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COGNITIVE NEUROSCIENCE

Lateralization and gender differences in the dopaminergic response to unpredictable reward in the human ventral striatum

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Abstract

Electrophysiological studies have shown that mesostriatal dopamine (DA) neurons increase activity in response to unpredicted rewards. With respect to other functions of the mesostriatal dopaminergic system, dopamine's actions show prominent laterality effects. Whether changes in DA transmission elicited by rewards also are lateralized, however, has not been investigated. Using [^{11}C]raclopride-PET to assess the striatal DA response to unpredictable monetary rewards, we hypothesized that such rewards would induce an asymmetric reduction in [^{11}C]raclopride binding in the ventral striatum, reflecting lateralization of endogenous dopamine release. In 24 healthy volunteers, differences in the regional $D_{2/3}$ receptor binding potential (ΔBP) between an unpredictable reward condition and a sensorimotor control condition were measured using the bolus-plus-constant-infusion [^{11}C]raclopride method. During the reward condition subjects randomly received monetary awards while performing a 'slot-machine' task. The ΔBP between conditions was assessed in striatal regions-of-interest and compared between left and right sides. We found a significant condition × lateralization interaction in the ventral striatum. A significant reduction in binding potential (BP_{ND}) in the reward condition vs. the control condition was found only in the right ventral striatum, and the ΔBP was greater in the right than the left ventral striatum. Unexpectedly, these laterality effects appeared to be partly accounted for by gender differences, as our data showed a significant bilateral BP_{ND} reduction in women while in men the reduction reached significance only in the right ventral striatum. These data suggest that DA release in response to unpredictable reward is lateralized in the human ventral striatum, particularly in males.

Introduction

The mesostriatal dopaminergic system plays a major role in the neural processing underlying motivated and reward-related behavior. With respect to some functions of this system, dopamine (DA) transmission in the striatum shows prominent laterality effects. In rodents, these laterality effects depended upon the direction of motor behavior and the type of reinforcement schedule in some experimental conditions (Zimmerberg *et al.*, 1974; Glick *et al.*, 1980, 1981; Yamamoto *et al.*, 1982; Yamamoto & Freed, 1984; Szostak *et al.*, 1986; Morice *et al.*, 2005), whereas in others the lateralization of DA release appeared fixed with respect to function or task (Besson & Louilot, 1995; Silva *et al.*, 2007). It has been hypothesized that the observed lateralization effects are attributable to an asymmetry in the nigrostriatal projections (Kelly & Moore, 1977; Pycock & Marsden, 1978), which has been conceptualized as one of the biological bases for lateralized behavior (Rodriguez *et al.*, 1994; Alonso *et al.*, 1997).

In humans, laterality effects in elements of the DA systems appear regionally selective. In the putamen, DA transporter (DAT) and D_1-receptor binding were higher on the left than the right, whereas in the caudate and/or accumbens DAT, D_1-receptor and $D_{2/3}$-receptor binding and DA synthesis capacity were higher on the right than the left (Hietala *et al.*, 1999; Laakso *et al.*, 2000; van Dyck *et al.*, 2002; Vernaleken *et al.*, 2007; Cannon *et al.*, 2009). A meta-analysis of positron emission tomography (PET) and single-photon emission computed tomography (SPECT) studies on D_2 binding in healthy humans (Larisch *et al.*, 1998) indicated a preponderance of DA D_2 receptors on the right side in the striatum. In addition, the resting asymmetry in $D_{2/3}$-receptor availability was associated with greater positive incentive motivation (Tomer *et al.*, 2008). Whether hemispheric asymmetries exist in the mesostriatal DA response to rewarding stimuli, however, has not been investigated.

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In response to unpredicted rewards, mesostriatal DA neurons emit a phasic burst of electrophysiological spike activity (Horvitz *et al.*, 2007; Schultz, 2007) which in the accumbens is associated with an elevation of intrasynaptic DA concentrations (Garris *et al.*, 1994). PET studies showed that the binding of [^{11}C]raclopride, a radiotracer that is sensitive to changes in intrasynaptic DA concentrations, decreased in the ventral striatum in subjects playing a video game for points relative to rest (Koepp *et al.*, 1998) or in response to large monetary rewards vs. large monetary losses (Pappata *et al.*, 2002), and decreased in the caudate in response to unpredictable monetary rewards (Zald *et al.*, 2004), putatively reflecting the effects of increased DA release.

Here, we applied a bolus-plus-constant-infusion (B/I) method for administering [^{11}C]raclopride to obtain binding potential (BP) values that are measured under equilibrium conditions (Lassen, 1992; Carson *et al.*, 1997). We tested for the first time the hypothesis that the ventral striatal DA response to reward is lateralized. Because the previous PET studies of reward-related DA release did not control for lateralization effects, it was not clear on which side of the ventral striatum this increase would occur.

Materials and methods

Subjects

Twenty-four right-handed healthy volunteers (12 women) between ages 20 and 46 (mean ± SD, 32 ± 8.1) years participated. Male and female participants were group-matched for age (mean ages: men, 32.1 ± 9.2; women, 33.5 ± 7.2 years). There was no significant age difference between men and women ($t = 0.4$, $P < 0.6$). Volunteers were screened via medical history, physical examination, laboratory testing (including drug screening), neuromorphological MRI, structured (Structured Clinical Interview for DSM-IV; Spitzer *et al.*, 2002) and unstructured psychiatric interviews, and intelligence testing (Wechsler Abbreviated Scale of Intelligence; mean IQ, 123 ± 15.0). Handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). Volunteers were excluded if they had: a current or past psychiatric disorder; a major medical or neurological disorder; exposure to drugs likely to affect cerebral physiology, monoaminergic neurotransmitter function or vascular function within 3 weeks; illicit drug use or alcohol abuse within 1 year; lifetime history of alcohol or drug dependence; tobacco use within 1 year; gambling history or pathological gambling behavior as assessed with the lie/bet screen (Gotestam *et al.*, 2004) and South Oaks Gambling Screen (SOGS; Stinchfield, 2002), intelligence quotient < 85; current pregnancy or breast feeding; general MRI exclusions. Participants provided written informed consent after receiving a full explanation of the study procedures and risks, as approved by the NIMH IRB and in accordance with the declaration of Helsinki (Rickham, 1964).

Behavioral conditions

The slot-machine task involved two conditions, each consisting of 180 trials, each of average duration 8 s. In the monetary-reward condition subjects received financial rewards unpredictably, in a pseudo-randomized order with an average of one reward per four trials. In the sensorimotor control condition subjects performed the same task without receiving rewards, to control for motor activation or other nonspecific aspects of task performance (Fig. 1A).

Before scanning, subjects performed a short practice session of each task. During scanning subjects rested for the initial 20 min to allow [^{11}C]raclopride to approach equilibrium. During the subsequent 24.6 ± 2.0 min subjects performed the sensorimotor control task. Beginning 50 min after the start of the [^{11}C]raclopride infusion, subjects performed the monetary reward condition for 24.1 ± 1.7 min (Fig. 1B). This timing allowed the distribution of [^{11}C]raclopride to come into equilibrium for each of the two task conditions during the scanning epochs described below. During the 24-min epochs that corresponded to each task condition, subjects alternated between 2-min periods in which they actively performed the task and 1-min periods when they rested to minimize fatigue. Each subject won a total of $33 during the rewarded condition, which they received by check following the study.

Image acquisition

PET scans were acquired using a GE-Advance scanner in 3D mode (3D resolution 6 mm full width at half-maximum). During scanning the subject's head was immobilized using a thermoplastic mask. The PET data were reconstructed using a Hanning filter and Gaussian-fit scatter-correction method. A transmission scan was acquired using rotating ^{68}Ge/^{68}Ga rods to perform attenuation correction of the emission scans.

The [^{11}C] raclopride (20 mCi) was administered as an initial bolus over 60 s after Watabe *et al.* (2000), followed by a maintenance infusion over the remainder of the scanning session (a total of 90 min) using a computer-operated pump (Harvard Instruments, Natick, MA, USA). Dynamic emission scanning (27 frames of increasing length) was initiated with injection of the [^{11}C] raclopride bolus.

MRI images were acquired at 3 or 1.5 Tesla, using T1-weighted sequences to provide an anatomical framework for image analysis (in-plane resolution, 0.86 mm; slice thickness, 1.2 mm).

PET data analyses

Corrections for subject motion during the 100-min PET acquisition were performed with a mutual information registration of each image-frame to a standard frame (10–15 min after injection) before attenuation correction. Based on the calculated motion, the transmission images were resliced and projected for final attenuation correction, reconstruction and realignment. The realigned frames acquired during the first 8 min of scanning, during which the radiotracer distribution was most sensitive to cerebral blood flow (CBF) so that cortical outlines were sufficiently evident to guide image co-registration, were summed to generate an image that was co-registered to the corresponding MRI image using FLIRT (FMRIB Software Library; fmrib.ox.ac.uk; University of Oxford, UK). The derived transformation matrix was applied to the composite images consisting of (i) the baseline (frames acquired between 40 and 50 min) and (ii) the reward condition (frames acquired between 60 and 80 min) images, which were acquired under equilibrium conditions achieved as subjects performed the sensorimotor control and monetary reward tasks (Fig. 2), respectively, after Garraux *et al.* (2007).

Mean tissue radioactivity concentrations from the baseline and reward images were extracted using MRI-based regions of interest (ROIs), defined on a template MRI image using MEDx software (Medical Numerics, Sterling, VA, USA) in the anteroventral striatum, ventral putamen, dorsal putamen, middle caudate, dorsal caudate and cerebellum (Fig. 3), after Drevets *et al.* (1999, 2001). Each individual's MRI was registered to the template brain and the ROIs were repositioned as needed to accommodate individual differences in anatomy. The anatomical accuracy and symmetry of each set of individual ROIs was verified by a neuroscientist familiar with striatal

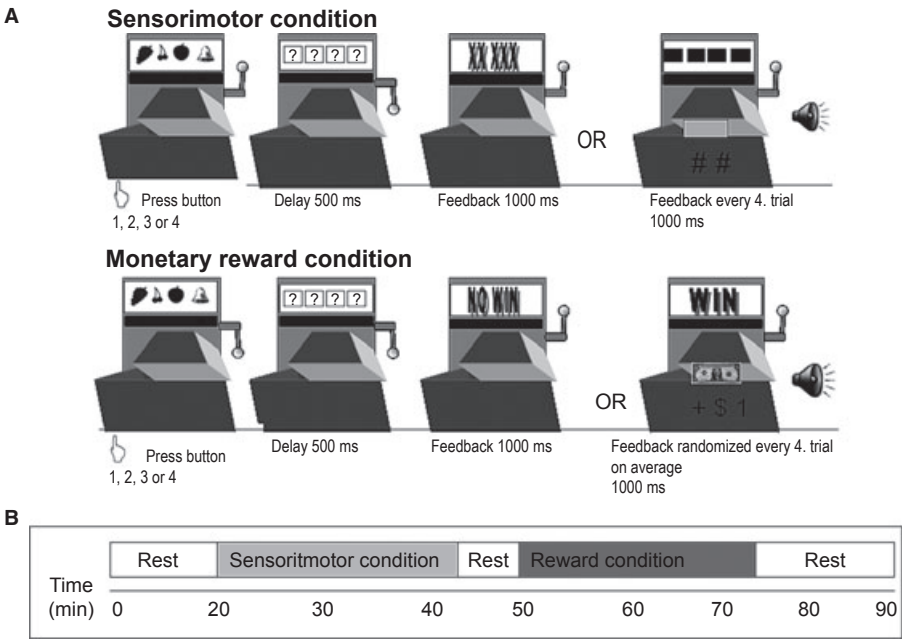

FIG. 1. Illustration of the experimental task. (A) Illustration of a sensorimotor and a rewarded trial. During each trial, subjects were presented with four distinct pictures (apple, grape, cherry, bell) presented in a 'slot-machine' motif. Subjects were asked to choose one of the four with a button press on a four-button response box using their right hand. This response was followed by a 500-msec delay. In the rewarded trials a one-dollar bill appeared for 1000 msec and subjects heard the characteristic sound of an opening cash-register drawer. These monetary gains were provided in a pseudo-randomized order with an average of one reward every fourth trial. In the sensorimotor control trials, subjects were presented instead with a meaningless symbol accompanied by a click sound on every fourth trial. After receiving the trial outcome, subjects were presented with their running total of earnings for 1000 msec. Displaying the actual balance account prevented rapid discounting of the rewards presented. At the end of each trial subjects viewed a blank screen for 1000 msec. During the reward task subjects were unaware of which trial or picture would lead to the receipt of a reward, except that the same picture could not provide a reward in two consecutive trials. Subjects thus were instructed not to select the same picture more than twice in a row (selection of the same picture twice in a row led to interruption of the task, and the task continued only after another picture was selected). (B) Timeline of the experiment. Subjects rested for the initial 20 min to allow [^{11}C]raclopride to approach equilibrium. During the subsequent 24.6 ± 2.0 min subjects performed the sensorimotor control task. Beginning 50 min after the start of the [^{11}C]raclopride infusion, subjects performed the monetary reward condition for 24.1 ± 1.7 min. The timing of the tasks relative to scanning was based upon previous optimization studies for PET-[^{11}C]raclopride imaging using the bolus plus constant infusion approach (Watabe *et al.*, 2000; Garraux *et al.*, 2007).

anatomy (W.C.D.). These ROIs then were back-transformed into the subject's native MRI space and applied to the co-registered PET images. To improve sensitivity the anteroventral striatum and ventral putamen ROIs were combined into a single ventral striatal ROI. In primates, the cells with histochemical and connectional features of the nucleus accumbens shell implicated in reward learning are scattered through the accumbens area, ventromedial caudate and anteroventral putamen (Heimer & Alheid, 1991), and previous PET studies of amphetamine-induced DA release showed that euphoria correlated with DA release in both the anteroventral striatum and the ventral putamen (Drevets *et al.*, 2001; Martinez *et al.*, 2003). Results for these ROIs considered separately were addressed *post hoc* (see Supporting Information Data S1).

Decay-corrected tissue radioactivity concentrations (C) were obtained from each ROI using a calibrated phantom standard to convert tomographic counts to becquerels per milliliter. C′, the mean radioactivity in the reference region (cerebellum), was used to factor out the effects of free and nonspecifically bound [^{11}C]raclopride. The percentage change in [^{11}C]raclopride binding was computed as the difference in $BP_{ND\ (non\text{-}displaceable)}$ between baseline and reward images (Watabe *et al.*, 2000):

$$\Delta BP = \frac{\frac{C_{reward}-C'_{reward}}{C'_{reward}} - \frac{C_{baseline}-C'_{baseline}}{C'_{baseline}}}{\frac{C_{baseline}-C'_{baseline}}{C'_{baseline}}} \times 100$$

The *a priori* hypothesis was tested using two-factorial ANOVAs with task conditions and lateralization as factors on the BP_{ND} obtained in the ventral striatum, with a null hypothesis that there is no effect of condition, and no interaction between condition and laterality. Where the ANOVA results indicated significant laterality × condition effects, specific contrasts between sides and conditions were performed using paired *t*-tests with the *P*-values corrected (Bonferroni) for comparisons in the left, right and right-vs.-left ventral striatum (i.e. significance threshold set at $\alpha = 0.0167$) for two-tailed *P*-values.

The significance of ΔBP and laterality differences in other ROIs was assessed *post hoc* to evaluate the specificity of the ventral striatal findings. A three-factorial ANOVA with region, task condition and laterality was performed to assess differential responses between regions. Additional *post hoc* analyses explored laterality effects in the baseline BP_{ND} values, correlations between age and ΔBP, and gender differences in ΔBP (McGeer *et al.*, 1977; Antonini & Leenders, 1993; Pohjalainen *et al.*, 1998; McCormack *et al.*, 2004). A four-factorial ANOVA with region, task condition, laterality and gender was performed to test for an effect of gender on the differential responses between regions.

Finally, to more specifically localize the changes in [^{11}C]raclopride BP between conditions, we performed a voxel-wise analysis *post hoc* using statistical parametric mapping software (SPM8b; Wellcome Department of Imaging Neuroscience, London, UK) implemented within Matlab 7.7. (MathWorks, Natick, MA, USA). The two condition-specific composite images of raclopride BP_{ND} were spatially

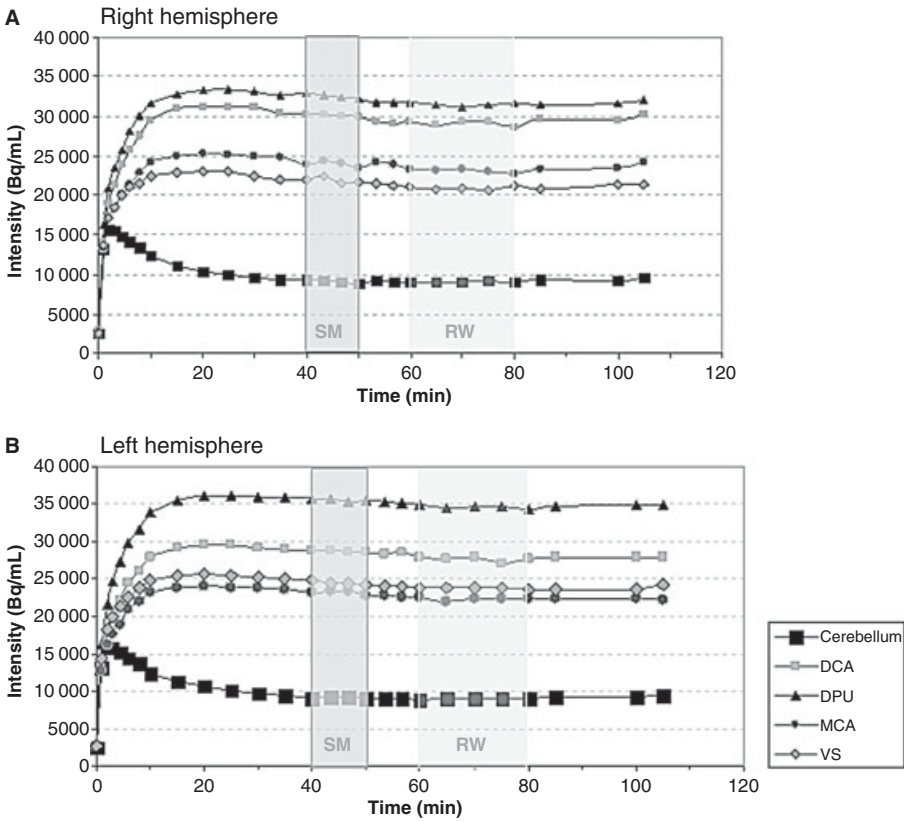

FIG. 2. Decay-corrected tissue radioactivity concentrations across time obtained using PET in the predefined ROIs within (A) the right and (B) the left hemispheres, with indication of the time epochs in which PET data were analyzed to reflect the sensorimotor (darker shading) and reward (lighter shading) conditions. The timing of the image acquisition for each task condition was optimized for PET-[^{11}C]raclopride imaging studies applying the B/I approach by Watabe *et al.* (2000). Bq, becquerels; VS, ventral striatum; DPU, dorsal putamen; MCA, middle caudate; DCA, dorsal caudate; SM, sensorimotor condition; RW, reward condition.

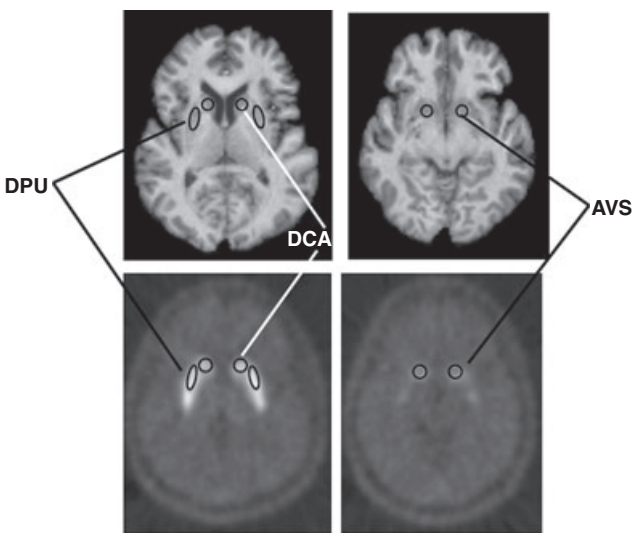

FIG. 3. Location of the MRI-based ROIs defined *a priori* in the putamen, caudate and anteroventral striatum (after Drevets *et al.*, 2001). Regional PET measures were extracted from each ROI and compared between conditions. DPU, dorsal putamen; DCA, dorsal caudate; AVS, anteroventral striatum.

normalized to the Montreal Neurological Institute spatial array (http://www.bic.mni.mcgill.ca) and smoothed using a 6-mm full width at half-maximum Gaussian kernel. Processed raclopride binding images then were analyzed voxel-wise within the general linear model framework using a paired *t*-computation that tested for a change in [^{11}C]raclopride BP_{ND} during the reward vs. the baseline conditions. MNI coordinates were nonlinearly translated to the stereotaxic spatial array of Talairach & Tournoux (1988) (http://www.bioimagesuite.org/Mni2Tal/index.html). The analysis was constrained by searching only areas where receptor-specific binding exceeded a BP_{ND} threshold ≥ 1.2, which essentially limited the search area to the striatum. We report results that remained significant after applying the small-volume correction for multiple comparisons using the cluster test (provided within SPM software; Worsley *et al.*, 1996) within an atlas-based masked image for the entire striatum (right and left) with the voxel *t*-value threshold for defining clusters-of-interest set at $P < 0.01$.

Results

ROI analyses

Mean BP and ΔBP values appear in Table 1 and Fig. 4A. The three-factorial ANOVA of region × laterality × condition showed significant main effects of region ($F_{3,69} = 62.1$, $P < 0.001$) and condition ($F_{1,23} = 4.37$, $P < 0.005$), as well as a significant region × laterality interaction ($F_{3,69} = 45.9$, $P < 0.001$). Subsequent paired *t*-tests showed a trend for ΔBP differences between the reward and the sensorimotor control conditions at a Bonferroni-corrected level of significance of $P < 0.004$ (α level of 0.05 corrected for 12 comparisons) in the following comparisons: right ventral striatum vs. right middle caudate ($P < 0.005$), right ventral striatum vs. right dorsal

TABLE 1. Mean regional binding potential (BP_{ND}) values for each condition and mean changes in BP_{ND} between conditions

Region	Regional BP_{ND}		Difference (ΔBP; %)	*t*-value	*P*-value
	Control	Reward			
Right ventral striatum*	1.90 ± 0.63	1.82 ± 0.68	−5.65 ± 9.53	2.9	0.008
Left ventral striatum*	2.20 ± 0.56	2.1 ± 0.62	−2.32 ± 6.74	1.69	0.1
Right dorsal putamen	2.78 ± 0.36	2.73 ± 0.35	−1.51 ± 5.03	1.47	0.15
Left dorsal putamen	2.92 ± 0.36	2.89 ± 0.30	−0.62 ± 4.2	0.72	0.47
Right middle caudate	1.94 ± 0.53	1.92 ± 0.59	−1.52 ± 8.59	0.86	0.39
Left middle caudate	1.79 ± 0.51	1.74 ± 0.5	−2.81 ± 7.22	1.9	0.06
Right dorsal caudate	2.48 ± 0.34	2.45 ± 0.32	−1.00 ± 5.81	0.84	0.4
Left dorsal caudate	2.26 ± 0.33	2.20 ± 0.32	−2.43 ± 6.83	1.746	0.09

*Regions in which the *a priori* hypotheses were tested. Mean values are ± 1SD. Levels of significance (two-tailed) and *t*-values are given for the one-sample *t*-tests of ΔBP.

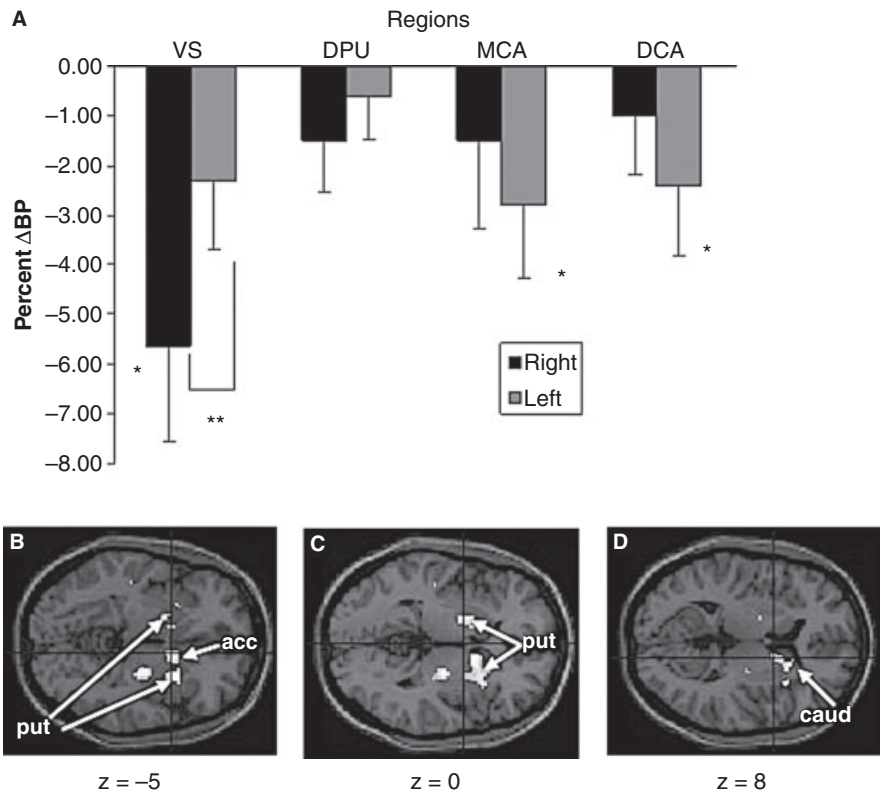

FIG. 4. Reward-related changes in regional binding potentials for [^{11}C]-raclopride. (A) Plot of mean percentage change in binding potential (ΔBP) in the ROI analyses. The mean ΔBP value was significant in the right ventral striatum and we found a nonsignificant trend in the left middle caudate and left dorsal caudate (Table 1). A significant laterality difference was evident in the ventral striatum. VS, ventral striatum; DPU, dorsal putamen; MCA, middle caudate; DCA, dorsal caudate. *$P < 0.01$, **$P < 0.005$, *trend: $0.05 < P < 0.1$. (B–D) Statistical parametric maps of voxel *t*-values corresponding to the reduction in BP_{ND} in the monetary reward task condition vs. the sensorimotor control condition. This analysis was conducted *post hoc* to more precisely locate the areas of greatest effect size, so all voxels for which $P < 0.01$ are displayed. Results are shown superimposed on a T1-weighted MRI image (provided within SPM software) on horizontal slices situated parallel to a plane containing both the anterior and posterior commissures, located 5 mm below ($z = -5$), at ($z = 0$) or 8 mm above ($z = 8$) this reference plane in B, C and D, respectively. The coordinates for the peak voxel *t*-values are provided in Table 3. The right side is toward the bottom of the page. acc, accumbens area (in ventral striatum); caud, caudate nucleus; put, putamen.

caudate ($P < 0.007$) and right ventral striatum vs. right dorsal putamen ($P < 0.01$).

Ventral striatum

The test of the *a priori* hypothesis showed significant effects of lateralization ($F_{1,23} = 57.8$, $P < 0.001$), condition ($F_{1,23} = 5.50$, $P < 0.05$) and lateralization × condition interaction ($F_{1,23} = 6.22$, $P < 0.05$) in the ventral striatum. Mean BP was lower in the right than the left ventral striatum both at baseline and during reward (both $P < 0.001$). The BP decreased significantly during the reward vs. the sensorimotor conditions in the right but not the left ventral striatum ($P = 0.003$ and 0.2 respectively). The mean ΔBP was greater on the right than the left ($P < 0.005$). These differences remained significant

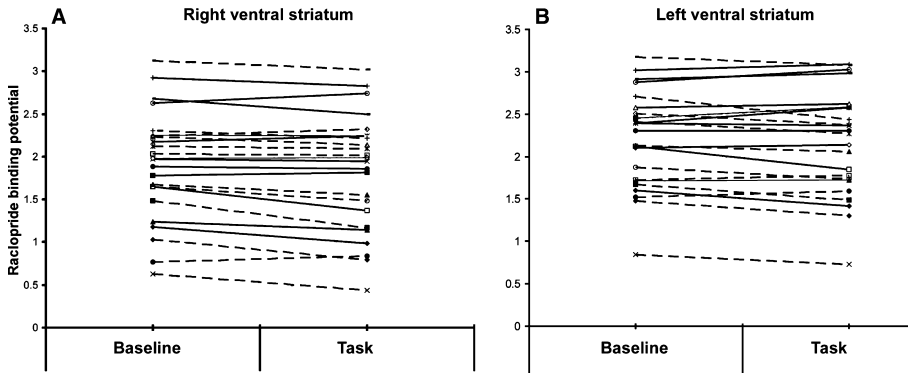

FIG. 5. Individual raclopride binding potential (BP) values in the sensorimotor and the reward tasks in (A) the right and (B) the left ventral striatum.

TABLE 2. Mean regional binding potential (BP_{ND}) values for each condition and mean changes in BP_{ND} (ΔBP) between conditions for men and women

	Women					Men					
	Regional BP_{ND}					Regional BP_{ND}					
Region	Control	Reward	Difference (ΔBP; %)	t	P	Control	Reward	Difference (ΔBP; %)	t	P	Group comparison P
Right ventral striatum	1.77 ± 0.72	1.67 ± 0.75	−7.65 ± 11.52	2.30	0.04	2.02 ± 0.54	1.97 ± 0.58	−3.65 ± 6.9	1.81	0.08	0.315
Left ventral striatum	2.03 ± 0.64	1.95 ± 0.64	−4.7 ± 6.47	2.56	0.02	2.37 ± 0.44	2.39 ± 0.53	0.14 ± 6.3	0.07	0.94	0.072
Right dorsal putamen	2.81 ± 0.37	2.7 ± 0.37	−3.74 ± 4.3	2.99	0.01	2.74 ± 0.37	2.75 ± 0.35	0.7 ± 4.8	0.5	0.62	0.02
Left dorsal putamen	2.97 ± 0.43	2.88 ± 0.39	−2.69 ± 3.1	2.94	0.01	2.86 ± 0.3	2.9 ± 0.2	1.44 ± 4.1	1.2	0.25	0.01
Right middle caudate	1.79 ± 0.53	1.73 ± 0.57	−3.83 ± 9.8	1.34	0.2	2.09 ± 0.52	2.11 ± 0.57	0.79 ± 6.7	0.41	0.68	0.193

Mean values are ± 1SD. Levels of significance (two-tailed) and t-values are given for the one-sample t-tests of ΔBP for each gender analyzed separately and for independent-samples t-tests for the ΔBP comparison between men and women.

at the Bonferroni-corrected threshold of $P < 0.0167$. Individual raclopride BP data for the sensorimotor vs. the reward condition in the right and left ventral striatum are illustrated in Fig. 5.

Dorsal putamen

Post hoc analyses additionally showed an effect of lateralization in the dorsal putamen ($F_{1,23} = 20.5$, $P < 0.001$). The mean BP was lower in both conditions on the right than the left (baseline, $P < 0.01$; reward, $P < 0.005$). Neither the effect of condition ($F_{1,23} = 1.9$, $P < 0.17$) nor the interaction between condition and lateralization ($F_{1,23} = 1.3$, $P < 0.24$) reached significance.

Middle caudate

The main effect of lateralization was significant in the middle caudate ($F_{1,23} = 9.4$, $P < 0.005$) but neither the effect of condition ($F_{1,23} = 3.1$, $P < 0.08$) nor the interaction between condition and lateralization ($F_{1,23} = 0.8$, $P < 0.37$) reached significance. The mean BP was lower in both conditions on the left than the right (baseline, $P < 0.01$; reward, $P < 0.004$).The decrease in BP during the reward vs. the sensorimotor conditions showed a trend on the left side ($P < 0.06$).

Dorsal caudate

There was an effect of lateralization in the dorsal caudate ($F_{1,23} = 36.6$, $P < 0.001$). The mean BP was lower in both conditions on the left than the right in dorsal caudate (baseline, $P < 0.001$; reward, $P < 0.001$). Neither the effect of condition ($F_{1,23} = 3.1$, $P < 0.09$) nor the interaction between condition and lateralization ($F_{1,23} = 0.8$, $P < 0.36$) reached significance.

Influence of gender and age

Using gender as a between-subjects factor in the four-factorial ANOVA demonstrated significant interactions for region × gender ($F_{3,66} = 4.6$, $P < 0.005$), condition × gender ($F_{1,22} = 4.31$, $P < 0.05$), and region × laterality × condition × gender ($F_{3,66} = 2.5$, $P < 0.05$). Subsequent separate paired t-tests for men and women showed a trend for ΔBP differences between the reward and the sensorimotor control conditions at a Bonferroni-corrected significance level of $P < 0.004$ ($\alpha = 0.05$ corrected for 12 comparisons) in men for the following comparisons: right dorsal putamen vs. right ventral striatum ($P < 0.01$), right middle caudate vs. right ventral striatum ($P < 0.05$), right dorsal caudate vs. right ventral striatum ($P < 0.005$), left dorsal putamen vs. left middle caudate ($P < 0.02$). We found no significant regional difference in women.

The region by region ANOVAs yielded significant results in the dorsal putamen for the condition × gender interaction ($F_{1,21} = 5.73$, $P < 0.05$) and a nonsignificant trend in the ventral striatum for the gender × condition × lateralization interaction ($F_{1,21} = 3.56$, $P < 0.07$)(Table 2). The mean ΔBP was greater in women than in men in the left and right dorsal putamen (left, $P < 0.01$; right; $P < 0.05$; two-tailed; Fig. 6) and showed a nonsignificant trend toward being higher in left ventral striatum ($P < 0.07$). The ΔBP between conditions was significant in right and left ventral striatum ($P < 0.05$), right and left dorsal putamen ($P < 0.005$ bilaterally) right

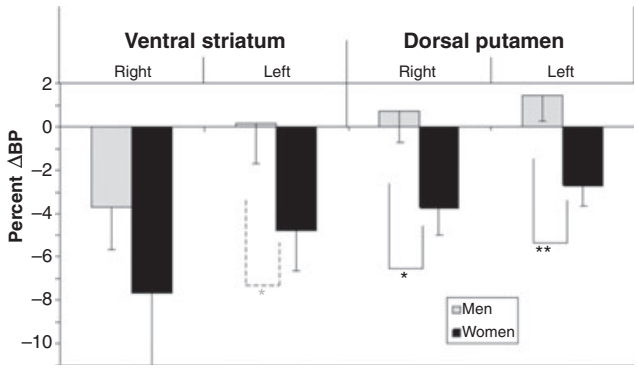

FIG. 6. Plot of the mean percentage change in binding potential (ΔBP) in regions where significant gender differences were found. Women showed greater ΔBP values than men in the right and left dorsal putamen, and showed a nonsigificant trend toward higher ΔBP values in the left ventral striatum. Considered separately, the mean ΔBP in the left ventral striatum as well as in the right and left dorsal putamen was significant in women only. Right–left differences in ΔBP were significant in the ventral striatum only in men ($P < 0.001$). *$P < 0.05$, **$P < 0.01$, *trend.

and left dorsal caudate ($P < 0.005$ on the right and $P < 0.03$ on the left) in women, but only in right ventral striatum ($P < 0.05$) in men. The comparisons of condition in men and women indicated a significant difference in ΔBP between the right and left ventral striatal ROI in men ($P < 0.005$, two-tailed) but not in women ($P < 0.17$).

Age did not correlate significantly with ΔBP in any ROI.

Whole-brain analysis

The voxel-wise analysis showed four clusters of voxels in which BP decreased significantly in the reward condition relative to the control condition. These clusters localized to subregions of the right ventral striatum (which included portions of the accumbens, ventromedial caudate and anteroventral putamen), the left anterolateral caudate nucleus (in an area encompassed by our left middle caudate ROI), and the right caudal putamen (Fig. 4B–D and Table 3; Talairach & Tournoux, 1988; Mai *et al.*, 2004). In contrast, no areas were identified where BP was significantly higher in the reward condition relative to the baseline condition at the specified significance threshold.

TABLE 3. Areas identified in the voxel-wise analysis conducted *post hoc* to more precisely localize changes in the [^{11}C]raclopride binding potential (BP_{ND}) in the monetary reward task condition relative to the sensorimotor control condition

Brain Regions	Cluster size (voxels)	Coordinates (x, y, z)	t
R accumbens area	233	11, 5, −2	2.32
R anteroventral putamen		27, 6, 0	2.25
R accumbens area/anteroventral putamen		13, 7, 1	2.50
R anterior caudate nucleus		11, 5, 9	2.25
R anterior caudate nucleus		17, 17, 8	2.16
R caudal ventral putamen	24	27, −13, 0	2.22
L caudal ventral putamen	12	−27 10 −3	2.42
L dorsal anterior caudate nucleus	12	−17, 14, 16	2.46

R, right; L, left. Cluster sizes correspond to the number of contiguous voxels (of dimension 2 mm^3 after reslicing the images within SPM8) with similarly valenced t-values for which the voxel t-value corresponded to $P < 0.01$. The coordinates and t-values for voxels containing the peak effect sizes are indicated for each group. Coordinates reflect the stereotaxic spatial system of Talairach and Tournoux (1988), in which each coordinate reflects the distance in millimeter from the anterior commissure, with positive x, y and z indicating right, anterior, and superior, respectively.

Discussion

We confirmed the *a priori* hypothesis that unpredicted monetary rewards elicit a lateralized increase in DA transmission in the ventral striatum. The significant interaction between task condition and lateralization in this region specifically was accounted for by a reduction in BP in the reward vs. the sensorimotor conditions in the right ventral striatum, where the mean ΔBP was more prominent on the right than on the left side. The reduction in [^{11}C]raclopride binding in the reward vs. the sensorimotor control condition presumably reflected greater endogeneous DA release in response to unpredictable monetary reward. The specificity of this finding is supported by the lack of significant difference in [^{11}C]raclopride binding in the reward vs. the sensorimotor control condition in the other striatal regions and by the nonsignificant trends evident in the comparisons between ΔBP in the right ventral striatum and the other right-sided striatal regions. These data thus constitute the first indication that the elevation in dopaminergic transmission in response to unpredicted reward shows a laterality effect toward the right ventral striatum in right-handed humans.

Baseline laterality differences in the regional binding potentials

In addition, the mean BP values were lower both at baseline and during reward on the right than on the left in the ventral striatum and dorsal putamen, but lower on the left than the right in the dorsal caudate. The laterality effect on baseline BP observed in the caudate was consistent with the previously reported finding of Vernaleken *et al.* (2007) that mean $D_{2/3}$ receptor binding was lower in the left than the right caudate and is consistent overall with the asymmetries reported in DA receptor binding studies under resting conditions (Larisch *et al.*, 1998). Notably, the lateralization in the ventral striatum under the baseline condition appears complementary to previous results showing that D_1-receptor binding in the ventral putamen is lower on the right than the left side (Cannon *et al.*, 2009).

Gender differences

The effect of gender on ΔBP in the putamen was novel and unexpected (Fig. 6, Table 2 and Supporting Information Data S1). In the dorsal putamen women, but not men, showed a significant difference in BP between conditions bilaterally, and the magnitude of the mean ΔBP was greater in women than men. In the ventral striatum the gender × condition interaction showed a nonsignificant trend, as ΔBP was significant in women bilaterally but in men only on the right side. Moreover, the right-to-left difference in ventral striatal ΔBP was significant in men ($P < 0.005$) but not in women ($P < 0.17$). The analysis of subregions within the ventral striatum (i.e., ventral putamen vs. accumbens area) more specifically revealed that the gender × condition × laterality interaction was highly significant in the ventral putamen (Supporting Information Data S1). Additionally, the comparisons of ΔBP between the different striatal regions showed nonsignificant trends between the ΔBP in the right ventral striatum relative to the ΔBP in other striatal regions tested only in men. Our data thus suggest that unpredicted rewards elicit DA release over a wider area of the striatum in women than men, and that reward-elicited DA release in the ventral striatum occurs bilaterally in women but

unilaterally in men. However, while the mean ΔBP values reached significance in women they showed a nonsignificant trend in men, possibly related to the small sample sizes of the gender-based subgroups.

Taken together, these data add to other evidence for gender effects on the striatal response to reward, as previous studies reported that the hemodynamic response to reward in the striatum is influenced by menstrual phase (Dreher *et al.*, 2007) and differs between men and women (Spreckelmeyer *et al.*, 2009), that striatal DAT binding is higher in women than men (Lavalaye *et al.*, 2000), and that dopaminergic transmission in the accumbens is modulated by estrogen and progesterone levels in women (Becker, 1999). Laterality effects have also been reported in experimental animals, as striatal DA D_2 receptor binding in pigs (Cumming *et al.*, 2003) and accumbens DA concentrations in rats show gender effects (Duchesne *et al.*, 2009). Finally, these results are in line with previous findings showing gender differences in the neural processing of emotional stimuli (Canli *et al.*, 2002; Wrase *et al.*, 2003).

Several limitations of our study design merit comment. First, the phase of menstrual cycle in which female subjects were imaged was not fixed and we did not evaluate differential effects of distinct menstrual phases on reward-induced DA release. Second, as the PET-[^{11}C]raclopride B/I approach permits imaging in only two conditions per scan session we did not measure BP in a resting state, so we could not assess whether BP differed between the sensorimotor condition and the resting state. Thus the effect of condition observed in our analyses is specific to the reward condition vs. the sensorimotor control condition. Finally, due to limitations in spatial resolution the regional BP_{ND} values in each ROI were influenced by the tissue radioactivity concentrations in adjacent ROI *via* partial-volume averaging effects. Demonstrating differential regional sensitivity to reward thus depended partly on showing that the magnitude of ΔBP was greater in the right ventral striatum than in adjacent ROI (Table 1; Drevets *et al.*, 1999, 2001). Nevertheless, in the gender-based analyses the apparent changes in BP in the dorsal putamen were at least partly influenced by partial volume effects from the more prominent changes in the adjacent ventral putamen (see Supporting Information Data S1; Drevets *et al.*, 1999, 2001). Thus the differences in BP observed in the dorsal putamen could not be resolved from the corresponding changes in ventral putamen, because the latter were greater in magnitude. In the left striatum, however, the magnitude of ΔBP was highest in left middle caudate, and lower in adjacent left ventral striatum and dorsal caudate. These data thus appeared compatible with those of Zald *et al.* (2004), in which the reduction in BP within the left striatum during unpredictable reward showed the greatest effect size in left middle caudate. Finally, the lack of a significant age effect could be related to the small age range of the participants studied.

Although previous PET-[^{11}C]raclopride studies of DA release during reward processing did not specifically address laterality effects, our data appeared partly compatible with their results (Pappata *et al.*, 2002; Zald *et al.*, 2004). Pappata *et al.* (2002) showed that [^{11}C]raclopride binding decreased in the ventral striatum bilaterally in response to large monetary rewards vs. large monetary losses (n = 8, all males). Consistent with our observations in the left middle caudate (Fig. 4A, Table 3), Zald *et al.* (2004) found that [^{11}C]raclopride binding decreased in response to unpredictable rewards in a left 'medial caudate' area that overlapped our 'middle caudate' ROI (n = 10, four males). However, Zald *et al.* (2004) also reported that [^{11}C]raclopride binding *increased* in the left lateral putamen (at $x = -30$, $y = -2$, $z = 0$; coordinates interpreted as in Table 3) in response to unpredictable reward, which we did not confirm. This group subsequently reported that [^{11}C]raclopride binding also increased in the caudate and putamen in response to unpredicted rewards (n = 12, all males; Hakyemez *et al.*, 2008), although the passive monetary reward task used in this study differed from the active behavioral engagement required in our task. Our sample size (n = 25) was substantially larger than those in previous studies (in which n ranged from 8 to 12). Another major methodological difference across studies was that these previous studies relied on the bolus method for infusing [^{11}C]raclopride while ours applied the B/I method.

Binding measures obtained following bolus administration of [^{11}C]raclopride can be influenced by CBF changes, and these previous studies employed tasks likely to increase striatal CBF (Delgado *et al.*, 2000; Berns *et al.*, 2001). In contrast, the B/I method allows neuroreceptor quantitation under equilibrium conditions (Lassen, 1992; Breier *et al.*, 1997; Marenco *et al.*, 2004), such that measures of BP are relatively insensitive to changes in local CBF (Cumming *et al.*, 2003; Rosa-Neto *et al.*, 2004). Our findings might show a greater specificity for reflecting intrasynaptic DA release.

A novel finding of our study was that in right-handed humans the dopaminergic response to unpredictable rewards in the ventral striatum appears right-lateralized. Our findings appear consistent with preclinical evidence for lateralization of DA release during motor activation and motor learning (Yamamoto & Freed, 1982; Morice *et al.*, 2005; Silva *et al.*, 2007; Lappin *et al.*, 2009), and follow-up studies must address the contributions of motor dominance ('handedness') and interactions between behavioral incentive and motor response. Nevertheless, our data regarding both reward-related DA release and baseline DA $D_{2/3}$ receptor binding converge with a variety of evidence indicating that several elements of the mesostriatal dopaminergic system are lateralized in humans.

Interestingly, we found significant gender differences that influence the lateralization observed in the ventral striatum in response to reward. Men showed a significant lateralization effect in this region and appeared to increase DA release only in right ventral striatum during unpredicted reward, while women showed a significant increase in DA release in the ventral striatum bilaterally, although the magnitude of this effect tended to be greater on the right. These results may illuminate the significance of laterality differences in striatal function in mood disorders (Starkstein *et al.*, 1989; Drevets *et al.*, 1992; Steffens *et al.*, 1998) characterized by disturbances of hedonic capacity and motivation, which show lateralized abnormalities in striatal D_1 receptor binding that are specific for women (Cannon *et al.*, 2009). These findings could also relate to the gender differences observed in the association between depression and pathological gambling (Desai & Potenza, 2008). Our data further suggest that previously reported associations between depression and lateralized abnormalities of striatal function (Starkstein *et al.*, 1989; Drevets *et al.*, 1992; Steffens *et al.*, 1998) or between schizophrenia and the disruption of interhemispheric asymmetries in the DA function (Hietala *et al.*, 1999; Laakso *et al.*, 2000) require re-examination for gender effects.

In conclusion, our data further suggest a gender-specific hemispheric asymmetry in the mesostriatal DA response to rewarding stimuli that should be taken into account in future studies on the neural basis of reward processes.

Supporting Information

Additional supporting information may be found in the online version of this article:

Data S1. Separate results for the anteroventral striatum and the ventral putamen.

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Statement of Interest

None.

Abbreviations

B/I, bolus-plus-constant-infusion; BP, binding potential; C, decay-corrected tissue radioactivity concentration; CBF, cerebral blood flow; DA, dopamine; DAT, DA transporter; IQ, intelligence quotient; MRI, magnetic resonance imaging; ND, non-displaceable; PET, positron emission tomography; ROI, region of interest; SPECT, single-photon emission computed tomography; SPM, statistical parametric mapping.

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