum integrates signals from subcortical and limbic regions and from prefrontal cortex (PFC) including

regions necessary to instantiate self-control, in ways that can lead to adaptive (regulated) or maladaptive (impulsive) behavioral actions. The ventral striatum (VS), which receives projections from the medial ventral PFC, is associated with reward and salience attribution [Pessiglione et al., 2006; Volkow et al., 2011], while the dorsal caudate (CD), which receives projections from the dorsolateral PFC, is associated with behavioral control [Grahn et al., 2008] and cognition [Levy et al., 1997]. However, cortical projections to striatal subregions overlap significantly [Averbeck et al., 2014], suggesting a high level of coordination between them. The indirect striatocortical pathway, which signals through dopamine (DA) D₂ receptors, is necessary for proper PFC function [Tomasi and Volkow, 2013]. Specifically, in humans, D₂/D₃R in VS have been associated with activation of prefrontal and limbic regions involved in reward processing [Asensio et al., 2010], whereas D₂/D₃R in dorsal striatum have been associated with baseline activity in prefrontal regions implicated in executive function [Volkow et al., 1993b, 1998] and with activation in frontostriatal circuitry implicated in

Additional Supporting Information may be found in the online version of this article.

Contract grant sponsor: The National Institute of Health's Intramural Research Program, National Institute on Alcohol Abuse and Alcoholism; Contract grant number: 2RO1AA09481; Contract grant sponsor: Infrastructure of Brookhaven National Laboratory; Contract grant number: DE-AC02-98CH10886

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Received for publication 19 January 2015; Revised 27 April 2015; Accepted 28 April 2015.

DOI: 10.1002/hbm.22834

Published online 9 June 2015 in Wiley Online Library (wileyonlinelibrary.com).

inhibitory control [Ghahremani et al., 2012]. However, the level of D₂/D₃R-mediated coordination between striatal subregions is mostly unknown. Here, we hypothesize that tasks that differentially engage CD (control of behaviors) and VS (impulsive behaviors) require an opposing D₂/D₃R-mediated modulation from VS and CD, rather than from each of them separately. Direct modulation of striatal activity by D₂/D₃R in the same striatal region was demonstrated in a nonhuman primate study that measured D₂/D₃R with positron emission tomography (PET) while monitoring functional magnetic resonance imaging (fMRI) responses to a pharmacological challenge [Sander et al., 2013].

Since disruptions in striatal function and in D₂/D₃R signaling are implicated in addiction pathology [Volkow et al., 2011], and cannabis abusers display blunted reactivity to DA stimulation [Volkow et al., 2014b], we also hypothesized that the striatal fMRI responses would be differentially modulated by D₂/D₃R within striatal subregions in healthy subjects but that this modulation would be disrupted in cannabis abusers.

To test these hypotheses, we studied 14 healthy controls (NML) and 18 cannabis abusers (CNB) with sequential PET-fMRI. PET was used with [¹¹C]raclopride to measure D₂/D₃R in striatum and fMRI was used to measure the activation of the striatum to a sensorimotor reaction time (SM-RT) task.

MATERIALS AND METHODS

Subjects

The 18 CNB and 14 NML participants in this study were recruited from advertisements in local newspapers. Table I highlights demographics and clinical characteristics of participants. All subjects had physical, psychiatric, and neurologic examinations. At least two clinicians interviewed the patients with a semistructured standardized interview to ensure they met Diagnostic Statistical Manual IV criteria for cannabis abuse or dependence. All subjects had Hamilton's Anxiety and Depression scores <19. Drug screens were done on the days of the scans to exclude the use of psychoactive drugs (other than marijuana in cannabis abusers). Subjects were instructed to discontinue any over-the-counter medication 2 weeks prior to scanning days. Food and beverages (except for water) were discontinued at least 4 h prior to the study. Tobacco cigarette smoking was discontinued at least 2 h prior to the study. Cannabis abusers were excluded if they had a history of substance abuse or addiction other than cannabis or nicotine, history of other psychiatric or neurological diseases, medical conditions that may alter cerebral function (i.e., cardiovascular, endocrinological, oncological, or autoimmune diseases), current use of prescribed or over-the-counter medications, and/or head trauma with loss of consciousness of more than 30 min. Same exclusion criteria were applied to the control group, except that control subjects who smoked more than one joint of cannabis a month

TABLE I. Demographics and clinical characteristics of participants

Parameter	Healthy controls	Marijuana abusers	<i>P</i>
Age (years)	26.2 ± 5	27.2 ± 8	NS
Sex (M/F)	9/5	9/9	NS
Education (years)	13.7 ± 2	13.2 ± 1	NS
Handedness (R/L)	14/0	16/2	NS
Tobacco	3 active	8 active	NS
Initiation (years)	15 ± 2	17 ± 4	NS
Cigarettes per day	2 ± 3	3 ± 5	NS
Years of smoking	3 ± 5	3 ± 4	NS
Breath CO (ppm)	6 ± 7	10 ± 6	NS
Marijuana initiation (years)		15 ± 3	
Days per week		5 ± 3	
Joints per day		5 ± 3	
Years of abuse		11 ± 8	

NS: no significant group difference (*P* > 0.2).

were additionally excluded from the study. There were no statistically significant differences in age, sex, education, handedness, and tobacco smoking between the CNB and NML groups (Table I). This study was approved by the Committee on Research in Human Subjects at Stony Brook University and written informed consent was obtained from all subjects.

SM-RT Task

The SM-RT task involved visual perception and measured the reaction time (RT) required for the subjects' response to the target, an open circle covering 10 and 12% of the horizontal and vertical visual fields (Fig. 1). A static white fixation cross was shown at the center of the black screen during 96% of the intertrial interval (ITI). During each trial, the target flashed for 200 ms, randomly at one of the four corners of the screen (peripheral visual field). The subjects' task was to fixate on the center cross and respond to the appearance of the target by pushing an in-house MRI compatible response button with their right index finger as quickly as possible upon target presentation. The response window that followed the target was used to classify a button press response as successful (RT ≤ 600 ms; "hit") or unsuccessful (RT > 600 ms; "miss"). After an expectation period of 1.3 s an outcome message, "\$" for a hit or "X" for a miss, briefly (500 ms) replaced the fixation cross at the center of the visual field as a feedback to inform the subjects about their accuracy during the trial; after the outcome only the fixation cross was displayed for 9–11 s, until the onset of the next target. Thus, the SM-RT task had 4-min duration and included 20 trials with pseudorandom ITI (12 s; 2 s jittering).

Button press responses were recorded to determine RT (average time difference between targets and responses) and performance accuracy (percentage of successful events

Figure 1.

fMRI task: (A) Time course of the SM-RT task, highlighting the target (red), response window (green), and the presentation of outcome (pink) within one intertrial interval (ITI = 11–13 seconds). (B) Spatiotemporal distribution of events, responses and

outcomes for the task within the ITI. (C) Performance accuracy during the task and RT for successful (hit) and unsuccessful (miss) trials for all subjects. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

relative to total number of events). In addition, the subject's responses were used for general lineal modelling (GLM) of brain activation responses, independently for hits and misses. The visual stimuli were presented to the subjects on MRI-compatible goggles (Resonance Technology Inc., Northridge, CA) connected to a personal computer. The software used to display the stimuli and record subject's responses was developed in Visual Basic and Visual C (Visual Studio; Microsoft Corp., Redmond, WA) and was synchronized precisely with MR acquisition using an MRI trigger pulse. Prior to the MRI session, the participants completed a brief training session (<5 min) outside the MRI scanner to ensure they understood and were able to perform the task.

PET Acquisition and Data Analysis

To quantify D_2/D_3R in the striatum, we used [^{11}C]raclopride as the radiotracer and an HR+ tomograph (resolution $4.5 \times 4.5 \times 4.5$ mm full width half-maximum, FWHM; 63 slices) using methods previously described [Volkow et al., 1993a]. Briefly, 20 dynamic emission scans were obtained from time of injection up to 54 min immediately after injection of 4–8 mCi (specific activity 0.5–1.5 Ci/ μ M). Arterial sampling was used to quantify total carbon-11 and unchanged [^{11}C]raclopride in plasma. The distribution volume (DV), which corresponds to the equilibrium radiotracer tissue-to-plasma concentration ratio, was computed for each imaging voxel using a graphical analysis technique for reversible systems [Logan et al., 1990]. These images were then spatially normal-

ized to the stereotactic space of the Montreal Neurological Institute (MNI) using a 12-parameter affine transformation. A custom MNI template, which was previously developed using DV images acquired with [^{11}C]raclopride and the same PET scanning sequence [Wang et al., 2011] was used for the spatial normalization of the DV images. Then, the intensity of the DV images was normalized to that in the cerebellum (left and right regions-of-interest) to quantify the nondisplaceable binding potential (BP_{ND}) in each voxel. A D_2/D_3R mask, which comprised putamen (PU), globus pallidus (GP), CD, and VS (Fig. 2, pink contour), was developed using a threshold $BP_{ND} = 1.6$ to restrict the searching volume to striatal regions with high density of D_2/D_3R in group level statistical analyses based on simple linear regression (SLR) and multiple linear regression (MLR).

Anatomical ROI-Analyses

In-house software written in IDL (Exelis Visual Information Solutions, Boulder, Co) and the automated anatomical labeling (AAL) atlas [Tzourio-Mazoyer et al., 2002] were used to define bilateral anatomical regions-of-interest (ROIs): PU, GP, CD, and VS (Fig. 2A). The CD ROI included all voxels in CD, as defined in the AAL atlas planes -6 mm $< z < 14$ mm. The VS ROI encompassed VS, which included the inferior planes of precommissural caudate and PU (6 mm $< y \leq 27$ mm; -11 mm $< z \leq -6$ mm) in the AAL atlas. Average BP_{ND} values were computed for each subject independently for these ROIs.

Figure 2.

Anatomical ROIs and D₂/D₃R: (A) PU, GP, CD, and VS regions-of-interest superimposed on axial views of the human brain. (B) BP_{ND} of [¹¹C]raclopride superimposed on axial views of the human brain highlighting the distribution of D₂/D₃R for the CNB and NML groups; the pink contours delineate the boundary of the D₂/D₃R mask used for

multiple comparison corrections within the striatum. The bar plots reflect the average measures in the selected bilateral ROIs across 18 cannabis abusers (CNB) and 14 control subjects (NML). Error bars are standard errors of the mean. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

MRI Data Acquisition

A 4-Tesla whole-body Varian (Palo Alto, CA)/Siemens (Erlangen, Germany) MRI scanner with a T2*-weighted single-shot gradient-echo planar imaging (EPI) pulse sequence (echo time (TE)/repetition time (TR) = 20/1,600 ms, 4-mm slice thickness, 1-mm gap, 35 coronal slices, 64 × 64 matrix size, 3.125 × 3.125 mm² in-plane resolution, 90°-flip angle, 157 time points, 200.00 kHz bandwidth) with ramp-sampling and whole brain coverage was used to collect functional images with blood oxygenation level-dependent (BOLD) contrast. Padding was used to minimize head motion. Earplugs (−28 dB sound pressure level attenuation; Aearo Ear Taper-Fit 2; Aearo Co., Indianapolis, IN), headphones (−30 dB sound pressure level attenuation; Commander XG MRI Audio System, Resonance Technology inc., Northridge, CA) and a “quiet” EPI acquisition approach were used to minimize the interference effect of scanner noise during fMRI [Tomasi et al., 2005]. Anatomical images were collected using a T1-weighted three-dimensional-modified driven equilibrium Fourier transform pulse sequence (TE/TR = 7/15 ms,

0.94 × 0.94 × 1.00 mm³ spatial resolution, axial orientation, 256 readout and 192 × 96 phase-encoding steps, 16 min scan time) and a modified T2-weighted hyperecho sequence (TE/TR = 0.042/10 s, echo train length = 16, 256 × 256 matrix size, 30 coronal slices, 0.86 × 0.86 mm² in-plane resolution, 5-mm thickness, no gap, 2-min scan time) to rule out gross morphological abnormalities of the brain.

Data Processing

The first four imaging time points were discarded to avoid nonequilibrium effects in the fMRI signal. The statistical parametric mapping package SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK) was used for subsequent analyses. Ascending linear interpolation was used for the temporal realignment of the slices (i.e., “slice time correction”), which were acquired in sequential order. Spatial realignment was performed with a fourth degree B-spline function without weighting and without warping; head motion was less than 2-mm translations and 2°-

rotations for all scans. Spatial normalization to the stereotactic space of the MNI was performed using a 12-parameter affine transformation with medium regularization, 16-nonlinear iterations, $3 \times 3 \times 3 \text{ mm}^3$ voxel size and the standard SPM8 EPI template. Spatial smoothing was carried out using an 8-mm FWHM Gaussian kernel.

Subject-Level Statistical Analyses

A GLM was used to estimate the fMRI responses during the SM-RT task for each subject. Specifically, the first-level GLM was based on two regressors modeling the canonic hemodynamic response function (HRF) elicited by the onsets of hits and misses, as well as four additional regressors modelling their first- and second- (dispersion) order time derivatives. These regressors were convolved with low-pass (HRF) and high-pass (cut-off frequency: 1/128 Hz) filters to minimize field drifts and high frequency noise. The six time-varying motion parameters (3 rotations and 3 translations) obtained from image realignment were used as covariates in the GLM to remove motion confounds on brain activation patterns. Thus, two independent contrast maps reflecting the % BOLD-fMRI signal change from baseline (black screen with a fixation cross) caused by hits and by misses were obtained for each subject.

Group-Level Statistical Analyses

Voxelwise one-way analysis of variance, with age, gender, and smoking status covariates (ANCOVA), was used for between-group comparisons of imaging data. Independent between-group comparisons were conducted for BP_{ND} images and fMRI contrast maps. Statistical significance was set by a cluster-level $P_{FWE} < 0.05$, corrected for multiple comparisons in the whole-brain with the random field theory and a familywise error correction at the cluster level, using a cluster forming threshold $P < 0.001$ and a minimum cluster volume of 100 voxels.

SLR was used to test the association of PET and fMRI signals within the D_2/D_3R mask across subjects, separately for BP_{ND} in PU, GP, CD, and VS as well as for the $BP_{ND}^{VS}/BP_{ND}^{CD}$ ratio. MLR was used to test the linear association between fMRI activation signals within the striatum and D_2/D_3R across subjects, together for BP_{ND}^{VS} and BP_{ND}^{CD} . Specifically, the fMRI responses at a given voxel, $BOLD(x, y, z)$, were modeled using the affine transformation:

$$BOLD(x, y, z) = \alpha_{CD}(x, y, z)BP_{ND}^{CD} + \alpha_{VS}(x, y, z)BP_{ND}^{VS} + \varepsilon(x, y, z), \quad (1)$$

where the scalar maps $\alpha(x, y, z)$ are the slopes that quantify the efficiency of the DAergic modulation of brain activation (i.e., the multilinear relationship between BOLD signals and BP_{ND}^{VS} and BP_{ND}^{CD}) and ε is the intercept of the MLR. Independent MLR analyses were carried for CNB and NML as well as for the combined CNB and NML sample. The

regressors had low standard error ($\delta BP_{ND} < 1.3\%$), compared to that of the independent variable ($\delta BOLD \sim 38\%$), which satisfied the MLR requirement of weak exogeneity. For these voxelwise SPM8 group-level analyses, statistical significance was set by a cluster-level $P_{FWE} < 0.05$, corrected for multiple comparisons within the D_2/D_3R mask at the cluster level, using a cluster forming threshold $P < 0.001$ and a minimum cluster volume of 10 voxels. Independent MLR in IBM SSPS Statistics v20 (IBM Corp, Armonk, NY) and $P < 0.05$ were used to corroborate SPM8 findings using the average fMRI response in the VS ROI.

RESULTS

D2/D3 Receptors

The BP_{ND} was high within the striatum, reaching maximum in PU, and low in the rest of the brain (Fig. 2B). CNB and NML did not show statistically significant differences in BP_{ND} in any striatal region.

Behavioral Responses

Subjects' RT ($0.65 \pm 0.07 \text{ s}$) and accuracy ($46 \pm 31\%$) during the SM-RT task were normally distributed (NML: $P > 0.13$, CNB: $P > 0.08$; Shapiro–Wilk test) and did not differ significantly between CNB and NML ($P > 0.47$, t -test). RT was significantly shorter for successful (“hit”; NML: $0.58 \pm 0.02 \text{ s}$; CNB: $0.56 \pm 0.02 \text{ s}$) than for unsuccessful (“miss”; NML: $0.72 \pm 0.06 \text{ s}$; CNB: $0.75 \pm 0.07 \text{ s}$) trials, independently for each group ($P < 1.3 \times 10^{-6}$, paired t -test; Fig. 3). RT did not differ significantly between CNB and NML, either for hits or misses ($P > 0.15$, t -test). Performance accuracy during the SM-RT task showed a negative correlation with age at onset of cannabis use in the CNB group ($R = -0.65$; $P = 0.003$; Fig. 3C).

Whole-Brain fMRI Patterns

Across all subjects, the SM-RT task caused positive fMRI signals (brain activation) in visual, somatosensory, motor, and premotor and limbic cortices (Brodmann areas, BAs 1, 3–6, 23, and 24), cerebellum and thalamus, regions traditionally associated with visual search, and negative fMRI signals (brain deactivation) in premotor, dorsolateral prefrontal, ventral orbitofrontal, posterior parietal, and VS (Fig. 3A, $P_{FWE} < 0.05$, corrected for multiple comparisons in the whole brain; one-sample t -test; $df = 31$).

Striatal Deactivation and Performance

The task caused VS deactivation for hits but not for misses ($P_{FWE} < 0.04$; corrected for multiple comparisons in within the striatum; Fig. 3B), which did not differ for NML and CNB. For the CNB group, the fMRI deactivation responses in VS showed a negative correlation with

Figure 3.

fMRI patterns and accuracy: **(A)** statistical significance of whole-brain activation and deactivation (blue–green t -score map) patterns elicited by the SM-RT task across all participants, superimposed on lateral (left) and ventral surface views of the human cerebrum; **(B)** statistical significance (blue–green t -score map) of brain deactivation elicited by the SM-RT task within the striatum across all subjects superimposed on coronal and axial center views of the human brain; and **(C)** scatter plots showing the correlation of performance accuracy with fMRI signals in VS during the SM-RT task for the cannabis (CNB) and control (NML) groups (left panel), and with the age at onset of cannabis use (right panel). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

performance ($R = -0.68$) such that the stronger the VS deactivation the better the performance (Fig. 3C). Though the NML group showed a similar association between accuracy and VS deactivation, the correlation was not significant ($R = -0.28$, $P = 0.33$).

Modulation by Striatal D₂/D₃R

Voxelwise MLR analyses revealed a multiple linear association between fMRI signals in VS and D₂/D₃R in VS and CD that accounted for 50% of the variance in the BOLD signal to target onset in VS. Specifically, for hits, the predicted fMRI responses in VS linearly increased with D₂/

D₃R in VS and decreased with D₂/D₃R in CD (Fig. 4; $P_{FWE} < 0.05$); this association, however, was not significant for miss trials. Voxelwise MLR results were confirmed by SPSS analysis using the average fMRI signals extracted from the VS ROI. Specifically, the predicted fMRI responses to hits $BOLD^{VS} = BOLD - \alpha_{CD}BP_{ND}^{CD}$ showed positive correlation with BP_{ND}^{VS} , whereas those for CD ($BOLD^{CD} = BOLD - \alpha_{VS}BP_{ND}^{VS}$) showed negative correlation with BP_{ND}^{CD} ($|R| > 0.88$; Fig. 4B).

By contrast, SLR analyses for BP_{ND}^{VS} and BP_{ND}^{CD} did not reveal simple and direct associations of D₂/D₃R with fMRI responses within the striatum. However, SLR with $BP_{ND}^{VS}/BP_{ND}^{CD}$ as the only regressor revealed a similar pattern of linear associations that accounted for 27% of the variance in the fMRI data and encompassed bilateral VS and CD (Fig. 5A,B).

Because the D₂/D₃R regressors exhibited high correlation ($R > 0.88$), we evaluated the risk of multicollinearity in the MLR model using the variance inflation factor, $VIF = 1/(1 - R^2)$, and condition number, $\kappa = \lambda_{\max}/\lambda_{\min}$, a standard measure reflecting the ratio between the maximum and minimum eigenvalues, λ , of the correlation matrix computed from BP_{ND}^{VS} and BP_{ND}^{CD} . Depending on κ and VIF the significance of the multicollinearity problem is usually classified as low ($\kappa < 30$, $VIF < 10$) or high ($\kappa > 30$, $VIF > 10$) [Freund and Littell, 2003; O'Brien, 2007]. For the BP_{ND}^{CD} and BP_{ND}^{VS} regressors $\kappa = 28$ and $VIF = 6$, indicating low risk of multicollinearity. Note that the correlation between BP_{ND}^{CD} and BP_{ND}^{VS} regressors did not differ significantly between the CNB and NML groups ($P > 0.52$; Fig. 5C). Conversely, BP_{ND} values within the PU and GP ROIs had high risk of multicollinearity ($R = 0.98$; $\kappa = 100$, $VIF = 24$), preventing MLR analyses between BOLD signals in the striatum and receptor levels in PU and GP.

Exhaustive MLR analyses of 32 independent subsamples ($N = 31$) obtained by removing one of the 32 subjects in the original sample demonstrated the good stability of the MLR solutions. Specifically, the MLR slopes and intercept ($\alpha_{VS} = 2.1 \pm 0.1$, $\alpha_{CD} = -1.5 \pm 0.1$, and $\varepsilon = -1.7 \pm 0.1$) exhibited Gaussian distributions and did not differ significantly from those obtained with the full sample indicating that findings were not driven by outliers (Supporting Information Fig. 1).

Complementary analyses were performed with PU as a control region to ensure the regional specificity of the MLR findings. Specifically, the average D₂/D₃R in the PU (BP_{ND}^{PU}) was used as a regressor instead of one of the original regressors (either BP_{ND}^{VS} or BP_{ND}^{CD}) in two independent MLR models with low risk of multicollinearity ($\kappa = 16$ and $VIF = 4.5$). These analyses did not reveal significant associations between D₂/D₃R and fMRI signals within the striatum, which confirmed the specificity of the association between VS-fMRI responses and D₂/D₃R in CD and VS.

Modulation by D₂/D₃R in Cannabis Abusers

Independent voxelwise MLR analysis for each subject group demonstrated that for NML subjects the fMRI

Figure 4.

DAergic modulation and action speed: statistical significance of differences between MLR slopes (α_{VS} and α_{CD}) associated with D_2/D_3R in VS (BP_{ND}^{VS}) and CD (BP_{ND}^{CD}), superimposed on three orthogonal views of the human brain (A), and scatter plots exemplifying the linear associations of $BOLD^{VS}$ and $BOLD^{CD}$, the predicted

fMRI signals in VS, as a function of BP_{ND}^{VS} and BP_{ND}^{CD} , for successful (hit; green) and unsuccessful (miss; red) trials (B). Color bars are t -score values. Red and blue contour lines highlight the boundaries of the VS and CD ROIs. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

responses to hits linearly decreased with D_2/D_3R receptors in CD and increased with D_2/D_3R in VS ($P_{FWE} < 0.05$; Fig. 6 and Tables II and III), whereas for CNB subjects, these associations were not significant. The association between fMRI responses to miss trials and D_2/D_3R was not significant, either for NML or for CNB.

Independent analyses based on average fMRI responses in the VS ROI confirmed the voxelwise results (Fig. 6C,D). For hit trials, the MLR slopes and the intercepts were statistically significant, both for NML and for CNB ($|R| > 0.66$; $P < 0.003$). However, the amplitudes of the slopes were larger for the NML group than for the CNB group ($P < 0.043$). For miss trials, the average fMRI responses in the VS ROI did not show significant linear associations with D_2/D_3R .

DISCUSSION

Here, we present the first reported evidence that fMRI responses associated with action speed rely on opposite

D_2/D_3R modulation from CD and VS (Fig. 7). Specifically, we found that the hemodynamic responses elicited by a simple sensorimotor RT task in VS were down-regulated by D_2/D_3R in CD and upregulated by D_2/D_3R in VS, such that the fMRI signal in VS increased linearly with BP_{ND}^{VS} -to- BP_{ND}^{CD} ratio. Interestingly, we found no such significant D_2/D_3R mediated modulation in cannabis abusers.

Our findings suggest that D_2/D_3R in CD and VS have differential but coordinated roles in the modulation of fMRI responses in VS during the SM-RT task. Indeed, the association between fMRI signals to hit trials and D_2/D_3R was significantly stronger when two regressors (BP_{ND}^{VS} and BP_{ND}^{CD} ; $R^2 = 0.50$, $P < 0.001$) were used in the MLR model, compared to one regressor ($BP_{ND}^{VS}/BP_{ND}^{CD}$; $R^2 = 0.27$, NS). By the same token, while D_2/D_3R in CD and VS cannot explain independently the variance in the hemodynamic signal, a linear model that includes D_2/D_3R from both regions (CD and VS) does. The significant correlation between the fMRI responses in VS and the ratio between the D_2/D_3R measures from VS and CD ($P = 0.002$) provides strong support for the existence of a balanced D_2/D_3R

Figure 5.

(A) Scatter plot showing the linear association between the relative D₂/D₃R measure ($BP_{ND}^{VS}/BP_{ND}^{CD}$) and the average fMRI signal in VS during the SM-RT task. (B) Statistical significance of the slope, $\alpha_{VS/CD}$, derived from the SLR model that links the fMRI responses to the task and the relative $BP_{ND}^{VS}/BP_{ND}^{CD}$ measures

across subjects. (C) Scatter plot showing the correlation between D₂/D₃R in CD (BP_{ND}^{CD}) and VS (BP_{ND}^{VS}) for cannabis abusers (CNB) and controls (NML). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

D₃R modulation from CD and VS. The slopes of the MLR model, α_{VS} and α_{CD} , provide a measure of the underlying “DAergic modulation,” defined here as the relationship between D₂/D₃R and the amplitude of hemodynamic fMRI responses.

The anatomical segregation of cortical projections into striatal subregions is consistent with their unique functions, while the extent of the reported overlaps in their arriving fields suggests important functional interactions among them [Draganski et al., 2008; Haber et al., 2006]. The inputs from multiple frontal regions [Averbeck et al., 2014] that converge on the rostral caudate provide a good example that suggests this region might be a “hub” involved in integrating signals within the whole striatum. The opposite influence from D₂/D₃R in CD and from D₂/D₃R in VS as described here could therefore reflect the indirect modulation of the VS by the caudate through striatocortical pathways. However, we cannot rule out the alternative possibility of a local circuitry within the striatum that might rely on interneurons [Adler et al., 2013].

The sensorimotor loop involves the cortex (frontal and parietal) and the basal ganglia, which includes the striatum, and the thalamus [McHaffie et al., 2005]. DAergic

projections into the striatum modulate the activity of GABAergic medium spiny neurons, which constitute 90–95% of the neurons in the striatum, through excitatory D₁R in the direct pathway and inhibitory D₂R in the indirect pathway. D₃R and D₁R are not only coexpressed in the same neurons in VS but also they act synergistically [Rosa-Neto et al., 2004]. Since [¹¹C]raclopride signals in CD predominantly reflect D₂R [Rosa-Neto et al., 2004], whereas those in VS reflect to a greater extent D₃R, the opposite modulation effects of D₂/D₃R in CD and VS might reflect the differential involvement of the direct and indirect basal ganglia pathways during the SM-RT task in these striatal subregions. Because D₂/D₃R levels in different striatal regions are highly correlated, the opposite modulatory effects from D₂/D₃R in CD and VS make the sensorimotor feedback loop robust to between-subjects variability in D₂/D₃R (i.e., higher D₂/D₃R in CD balance out higher D₂/D₃R in VS).

Cannabis abusers demonstrated similar performance, D₂/D₃R levels and fMRI signals but weaker DAergic modulation in VS than control subjects, which is consistent with the robustness of the sensorimotor feedback loop and with VS activation during reward processing in cannabis

Figure 6.

Effect of cannabis: statistical significance of differences between MLR slopes (α_{VS} and α_{CD}) associated with D_2/D_3R in VS (BP_{ND}^{VS}) and CD (BP_{ND}^{CD}), superimposed on coronal and axial views of the human brain (A and B). Scatter plots exemplifying the linear associations of $BOLD^{VS}$ and $BOLD^{CD}$, the predicted fMRI signals to hits in VS, as a function of BP_{ND}^{VS} and BP_{ND}^{CD} , for control sub-

jects (NML; black) and cannabis abusers (CNB; red) (C and D). Color patterns are t -score values. Red and blue contour lines highlight the boundaries of the VS and CD ROIs. P -values in scatter plots highlight the statistical group differences in slopes. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

abusers. The fMRI responses in VS showed significant correlation with performance accuracy during the SM-RT task, such that higher VS-deactivation was associated with improved performance for CNB but less so for NML ($Z = 1.4$, $P = 0.08$). Since brain deactivation likely reflects neuronal inhibition to minimize task-irrelevant neural processes [Tomasi et al., 2006], the correlation between VS deactivation and performance accuracy suggests that inhibition of VS-mediated impulsive responses is relevant to accurate performance. The association between accuracy and VS-deactivation captured more than 46% of the variance of the fMRI data in CNB's but less than 8% in NML's, highlighting the importance of controlled behavior for RT in CNB abusers. The stronger association between D_2/D_3R in VS and VS-deactivation during correct trials suggests less efficient DAergic modulation of impulsive responses for CNB abusers than for NML subjects. Together with the negative correlation between accuracy and onset of cannabis use, these group differences suggest effects of long-term cumulative exposure to cannabis. We

had reported that, whereas CNB show no significant differences in D_2/D_3R availability when compared to controls they showed significantly attenuated responses to increases in striatal DA, which we interpreted as reflecting a blunted reactivity to DA stimulation [Volkow et al., 2014b]. Our current findings are also consistent with a blunted modulation by D_2/D_3R mediated DA signaling.

Though there is evidence of long-lasting cognitive impairments in cannabis abusers (i.e., memory and attention), results have been inconsistent [Volkow et al., 2014a]. Similarly, studies have failed to demonstrate abnormal striatal fMRI responses for cannabis abusers, regardless of the cognitive or emotional domain being tested [Bolla et al., 2005; Chang et al., 2006; Filbey et al., 2009, 2013; Goldman et al., 2013; Gruber et al., 2009; King et al., 2011; Lopez-Larson et al., 2012; Schweinsburg et al., 2010, 2011; Smith et al., 2010; Tapert et al., 2007; Wesley et al., 2011], except for an fMRI study on associative memory that reported greater activity in dorsal striatum for cannabis abusers than for controls [Ames et al., 2013]. It should be

TABLE II. Statistical significance of the coefficient estimates (α_{CD} , α_{VS})

Region	MNI (mm)			MLR (t-score)	
	x	y	z	α_{CD}	α_{VS}
<i>Hit (MNL & CNB)</i>					
Ventral putamen	-18	11	-6	-4.6	5.0
Dorsal caudate	12	5	6	-2.9	2.9
<i>Miss (MNL & CNB)</i>					
Ventral putamen	-18	11	-6	NS	NS
Dorsal caudate	12	5	6	-1.4	1.3

Conjunction MLR merging 18 cannabis abusers (CNB) and 14 controls (NML).

TABLE III. Statistical significance of MLR coefficient estimates, independently for 18 cannabis abusers (CNB) and 14 controls (NML)

Region	MNI (mm)			α_{CD} (t-score)		α_{VS} (t-score)	
	x	y	z	CNB	NML	CNB	NML
<i>Hit</i>							
Ventral putamen	-18	11	-6	-1.3	-6.0	1.9	6.1
Dorsal caudate	12	5	6	NS	-3.0	NS	3.7
<i>Miss</i>							
Ventral putamen	-18	11	-6	NS	NS	NS	NS
Dorsal caudate	12	5	6	NS	-1.7	NS	1.8

Successful (hit) and unsuccessful (miss) trials of the SM-RT task were modeled independently.

noted, however, that the recently reported association between repeated marijuana exposure and observable changes in functional connectivity in the reward [Filbey and Dunlop, 2014] and inhibitory [Filbey and Yezhuvath, 2013] networks could be relevant vis á vis future efforts to map the impact of cannabis (and other drug) use on striatal microcircuitry and the regulation of goal directed behaviors. Conversely, PET studies using pharmacological challenges with stimulant drugs have also reported normal striatal DA release in cannabis abusers [Urban et al., 2012]. However, in a recent study, we reported impaired coupling between DA stimulation and downstream effects such as decreased reactivity [Volkow et al., 2014b], which would be in line with the results for CNB obtained here. Combined, these results are consistent with the conclusions of a recent meta-analysis of functional neuroimaging studies that uncovered changes in the patterns of resting brain activity while performing different tasks, again, suggestive of the emergence of compensatory mechanisms in chronic cannabis users [Batalla et al., 2013]. Specifically this meta-analysis reported that for most tasks, there were no differences in performance between cannabis abusers and controls but that in most instances cannabis abusers demonstrated an altered pattern of brain activity during

Figure 7.

Multilinear model: the DAergic modulation (equation) explains the fMRI signal in VS during the SM-RT task in terms of D₂/D₃R in CD (BP_{ND}^{CD}) and VS (BP_{ND}^{VS}). (A) Dopamine neurotransmission (red arrows from midbrain, MB), through D₂/D₃R in CD and VS, modulate cortical inputs (black arrows from PFC and OFC) to the striatum in opposite ways (1) directly by increasing VS activation via inhibition of medium spiny neurons in VS (red arrows), and (2) indirectly by decreasing VS activation via excitation of interneurons projecting from CD to VS (blue arrows). (B) The lower DAergic modulation highlighted by differences in MLR slopes reflects weaker dopaminergic modulation of VS for cannabis abusers (CNB) than for controls (NML). (C) The differentiator circuitry in the striatum minimizes the impact of group differences in DAergic modulation, such that differences in VS activation are not significant (pink output arrows) despite (both the positive and the negative) contributions to the fMRI signal are smaller for CNB than for NML. The slopes α_{VS} and α_{CD} are the free adjustable parameters of the MLR model, BP_{ND}^{VS} and BP_{ND}^{CD} are the independent variables, the fMRI signal the dependent variable, and ϵ the intercept that reflects the average fMRI signal. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

task performance that suggested the recruitment of alternative brain regions for proper task performance. Similarly for our study, the stronger correlation between VS deactivation and performance for CNB abusers than for controls could be interpreted as to reflect a greater reliance on VS deactivation for correct task performance in the CNB group. Conversely, the lack of an association between the VS deactivation and D₂/D₃R in CNB abusers despite the absence of group differences in D₂/D₃R availability could reflect either impaired D₂/D₃R downstream signaling [Volkow et al., 2014b] or the use of alternative neurotransmitters or DA receptors (i.e., D₁R) in the modulation of VS deactivation responses.

Our findings differ from those of a previous PET-fMRI study with the stop-signal RT task [Ghahremani et al., 2012]. Whereas that study showed significant linear associations between fMRI responses and D₂/D₃R, using

independent SLR models for D₂/D₃R in caudate, PU, and VS, simple linear associations with D₂/D₃R from single striatal regions did not emerge in this study. The reason for this discrepancy might reflect differences in task paradigms; whereas the study by Ghahremani et al. used an fMRI contrast reflecting inhibition, a simple RT task was used in the present study. Similarly, prior studies have associated D₂/D₃R in the striatum with cortical fMRI responses to emotion [Kienast et al., 2008], visual attention [Volkow et al., 2009], decision-making [Kohn et al., in press], and reward [Asensio et al., 2010] tasks also using SLR models that included D₂/D₃R from single striatal regions. These studies, however, failed to document an association between receptors and fMRI signals in the striatum, the brain region with highest D₂/D₃R density. More indirectly, D₂R have been associated with both cortical and striatal fMRI signals using pharmacological challenges with the D₂R antagonist sulpiride [Dodds et al., 2009] or the D₂R agonist bromocriptine [Stelzel et al., 2013]. However, these studies did not reveal the location within the striatum of the D₂R involved in the modulation of the fMRI signals.

The multilinear coupling of neuroreceptor binding and hemodynamic fMRI responses in VS was sensitive to the accuracy of the subjects during the SM-RT task. Hence, the association between fMRI signals in VS and receptors was strong for successful trials (hits) but not significant for unsuccessful trials (misses). Now, it is true that the multicollinearity of the D₂/D₃R regressors limits the generalizability of the approach. As the multicollinearity problem increases, the regression model estimates of the coefficients become unstable and their standard errors might get inflated. But considering that multicollinearity is considered a potential concern only if $VIF > 10$ or $\kappa > 30$, the MLR model in this study ($VIF = 6$ and $\kappa = 28$) was deemed viable. And based on this model, we speculate that successful trials resulted when DA increased sufficiently to activate D₂/D₃R in proportion to their availability thus accounting for the correlation; whereas when DA failed to increase this resulted in missed trials, thus accounting for the lack of a correlation. The robustness of the MLR model was further supported by (a) the similarity of the linear regression patterns for the NML and CNB groups; (b) the sensitivity to errors (misses) in both groups of subjects; (c) the lack of significant changes in MLR estimates when removing arbitrary samples (leave one out validation); and (d) the similar spatial pattern obtained for the SLR analysis with the relative regressor, $BP_{ND}^{VS}/BP_{ND}^{CD}$. Moreover, the lack of significant multilinear associations with D₂/D₃R in PU highlights the specificity of the association between receptors in CD and VS and fMRI signals in VS.

Since [¹¹C]raclopride cannot distinguish between D₂R and D₃R, which predominate in the CD and in the VS, respectively [Tziortzi et al., 2011], we cannot determine if the opposite modulation of the VS activation signals reflects differential signaling of D₂R in CD (inhibitory) or of D₃R in VS (stimulatory). Future studies with specific

D₂R ligands will be needed to address this question. Other limitations include imbalance of tobacco smokers between groups and unknown contribution of intrasynaptic DA to the D₂/D₃R measurements. Since cannabis use is highly correlated with tobacco and alcohol use, it is not possible to isolate the effect of cannabis. Since it is not possible to dissociate preexisting conditions from the effect of the drug, the weaker DAergic modulation in the striatum could reflect conditions that preceded use of cannabis or neuroadaptations triggered by chronic cannabis use.

ACKNOWLEDGMENTS

The authors thank Lisa Muench, Colleen Shea, Joanna Fowler and Youwen Xu for radiopharmaceutical preparation and quality control; Millard Jayne, Yana Studentsova, Frank Telang, Pauline Carter, and Barbara Hubbard for subject care and protocol oversight; Karen Apelskog for protocol coordination; Michael Schueller for cyclotron operations; Dave Alexoff and Jean Logan for pharmacokinetic modeling, Ruiliang Wang for MRI data acquisition; and Ruben Baler for assistance in manuscript preparation. The authors also thank the subjects who volunteered to participate in this study.

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