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ORIGINAL ARTICLE

Association between striatal dopamine D_2/D_3 receptors and brain activation during visual attention: effects of sleep deprivation

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Sleep deprivation (SD) disrupts dopamine (DA) signaling and impairs attention. However, the interpretation of these concomitant effects requires a better understanding of dopamine's role in attention processing. Here we test the hypotheses that D_2/D_3 receptors (D_2/D_3R) in dorsal and ventral striatum would distinctly regulate the activation of attention regions and that, by decreasing D_2/D_3, SD would disrupt these associations. We measured striatal D_2/D_3R using positron emission tomography with [^{11}C] raclopride and brain activation to a visual attention (VA) task using 4-Tesla functional magnetic resonance imaging. Fourteen healthy men were studied during rested wakefulness and also during SD. Increased D_2/D_3R in striatum (caudate, putamen and ventral striatum) were linearly associated with higher thalamic activation. Subjects with higher D_2/D_3R in caudate relative to ventral striatum had higher activation in superior parietal cortex and ventral precuneus, and those with higher D_2/D_3R in putamen relative to ventral striatum had higher activation in anterior cingulate. SD impaired the association between striatal D_2/D_3R and VA-induced thalamic activation, which is essential for alertness. Findings suggest a robust DAergic modulation of cortical activation during the VA task, such that D_2/D_3R in dorsal striatum counterbalanced the stimulatory influence of D_2/D_3R in ventral striatum, which was not significantly disrupted by SD. In contrast, SD disrupted thalamic activation, which did not show counterbalanced DAergic modulation but a positive association with D_2/D_3R in both dorsal and ventral striatum. The counterbalanced dorsal versus ventral striatal DAergic modulation of VA activation mirrors similar findings during sensorimotor processing (Tomasi *et al.*, 2015) suggesting a bidirectional influence in signaling between the dorsal caudate and putamen and the ventral striatum.

INTRODUCTION

Attention allows us to focus on one aspect of information (that is, the moving ball) while ignoring irrelevant information (that is, other moving objects in the scene), an ability severely compromised by sleep deprivation (SD).[1] Attention engages a distributed network of brain regions for focusing on specific stimuli or the surroundings, and for resolving conflict between multiple cues.[2] Several neurotransmitters are implicated in the modulation of these attention components, including cholinergic, noradrenergic and dopaminergic systems.[3,4] During the last decade, there has been an increased interest on the role of dopamine (DA) in the modulation of attention[5] as stimulant medications enhance DA signaling in the human brain[6–8] and improve attention under excessive sleepiness.[9,10]

Previous studies have shown that SD decreases striatal D_2/D_3R availability, impairs performance and alters brain activation during attention tasks.[11–17] Specifically, SD has been shown to impair performance to attention demanding cognitive tasks and to reduce arousal and alertness.[18–29] Concomitant with these behavioral changes, SD increases functional magnetic resonance imaging (fMRI) signals in the thalamus, which is essential for alertness,[30] while reducing fMRI signals in superior parietal (SPC) and prefrontal (PFC) cortices during a visual attention (VA) task.[30,31]

The role of DA in the regulation of thalamic and PFC activity is well established.[32,33] For instance, D_2/D_3 receptors (D_2/D_3R) in the ventral striatum (VS) have been associated with fMRI activation of the medial PFC during visual attention to rewards,[34] and D_2/D_3R in the dorsal striatum have been associated with neural processing in the PFC during inhibitory control[35] and executive functioning.[36,37] However, the role of DA in the regulation of the SPC has not been investigated. Thus, while SD-related changes in the PFC and thalamic activation[30] may have reflected the decreases in DA function during SD,[11,13] the association between the decreases in DA function and the changes in brain activation during SD are still largely unknown.

We recently showed that a balance between dorsal caudate versus VS in D_2/D_3R mediated the modulation of brain activation to a cognitive task.[38] Thus, we predicted that fMRI signals during an attention task would show distinct linear associations with the dorsal and ventral striatal regions such that higher D_2/D_3R availability in the dorsal versus VS regions would be associated with greater cortical activation, and that SD would disrupt these associations.

Hence, in this work, we test the linear association between D_2/D_3R in the dorsal and ventral striatum and VA activation in thalamus, SPC and PFC, which are the three critical components of the attention networks.[2] We measured D_2/D_3R using positron

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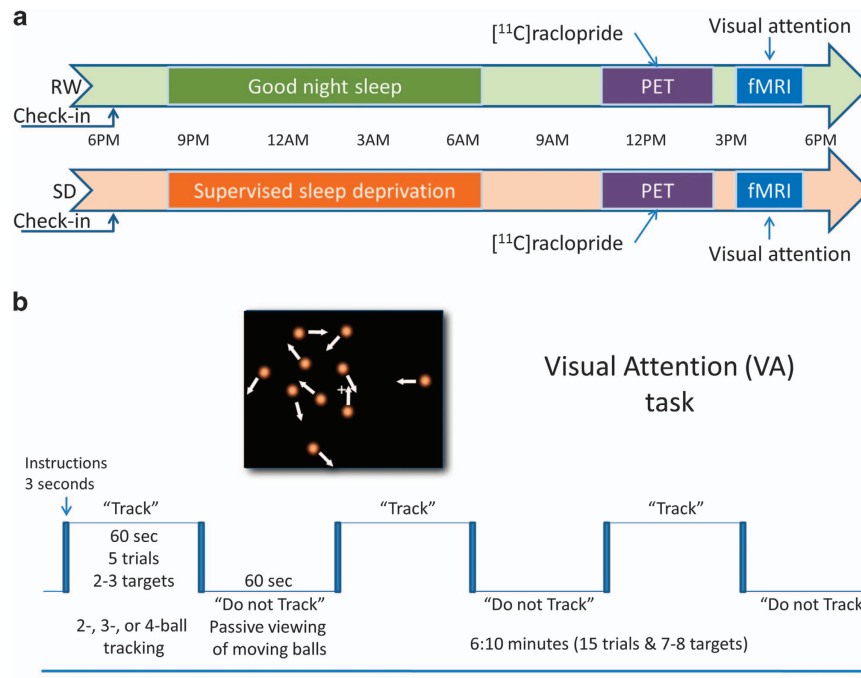E-mail: tomasidg@mail.nih.gov

Figure 1. Study design. (**a**) Fourteen healthy, non-smoking, right-handed men were kept overnight onsite before their scheduled imaging sessions to ensure that that they had a good night rest (rested wakefulness (RW) session) or they did not sleep during the night (sleep deprivation (SD) session). All the subjects underwent [^{11}C]raclopride positron emission tomography (PET) to assess D_2/D_3R in the striatum and 4-Tesla blood-oxygenation-level-dependent functional magnetic resonance imaging (BOLD-fMRI) to map brain activation to a visual attention (VA) task during RW and during SD. (**b**) The parametric VA task had a blocked design in which subjects either tracked 2, 3 or 4 balls out of 10 moving balls (task epochs) or viewed them passively (rest epochs).

emission tomography (PET) and VA activation with 4-Tesla fMRI in 14 healthy men. Subjects were scanned with PET and fMRI twice, after one night of normal sleep (that is, under rested wakefulness (RW)) and also after one night of SD. We hypothesized that cortical activation responses would reflect the relative availability of D_2/D_3R in the dorsal (caudate, putamen) versus ventral striatum, whereas thalamic responses that are necessary for alertness[30] would show an association with both dorsal and ventral striatum. We further predicted that SD would disrupt the modulation of striatal signaling in the indirect striatocortical pathway by virtue of the downregulation of striatal D_2/D_3 receptors that follows SD, which we have shown is associated with a concomitant impairment in cognitive performance.[11]

MATERIALS AND METHODS

Subjects

Fourteen healthy, non-smoking, right-handed men (age 32 ± 8 years, education: 16 ± 2 years) participated in the study. At $\alpha = 0.05$ and 80% power, this sample size allowed us to detect large effects ($r = 0.6$) of SD on the association between D_2/D_3R and fMRI activation. The subjects were included if they were able to understand and give informed consent, and were 18 to 50 years old. They were screened carefully with a detailed medical history as well as physical and neurological examinations. The subjects were excluded if they had (1) urine positive for psychotropic drugs; (2) present or past history of dependence on alcohol or other drugs of abuse; (3) present or past history of neurological or psychiatric disorders (including sleep disorders); (4) cardiovascular disease or diabetes; (5) history of head trauma with loss of consciousness for more than 30 min; (6) medical conditions that may alter the brain function; (7) used psychoactive medications in the past month (that is, opiate analgesics, stimulants, sedatives); (8) used prescription (non-psychiatric) medication(s); or (9) contraindications to MRI environment (metallic implants/claustrophobia). The study participants signed a written consent approved by the Institutional Review Board at Brookhaven National Laboratory before the

study. The subjects were asked to keep a diary of the number of hours slept per night for the 2-week duration of the study and this corresponded to an average of 7 ± 1 h per night (range, 5–8 h).

SD and RW sessions

All the subjects were kept overnight at the Brookhaven National Laboratory campus before their scheduled sessions (Figure 1a) to ensure that that they had a good night rest for the RW session (6.7 ± 0.9 h of sleep; range 5–8.5 h) or they did not sleep during the night for the SD session (supervised by a team member). For the SD session, the total time of sleep deprivation, computed from the subject's wake up time on the check-in day until the end of fMRI session, was 30–35 h. The SD and RW sessions were scheduled 2 weeks apart. The subjects did not have food after midnight and no caffeinated beverages were permitted during the study. PET and MRI acquisition were done sequentially on the same day, either after RW or SD. On the RW day, the subjects were awakened at 0700 h and brought to the imaging suite. A nurse remained with the subjects to ensure they stayed awake throughout the study. The PET sessions (RW and SD) took place between 1100 h and 1400 h and the MRI sessions (RW and SD) took place between 1500 h and 1700 h. Half the studies started with the RW session; the remaining studies started with the SD session to control for practice effects on brain activation.[39]

PET imaging

A Siemens HR+ tomograph with 4.5 mm isotropic resolution was used to collect dynamic PET images in three-dimensional mode. Twenty emission scans were obtained from the time of injection up to 54 min immediately after injection of [^{11}C]raclopride (4–8 mCi; specific activity 0.5–1.5 Ci μM^{-1}). Arterial sampling was used to quantify total carbon-11 and unchanged [^{11}C]raclopride in plasma. The distribution volume (DV) was computed for each imaging voxel using a graphical analysis technique for reversible systems.[40] These images were then spatially normalized to the stereotactic space of the Montreal Neurological Institute using a 12-parameter affine transformation. A custom Montreal Neurological Institute template, which was previously developed using DV images acquired with [^{11}C]raclopride and the same PET scanning sequence[41] was used for the spatial

normalization of the DV images. The intensity of the DV images was normalized to that in the cerebellum (left and right regions of interest) to quantify the non-displaceable binding potential (BP_{ND}) in each voxel. BP_{ND} images were spatially smoothed (8-mm isotropic Gaussian kernel) using the statistical parametric mapping package SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK).

Anatomical region of interest analyses

In-house software written in IDL (Exelis Visual Information Solutions, Boulder, CO, USA) and the Automated Anatomical Labeling (AAL) atlas[42] were used to define three bilateral anatomical regions of interest (ROIs): putamen (PU), caudate (CD) and VS (Figure 1a). The CD ROI included all voxels in dorsal caudate, as defined in the AAL atlas planes $-6\,\text{mm} < z < 14\,\text{mm}$. The VS ROI encompassed the inferior planes of pre-commissural caudate and putamen ($6\,\text{mm} < y \leqslant 27\,\text{mm}$; $-11\,\text{mm} < z \leqslant -6\,\text{mm}$) in the AAL atlas. Average BP_{ND} values were computed for each subject independently for these ROIs. We chose to report the average BPND values in the whole anatomy of the striatal regions to minimize human errors or potential confounds resulting from the utilization of arbitrary thresholds.

VA paradigm

After the PET session, the subjects underwent fMRI with a VA task that was described previously.[39,43–46] This fMRI task was used previously to assess visual attention activation in healthy controls,[39,44,47–49] human immunodeficiency virus patients,[45,50–52] marijuana[53] and cocaine[46,54] abusers as well as to assess the effects of functional connectivity,[54,55] sleep deprivation,[30] dopamine transporters[56] and stimulants[57] on VA activation. The ball-tracking task activates attention-related brain regions (prefrontal, parietal, and occipital cortices, thalamus, and cerebellum). The blocked VA task had 3 difficulty levels (2-, 3-, and 4-ball tracking). Each of the three fMRI runs lasted 6 min and was composed by three 'TRACK' epochs interleaved with three 'DO NOT TRACK' epochs. 'TRACK' epochs interleave five tracking and five respond periods (Figure 1b). In these epochs, a target set of balls (2, 3 or 4 out of 10 balls) is briefly highlighted. Then all the balls start to move. The subjects' task is to fixate on the center cross and track the target balls as they move randomly (simulated Brownian motion) across the display with instantaneous angular speed of 3° per second. At the end of tracking periods, the balls stop moving and a new set of balls is highlighted; the subjects' are instructed to press a button if the highlighted balls are the target set. After a 0.5-s delay, the original target balls are re-highlighted to re-focus the subjects' attention on the target balls. 'DO NOT TRACK' epochs are composed of five consecutive 'resting' periods. In these epochs, all the 10 balls move and stop in the same manner as during 'TRACK' epochs; however, no balls are highlighted, and subjects are instructed to not track the balls and view them passively. The subjects performed a brief training session (~10 min) of a shortened version of the paradigm outside of the scanner to ensure that they understood and were able to perform the tasks. There were three fMRI runs (two-, three- and four-ball tracking). Each one of these runs had 231 image volumes (4 dummy volumes, 7 fixation cross baseline volumes, 112 passive-viewing volumes and 112 ball-tracking volumes).

Different versions of the two-, three- and four-ball-tracking tasks were used in each session (SD and RW). The stimuli were created using Matlab (MathWorks, Natick, MA, USA) and presented to the subjects on MRI-compatible goggles (Resonance Technology, Northridge, CA, USA) connected to a personal computer. The display software was synchronized with the MRI acquisition using a trigger pulse. All button press events were recorded to determine reaction time (RT) and performance accuracy during fMRI.

MRI data acquisition

The blood-oxygenation-level-dependent (BOLD) contrast was used to assess fMRI activation in a 4-Tesla whole-body Varian/Siemens MRI scanner. A T2*-weighted single-shot gradient-echo planar imaging sequence (TE/TR = 20/1600 ms, 4 mm slice thickness, 1 mm gap, 35 coronal slices, 3.1 mm in-plane resolution, 64 × 64 matrix size, 90°-flip angle, 231 time points, bandwidth: 200.00 kHz) covering the whole brain was used for this purpose. Padding was used to minimize motion. Task performance and subject motion were determined immediately after each fMRI trial.[58] Anatomical images were collected using T2-weighted hyperecho (TE/TR = 42/10 000 ms, echo train length = 16, 256 × 256 matrix size, 30 coronal slices, 0.86 × 0.86 mm in-plane resolution, 5 mm thickness, 1 mm gap, 2-min scan time) and T1-weighted three-dimensional MDEFT

(TE/TR = 7/15ms, 0.94 × 0.94 × 1 mm spatial resolution, axial orientation, 256 readout and 192 × 96 phase-encoding steps, 16-min scan time) sequences. These structural MRI scans were reviewed to rule out gross morphological abnormalities in the brain.

Data processing

The first four volumes in the time series were discarded to avoid non-equilibrium effects in the fMRI signal. Subsequent analyses were performed with SPM8. 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 Montreal Neurological Institute was performed using a 12-parameter affine transformation with medium regularization, 16-nonlinear iterations, 3 × 3 × 3 mm³ voxel size and the standard SPM8 EPI template. Spatial smoothing was carried out using an 8-mm (full width at half maximum) Gaussian kernel. A general linear model[59] was used to calculate the BOLD contrasts for each VA load condition (two, three and four balls), session (RW and SD) and subject. The blocked analysis was based on a box-car design defined by the onsets of the 'TRACK' epochs, convolved with the canonical hemodynamic response function, as a low-pass filter, and a high-pass filter (256 s time cutoff).

Statistical analyses

Simple (SLR) and multiple (MLR) linear regression analyses were used to assess the association between the fMRI signals in the brain and the D₂/D₃R measures across subjects, using VA load and session as covariates in SPM8. Five SLR models were used with regressors that reflected the absolute BP_{ND} values extracted from CD (SLR1), PU (SLR2) and VS (SLR3), as well as the relative BP_{ND} measures CD/VS (SLR4) and PU/VS (SLR5). Two different MLR models were used to study the combined influence of receptors in VS and in CD (MLR1), as well as that of receptors in PU and VS (MLR2). Specifically, the fMRI responses at a given voxel, $S(x, y, z)$, were modeled using the affine transformation:

$$S(x,y,z) = a_i(x,y,z)BP^i_{ND} + a_j(x,y,z)BP^i_{ND} + \varepsilon(x,y,z), \quad (1)$$

where i and j are CD and VS, or PU and VS, the scalar maps a (x, y, z) are the slopes that quantify the efficiency of the linear association between D₂/D₃R and brain activation and ε is the intercept of the MLR. Independent MLR analyses were carried for RW and SD as well as for the combined RW and SD sample. For all analyses, statistical significance was set as $P_{FWE} < 0.05$, corrected for multiple comparisons in the whole brain with the random field theory and a family-wise error correction at the cluster level. A cluster-forming threshold $P < 0.001$ (two-sided) and a minimum cluster size of 100 voxels were used for this purpose.

RESULTS

Behavior

The fMRI and behavioral data in this work were previously reported in a study that documented SD-related decreases in VA performance and fMRI activation differences between RW and SD.[30] Briefly, subjects reported higher sleepiness before the SD session than before the RW session (RW: 3.8 ± 0.5; s.d.: 8.8 ± 0.4; $P < 0.0001$, paired t-test). Increased sleepiness correlated linearly with performance accuracy during the fMRI tasks ($R = 0.59$; $P = 0.025$). Performance accuracy during fMRI decreased with increased task difficulty (from two balls to four balls; $P < 0.0001$; two-way ANOVA) and was lower during the SD session than during the RW session ($P = 0.02$). RT during the fMRI did not differ significantly across tasks or sessions. There were no statistically significant load × session interaction effects on subject's performance (accuracy or RT). In the present study, we studied the association between brain activation during the VA task and D₂/D₃R measures in the dorsal and ventral striatum.

D₂/D₃R

The average BP_{ND} values, which were computed without BP_{ND} thresholds over the anatomical volumes of CD, PU and VS (see the Materials and methods section), were lower for SD than for RW for all striatal ROIs (VS: 1.21 ± 0.03 (RW) and 1.16 ± 0.02 (s.d.); CD:
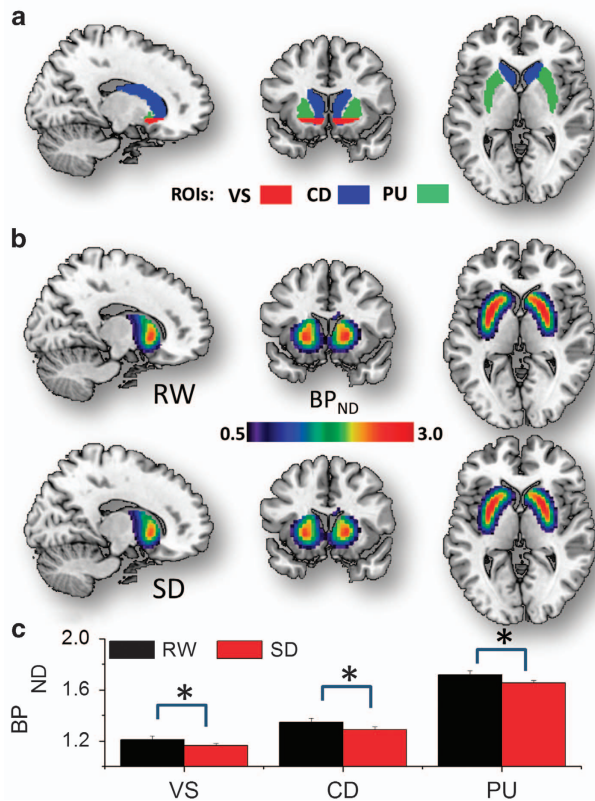
Figure 2. D2/D3R binding. (a) Average non-displaceable binding potential (BP$_{ND}$) values reflecting D$_2$/D$_3$R levels were computed in three bilateral anatomical striatal regions of interest (ROIs): ventral striatum (VS), dorsal caudate (CD) and putamen (PU), superimposed on three orthogonal views of the human brain. (b) Average BP$_{ND}$ maps across subjects for the sleep deprivation (SD) and rested wakefulness (RW) conditions, highlighting the high availability of D$_2$/D$_3$R in the striatum. (c) Bar plot quantifying the average BP$_{ND}$ measures in the ROIs for RW and SD and highlighting the significantly lower availability of D$_2$/D$_3$R for SD than for RW (*$P < 0.05$, two-sided). Sample size: 14 healthy, non-smoking, right-handed men. Error bars are s.e.m.

1.35 ± 0.03 (RW) and 1.29 ± 0.02 (s.d.); PU: 1.72 ± 0.03 (RW) and 1.65 ± 0.02 (s.d.); mean ± s.e.; $P < 0.05$, two-sided paired t-test, df = 13; Figure 2). The BP$_{ND}$ ROI measures showed high correlations across subjects and were higher during RW than during s.d. ($P < 0.05$). The differences in the 'relative' BP$_{ND}$ measures between RW and s.d. were not significant (CD/VS: 1.11 ± 0.01 (RW) and 1.11 ± 0.01 (s.d.); PU/VS: 1.42 ± 0.01 (RW) and 1.42 ± 0.01 (s.d.); $P > 0.2$, two-sided paired t-test, df = 13).

D$_2$/D$_3$R and brain activation

The SLR analysis revealed that fMRI signals in the thalamus increased linearly with D$_2$/D$_3$R across subjects during RW but not during SD, independently for CD, VS and PU ($P_{FWE} < 0.003$; Figure 3b and Table 1). The slopes of the linear associations between fMRI signals in the anterior thalamus and D$_2$/D$_3$R in the CD, and between fMRI signals in the posterior thalamus and D$_2$/D$_3$R in the VS were significantly steeper for RW than for SD ($P_{FWE} < 0.02$; Figure 3c and Table 1). During RW, higher availability of D$_2$/D$_3$R in the VS were associated with increased activation in precuneus and increased deactivation in cuneus; during SD only the fMRI signals in precuneus showed a linear association with D$_2$/D$_3$R in VS ($P_{FWE} < 0.001$; Figure 3b and Table 1). Figure 3d

exemplifies the linear associations between D$_2$/D$_3$R measures in the striatum and fMRI signals in the thalamus, precuneus and cuneus, independently for RW and for SD.

Balanced influence of D2/D3R in dorsal versus ventral striatum on fMRI signals

The SLR analysis also revealed significant linear associations between the 'relative' CD-to-VS ratio of D$_2$/D$_3$R measures and the fMRI signals in SPC (positive slope), regions that showed prominent brain activation to the VA task during RW but attenuated activation during SD (Table 2), and in precuneus (negative slope), a region that showed significant fMRI deactivation (negative BOLD signals) during the VA tasks, independently for RW and for SD ($P_{FWE} < 0.03$, cluster corrected for multiple comparisons in the whole brain; Figure 4 and Table 2).

The MLR analysis showed a bilinear association between brain activation responses in parietal cortex and D$_2$/D$_3$R in VS and in CD (Figure 5a). Specifically, in precuneus, the fMRI responses predicted by D$_2$/D$_3$R in VS showed a positive correlation with BP$_{ND}^{VS}$, whereas those predicted by D$_2$/D$_3$R in CD showed a negative correlation with BP$_{ND}^{CD}$ ($P_{FWE} < 0.0005$, cluster corrected for multiple comparisons in the whole brain; RW and SD conjunction contrast), and the MLR slope was significantly steeper for VS than for CD ($a_{VS} > a_{CD}$, $P_{FWE} < 0.0005$; Figure 5b). Conversely, the predicted responses in SPC showed negative correlation with BP$_{ND}^{VS}$ and positive correlation with BP$_{ND}^{CD}$ ($P_{FWE} < 0.0005$), and the MLR slope was significantly steeper for CD than for VS ($a_{CD} > a_{VS}$, $P_{FWE} < 0.002$; Figure 5b). Although the SLR association between the relative CD-to-VS D$_2$/D$_3$R measures and the fMRI signals accounted for less than 22% of the variance in the fMRI data, the MLR association accounted for more than 52% of the variance in the fMRI signal in SPC and precuneus. However, because the BP$_{ND}^{CD}$ and BP$_{ND}^{VS}$ regressors exhibited high correlation ($R = 0.91$ for RW and 0.71 for SD; Figure 5c), we evaluated the risk of multicollinearity in the MLR model using the variance inflation factor (VIF) = $1/(1 − R^2)$, and the 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).[60,61] In the present work, the risk of multicollinearity for the BP$_{ND}^{CD}$ and BP$_{ND}^{VS}$ regressors did not exceed these thresholds for any of the sessions and was lower for SD ($\kappa = 6$ and VIF = 2) than for RW ($\kappa = 28$ and VIF = 6).

The fMRI responses in supplementary motor area (SMA), a PFC region that was increasingly activated by parametric VA load increases (BOLD signal = 0.52 ± 0.07%; load effect = 0.16% ± 0.10%; mean ± 90% confidence interval; Table 2) and in anterior cingulate cortex (ACC) increased in proportion to the 'relative' PU-to-VS ratio (PU/VS) of BP$_{ND}$ measures. Visual cortex deactivation was enhanced by VA load increases and attenuated by SD, and decreased in proportion to the relative PU-to-VS ratio of BP$_{ND}$ measures during RW ($P_{FWE} < 0.005$; Figure 4 and Table 2). Similarly during SD, ACC activation showed a negative association with the PU-to-VS ratio of BP$_{ND}$ measures (Table 1; $P_{FWE} < 0.001$).

The MLR analysis confirmed the bilinear association between brain activation responses and D$_2$/D$_3$R in VS and PU during RW and SD (Figure 6a). Specifically, in SMA, the fMRI responses predicted by D$_2$/D$_3$R in VS showed a positive linear association with BP$_{ND}^{VS}$, whereas those predicted by D$_2$/D$_3$R in PU showed a negative linear association with BP$_{ND}^{PU}$ ($P_{FWE} < 0.03$; RW and SD conjunction contrast), and the MLR slope was significantly steeper for VS than for PU ($a_{VS} > a_{PU}$, $P_{FWE} < 0.005$; Figure 6b). In cuneus, the fMRI responses predicted by D$_2$/D$_3$R in PU showed a positive correlation with BP$_{ND}^{PU}$, whereas those predicted by D$_2$/D$_3$R in VS showed a negative correlation with BP$_{ND}^{VS}$ ($P_{FWE} < 0.001$; RW and SD conjunction contrast), and the MLR slope was significantly
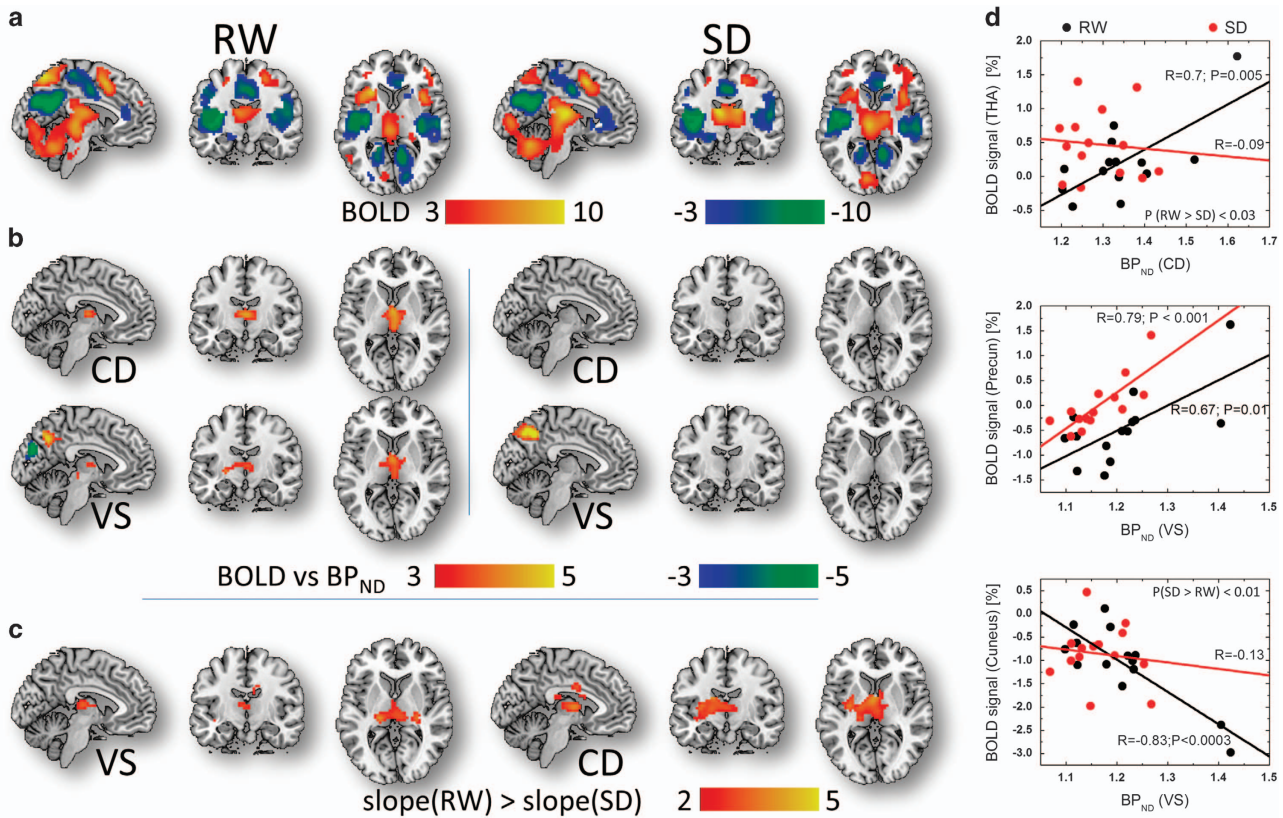
Figure 3. Visual attention activation versus dopamine (DA) receptors. Statistical significance (*t*-score) maps of brain activation responses for (**a**) rested wakefulness (RW) and for sleep deprivation (SD) conditions superimposed on three orthogonal views of the human brain ($P_{FWE} < 0.0001$) and (**b**) simple linear regression (SLR) slopes demonstrating the linear association across subjects between brain activation responses and D₂/D₃R separately for caudate (CD) and ventral striatum (VS; $P_{FWE} < 0.001$). (**c**) For VS and CD, the SLR slopes in the thalamus were significantly steeper for RW than for SD ($P_{FWE} < 0.02$). (**d**) Scatter plots showing the linear associations between D₂/D₃R measures in caudate (CD) and ventral striatum (VS), and the blood-oxygen-level dependent (BOLD) signals in thalamus, precuneus and cuneus, independently for the rested wakefulness (RW) and sleep deprivation (CD) conditions. Sample size: 14 healthy, non-smoking, right-handed men. FWE, family-wise error.

steeper for PU than for VS ($a_{PU} > a_{VS}$, $P_{FWE} < 0.005$). The SLR association accounted for 38% of the variance in the fMRI data in SMA during RW (27% during SD). The MLR association accounted for 52% of the variance in the fMRI signal in SMA during RW (27% during SD). The risk of multicollinearity for the BP_{ND}^{PU} and BP_{ND}^{VS} regressors was lower for SD ($\kappa = 2$ and VIF = 1) than for RW ($\kappa = 22$ and VIF = 6).

Sleep-deprivation effects: behavior vs brain activation

Across all ball-tracking conditions, SD-related decreases in performance accuracy were linearly associated with SD-related decreases in VA activation in the PFC (BA = 24; $R = 0.52$; $P < 0.0004$; linear regression, df = 41).

DISCUSSION

Here we demonstrate a distinct involvement of D₂/D₃R in the different striatal regions in the fMRI activation of brain regions involved in the alerting, orienting and executive components of attention[2] during the VA task. We found that D₂/D₃R in dorsal striatum counterbalance D₂/D₃R in ventral striatum in the modulation of activation responses to a VA task, which corroborates our previous findings using a sensorimotor RT task.[38] We also found that the SD-related reduction in the availability of D₂/D₃R in the striatum was associated with (1) decreased strength in the linear association between thalamic activation and D₂/D₃R in CD, PU and VS during SD and (2) a robust bilinear association between the activation of frontal and parietal regions and D₂/D₃R in dorsal relative to ventral striatal regions that attenuated the effects of SD. This study also documents a counterbalanced association between caudate versus VS D₂/D₃R in the deactivation of the default-mode network during VA.

Thalamus

The thalamus, the gateway to the cortex,[62] is essential for alerting attention[2] and for arousal[63] and has an important role in the regulation of sleep and wakefulness.[64] Here we believe we show for the first time the role of D₂/D₃R-mediated dopamine signaling in the activation of the thalamus. Specifically, thalamic activation increased in proportion to D₂/D₃R in the striatum during the RW condition but not during the SD condition, when D₂/D₃R availability was significantly reduced and thalamic activation was higher than for the RW condition. As the thalamus mediates the interaction between attention and arousal in humans[63] and is involved in the alerting component of attention,[2,65,66] the increased thalamic activation[14–17,30,67] likely reflects an adaptation to compensate for reduced DAergic signaling due to lower D₂/D₃R during SD. Previous studies have documented associations between striatal D₂/D₃R and cortical fMRI responses to emotion, visual attention, decision-making and inhibitory control tasks.[34,35,68–70] These studies, however, did not report an association between D₂/D₃R and fMRI signals in the thalamus.

Table 1. Statistical significance for the linear associations between striatal D$_2$/D$_3$R measures and brain activation responses (BOLD) during the VA task under SD and RW conditions

Region		MNI coordinates (mm)			Brain activation			Session	D$_2$/D$_3$R-BOLD SLR			
									Cluster level		Voxel level	
Name	BA/nucleus	x	y	z	VA, T	VA load, T	SD>RW, T		P$_{FWE-corr.}$	k	P$_{FWE-corr.}$	T
Caudate (CD)												
Thalamus	Anterior	0	−6	6	5.7	NS	NS	RW	0.001	220	< 0.0005	4.5
Middle Occipital	19	−27	−84	24	−4.1	−1.7	NS	SD	0.023	109	0.006	−4.5
Ventral striatum (VS)												
Precuneus	7	3	−63	39	−7.0	NS	NS	RW	0.001	222	< 0.0005	5.3
Thalamus	Anterior	0	−3	6	4.0	NS	NS	RW	0.003	179	0.001	4.2
Cuneus	18	6	−81	27	−12.0	−1.7	2.0	RW	0.03	101	0.008	−6.4
Precuneus	7	6	−54	45	NS	NS	2.2	SD	0.001	217	< 0.0005	5.8
Globus pallidus (GP)												
Thalamus	Ventral posterior	24	−15	0	NS	NS	NS	RW	0	389	< 0.0005	4.7
Precuneus	7	0	−63	36	−12.3	NS	NS	RW	0.004	170	0.001	4.7
Cuneus	18	6	−81	27	−12.0	−1.7	2.0	RW	0.031	101	0.008	−5.6
Middle Occipital	19	−27	−78	33	−9.0	−2.4	NS	RW	0.015	125	0.004	−5.6
Middle Occipital	39	42	−78	18	3.0	NS	NS	RW	0	283	< 0.0005	−4.9
Putamen (PU)												
Thalamus	Ventral posterior	24	−12	0	NS	NS	1.7	RW	0	355	< 0.0005	4.5
Middle Occipital	19	−27	−78	33	−9.0	−2.4	NS	RW	0.002	194	0.001	−6.7
Middle Occipital	39	42	−78	18	3.0	NS	NS	RW	0	340	< 0.0005	−5.3
Lingual	37	24	−51	−9	−3.9	NS	NS	RW	0.005	164	0.001	−4.6
CD												
Thalamus	Pulvinar	18	−24	15	8.3	NS	2.8	RW>SD	0.02	430	0.001	5.0
VS												
Thalamus	Pulvinar	18	−24	18	7.1	NS	2.5	RW>SD	0.002	665	< 0.0005	5.5

Abbreviations: BOLD, blood-oxygen-level dependent; FWE-corr., family-wise error corrected; NS, not significant; RW, rested wakefulness; SD, sleep deprivation; SLR, simple linear regression; VA, visual attention. Sample size: 14 healthy non-smoking men.
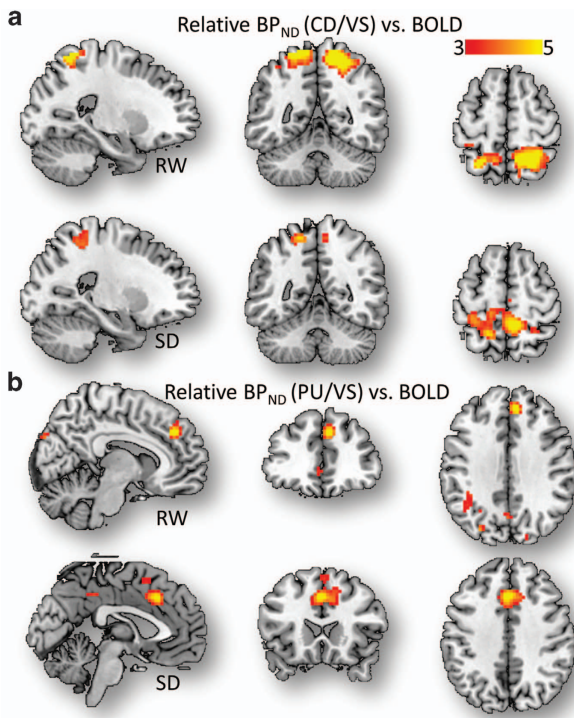
Table 2. Statistical significance for the linear associations between relative striatal D$_2$/D$_3$R measures and brain activation responses (BOLD) during the VA task under SD and RW conditions

Region		MNI coordinates (mm)			Brain activation			Session	Relative D$_2$/D$_3$R-BOLD SLR			
									Cluster level		Voxel level	
Name	BA	x	y	z	VA, T	VA load, T	SD>RW, T		P$_{FWE-corr.}$	k	P$_{FWE-corr.}$	T
Caudate-to-ventral striatum ratio (CD/VS)												
Superior parietal	7	27	−57	63	14.9	NS	−3.1	RW	0.003	186	0.001	7.3
Superior parietal	5	−18	−51	66	4.5	NS	−2.4	RW	< 0.0005	382	< 0.0005	6.5
Precuneus	7	3	−66	39	−9.6	NS	−1.9	RW	0.028	103	0.007	−4.4
Precuneus	5	−6	−42	60	−6.4	2.3	NS	SD	< 0.0005	514	< 0.0005	5.7
Precuneus	7	9	−69	33	−14.0	1.7	NS	SD	0.007	148	0.002	5.4
Globus pallidus-to-ventral striatum ratio (GP/VS)												
Supramarginal	40	−57	−39	27	−5.5	−1.8	NS	RW	0.005	160	0.001	4.8
Cingulum	32	0	21	42	11.9	3.5	NS	SD	0.004	172	0.001	−5.8
Putamen-to-ventral striatum ratio (PU/VS)												
Lingual	18	−15	−87	−6	−2.4	NS	NS	RW	< 0.0005	349	< 0.0005	5.8
Calcarine	17	15	−60	15	−14.1	−3.1	3.0	RW	< 0.0005	287	< 0.0005	5.5
Cingulum	24	0	24	39	7.8	1.7	NS	SD	0.006	155	0.002	−5.5

Abbreviations: BOLD, blood-oxygen-level dependent; FWE-corr., family-wise error corrected; NS, not significant; RW, rested wakefulness; SD, sleep deprivation; SLR, simple linear regression; VA, visual attention. Sample size: 14 healthy non-smoking men.

Figure 4. Parietal activation versus relative D$_2$/D$_3$R in dorsal to ventral striatum. (**a** and **b**) Statistical significance (*t*-score) maps for simple linear regression (SLR) slopes demonstrating the linear association across subjects between brain activation responses and the caudate (CD) to ventral striatum (VS) (**a**) and putamen (PU) to VS (**b**) ratios of D$_2$/D$_3$R measures for rested wakefulness (RW) and for sleep deprivation (SD), superimposed on three orthogonal views of the human brain. Sample size: 14 healthy, non-smoking, right-handed men. Significance threshold: $P_{FWE} < 0.002$, cluster corrected for multiple comparisons in the whole brain. BOLD, blood-oxygen-level dependent; FWE, family-wise error.

Dopamine is a neuromodulator that changes the efficacy of other neurotransmitters as a function of ongoing neuronal activity.[71] The effect of DA on neuronal firing is believed to improve signal to noise for the detection of task-specific neuronal activation in electrophysiological studies.[72,73] Thus, by decreasing non-task-related activity, DA stimulation increases efficiency and results in lower activation of task-specific regions.[72] Therefore, the higher thalamic activation for SD than for RW is consistent with decreased efficiency due to lower DAergic signaling during SD. Alternatively it could also reflect an increased modulation by noradrenergic signaling as SD also disrupt noradrenergic activity.[74]

SPC

The SPC is essential for orienting attention[2,75] and projects to multiple cortical and subcortical areas (including thalamus) and is engaged in cognitive operations such as selective attention and top-down control of attention.[31,76–84] Here we show that the fMRI signals in SPC increased in proportion to the relative availability of D$_2$/D$_3$R in CD to that in VS such that the higher the CD-to-VS ratio of D$_2$/D$_3$R, the higher the activation in SPC. The SPC, which is consistently activated by the VA task,[39,43,44,46,48,85] showed lower fMRI activation during SD than during RW.[30] However, significant differences between RW and SD in the linear association of SPC activation and striatal D$_2$/D$_3$R were not found. Thus, the lower cortical activation for SD than for RW commonly reported in neuroimaging studies[14–17,30,67,86–90] likely reflects effects of SD on other neurotransmitter systems (that is, cholinergic or noradrenergic).

The MLR findings suggest that D$_2$/D$_3$R in CD and VS have distinct roles in the modulation of SPC responses during VA. Indeed, the association between D$_2$/D$_3$R and fMRI signals in SPC was significantly stronger when two regressors (BP$_{ND}^{VS}$ and BP$_{ND}^{CD}$; $R^2 = 0.52$) were used in the MLR model, compared with one regressor (BP$_{ND}^{VS}$/BP$_{ND}^{CD}$; $R^2 = 0.22$). This finding supports the existence of a balanced D$_2$/D$_3$R modulation of cortical activation responses from CD and VS, which is consistent with our recent findings using a sensorimotor RT task in a different sample of healthy subjects.[38] The reproducibility of the MLR findings across the RW and SD conditions strongly supports the existence of a balanced D$_2$/D$_3$R modulation between CD and VS for the SPC activation to a VA task that is robust to the SD challenge.

SMA and ACC

The ACC and PFC have been implicated in the executive component of attention[2,75] and are involved in target detection and awareness.[91] We found an association between the relative availability of D$_2$/D$_3$R in the striatum and the fMRI signals in ACC and SMA, such that increased D$_2$/D$_3$R in VS proportionally increased the fMRI signal in ACC/SMA and increased D$_2$/D$_3$R in PU proportionally decreased it. These findings are consistent with the well-established role of DA on executive function in the human brain,[92] including its role in response control.[93] DA modulation in ACC is important for executive function,[94,95] and DA modulation in SMA is important for response inhibition and response initiation.[93,96,97] Though most studies on the DAergic modulation of executive function identify the CD as the striatal region that mediates this effect,[98–100] others implicate the PU.[101–103] Our findings suggest that during the VA task, DA modulates executive attention through counterbalanced D$_2$/D$_3$R signaling from PU and VS. Interestingly, fMRI activation in SMA and ACC and its association with D$_2$/D$_3$R did not differ for SD and RW, providing support for a robust and balanced DAergic modulation of executive attention.

Precuneus

The fMRI signals in the ventral anterior precuneus showed linear association with the 'relative' availability of D$_2$/D$_3$R in CD and VS such that the higher the CD-to-VS ratio of D$_2$/D$_3$R, the greater the deactivation in precuneus, both during RW and during SD. The MLR findings suggest that D$_2$/D$_3$R in CD and VS mediate a balanced modulation of deactivation in precuneus, which is reproducible across sessions and robust to the SD challenge. This is consistent with the role of DA in the modulation of the precuneus,[56,104] a major hub in the default-mode network[105,106] that deactivates during the VA task.[47] Note that a recent study on functional subdivisions of the precuneus revealed that ventral anterior precuneus, but not the dorsal precuneus, is connected to the default-mode network.[107] This major association area has reciprocal connections with superior and inferior parietal, pre-frontal, and occipital cortices as well as subcortical regions,[108] including the thalamus.[109] The precuneus, is also involved in alertness[110] and activates during spatial[43,47,111] and orienting[79,112] attention. Because DA innervation in the parietal cortex is scarce,[113,114] the association between D$_2$/D$_3$R documented here suggests indirect DA modulation through thalamo–cortical pathways rather than a direct modulation. The enhanced deactivation of the precuneus in subjects with higher CD-to-VS ratio of D$_2$/D$_3$R could reflect regulation of CD in orienting attention by facilitating attention processing while inhibiting the posterior default-mode network.

We have shown that SD decreases the specific binding of [^{11}C] raclopride (measured as reduced D$_2$/D$_3$ receptor availability in striatum), which we initially interpreted to reflect increased
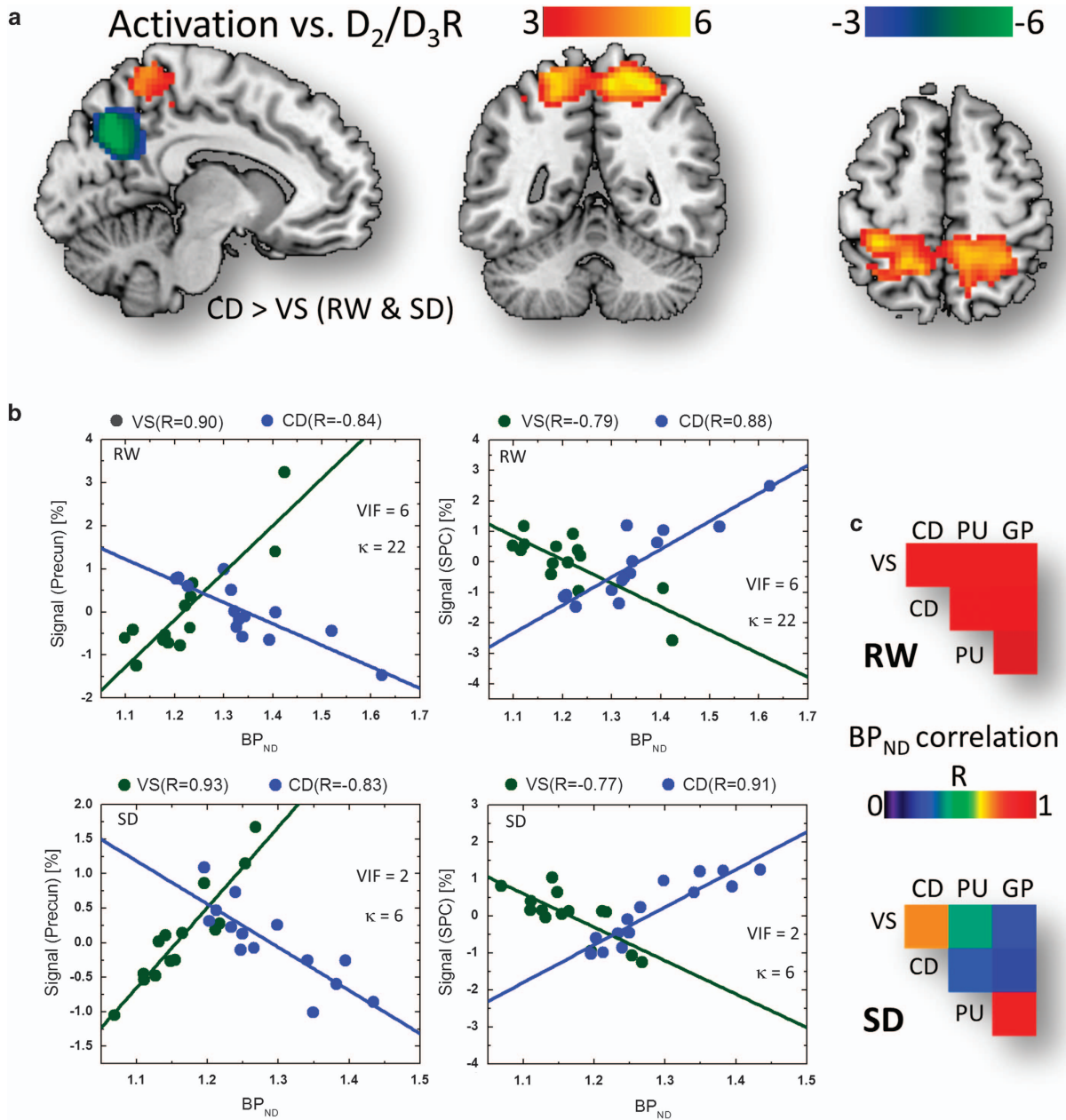
Figure 5. Balanced dopaminergic (DAergic) effects on parietal activation. (**a**) Statistical significance (*t*-score) maps for multiple linear regression (MLR) slopes demonstrating the linear associations across subjects between average non-displaceable binding potential (BP$_{ND}$) measures in caudate (CD) and ventral striatum (VS) and brain activation responses in the superior parietal cortex (SPC; red-yellow pattern) and precuneus (blue-green pattern) during visual attention for rested wakefulness (RW) and for sleep deprivation (SD; conjunction analysis), superimposed on three orthogonal views of the human brain. Significance threshold: $P_{FWE} < 0.002$, cluster corrected for multiple comparisons in the whole brain. (**b**) Scatter plots showing the linear associations between the predicted signals (BP$_{ND}^{VS}$ and BP$_{ND}^{CD}$; see the 'Methods' section) in SPC and precuneus and the corresponding BP$_{ND}$ measures in CD and VS. (**c**) BP$_{ND}$ correlation matrix showing the Pearson correlation factors (R; computed across subjects) between average D$_2$/D$_3$R measures in VS, CD, putamen (PU) and globus pallidus (GP), for RW and for SD conditions. Sample size: 14 healthy, non-smoking, right-handed men. FWE, family-wise error; κ, condition number; VIF, variance inflation factor.

competition for binding secondary to an increase in DA release during SD.[11] However, a follow-up study showed that the changes in DA triggered by the stimulant drug methylphenidate were not affected by SD, which was a finding not consistent with SD increasing DA release.[13] Moreover this was supported by microdialysis experiments in which we showed that SD did not increase DA release.[13] This led us to conclude that the decreases in [^{11}C]raclopride's specific binding reflected a downregulation of D$_2$/D$_3$ receptors in striatum by SD. Though the mechanisms

underlying the D$_2$/D$_3$ receptor downregulation by SD are unclear, we speculated that increases in adenosine following SD mediate the internalization of D$_2$/D$_3$ receptors.[115,116] Indeed, we subsequently showed that caffeine, which is an adenosine antagonist led to an increase in D$_2$/D$_3$ receptors in striatum, presumably by interfering with adenosine-mediated internalization of D$_2$/D$_3$ receptors.[117] Regardless of the mechanism, what our current findings are showing is that despite the overall reductions in striatal D$_2$/D$_3$ receptors with SD the activation/deactivation in ACC,
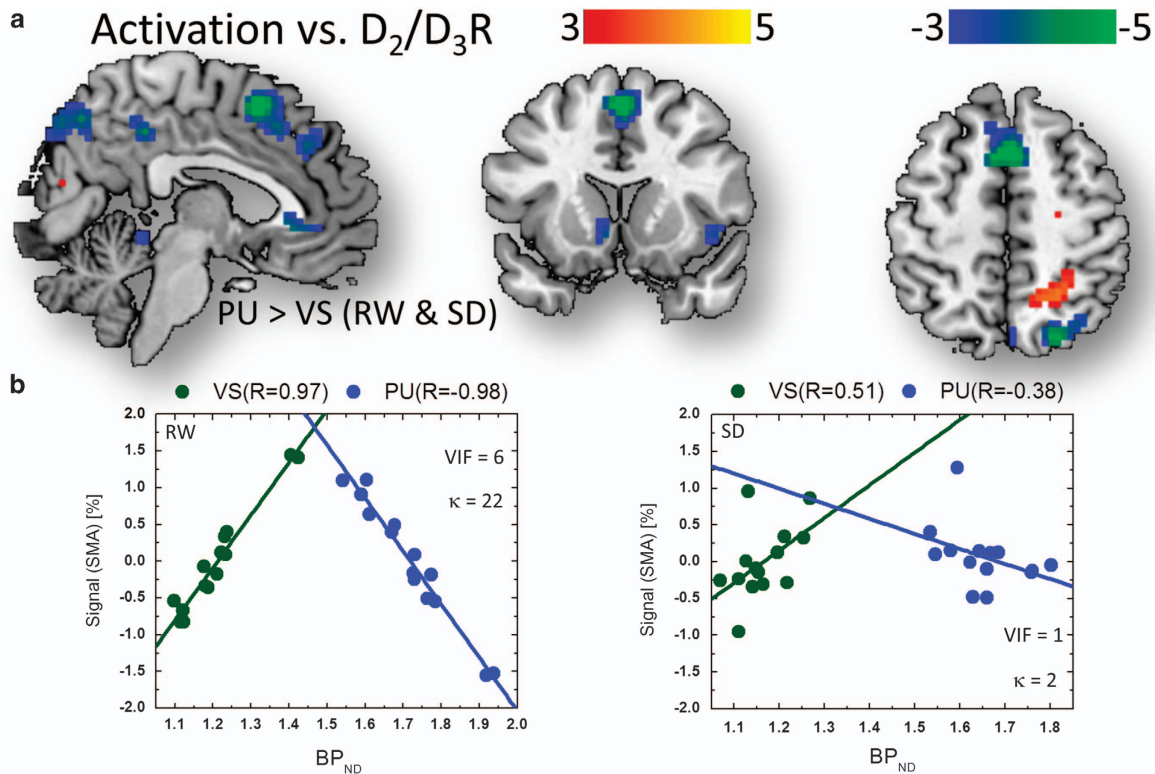
Figure 6. Balanced dopaminergic (DAergic) effects on prefrontal activation. (**a**) Statistical significance (*t*-score) maps for multiple regression analysis (MLR) slopes demonstrating the negative linear associations across subjects between average non-displaceable binding potential (BP_{ND}) measures in putamen (PU) and ventral striatum (VS) and brain activation responses in the supplementary motor area (SMA; blue-green pattern) during visual attention for rested wakefulness (RW) and for sleep deprivation (SD; conjunction analysis), superimposed on three orthogonal views of the human brain. Significance threshold: $P_{FWE} < 0.005$, cluster corrected for multiple comparisons in the whole brain. (**b**) Scatter plots showing the linear associations between the predicted signals (BP_{ND}^{VS} and BP_{ND}^{PU}; see the 'Methods' section) in SMA and the corresponding BP_{ND} measures in PU and VS.

SMA, SPC and precuneus to VA is buffered by the counterbalanced modulation of D_2/D_3 receptor signaling in the dorsal relative to the VS through the indirect striatocortical pathway.

Limitations

The multicollinearity of the D_2/D_3R regressors limits the generalizability of our approach. As the multicollinearity problem increases, the regression model estimates become unstable and their standard errors might get inflated. As multicollinearity is considered a potential concern only if $VIF > 10$ or $\kappa > 30$,[60,61] the MLR model for the RW condition ($VIF = 6$ and $\kappa = 28$) was deemed viable. Furthermore, similar MLR patterns were observed for the SD condition that had significantly lower multicollinearity risk ($VIF < 2$ and $\kappa < 6$) than the RW condition, demonstrating the reproducibility of the MLR findings. Also we ascribe a modulatory role to D_2/D_3R on the activation responses to the VA task on the basis of finding significant associations, but future studies that vary the levels of DA signaling are needed to confirm this. We cannot assess the influence of noradrenaline on VA activation. It is known that the DAergic circuits interact with NAergic circuits[118] and that wakefulness-promoting medications such as modafinil may enhance arousal in humans by activation of the NAergic locus coeruleus.[119] Thus, the SD-related activation changes may reflect noradrenaline changes to sustain arousal during SD.

In conclusion, our study documents a significant involvement of DA signaling through striatal D_2/D_3R in the orchestration of visual attention. SD disrupted DA's regulation of the thalamus but not that of the SPC and PFC. Our findings also corroborate a balanced involvement of D_2/D_3R signaling in dorsal striatum (CD and PU) versus that in VS for the regulation of brain activation in regions involved in the VA task.

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