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Net influx of plasma 6-[^{18}F]fluoro-L-DOPA (FDOPA) to the ventral striatum correlates with prefrontal processing of affective stimuli

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Abstract

Dopaminergic neurotransmission in the ventral and dorsal striatum interact with central processing of rewarding and reward-indicating stimuli, and may affect frontocortical–striatal–thalamic circuits regulating goal-directed behaviour. Thirteen healthy male volunteers were investigated with multimodal imaging, using the radioligand 6-[^{18}F]fluoro-L-DOPA (FDOPA) for positron emission tomography (PET) measurements of dopamine synthesis capacity, and also functional magnetic resonance imaging (fMRI) in a cognitive activation paradigm. We calculated the correlation between FDOPA net blood–brain influx (K_{in}^{app}; ml/g/min) in the ventral and associative dorsal striatum and BOLD signal changes elicited by standardized affectively positive, negative and neutral visual stimuli. The magnitude of K_{in}^{app} in the ventral striatum was positively correlated with BOLD signal increases in the left anterior cingulate cortex and right insular operculum elicited by positive vs. neutral stimuli, but not negative vs. neutral stimuli. In the dorsal striatum, the magnitude of K_{in}^{app} was positively correlated with processing of positive and negative stimuli in the left dorsolateral prefrontal cortex. These findings suggest that dopamine synthesis capacity in the ventral striatum correlates with the attentional processing of rewarding positive stimuli in the anterior cingulate cortex of healthy subjects. Dopaminergic neurotransmission in the associative dorsal striatum has been associated previously with habit learning. The observed correlation between dopamine synthesis capacity in the dorsal striatum and BOLD signal changes in the dorsolateral prefrontal cortex suggests dopaminergic modulation of processing of emotional stimuli in brain areas associated with motor planning and executive behaviour control.

Introduction

In the striatum, dopaminergic neurotransmission may facilitate information processing in the frontal cortex, by removing a blockade of extraneous stimuli not followed by reward (Contreras-Vidal & Schultz, 1999; O'Reilly *et al*., 2002). In nonhuman primates, unexpected rewards and conditioned reward-indicating stimuli elicit dopamine signalling (Schultz *et al*., 1997; Fiorillo *et al*., 2003), and reward value modulates the magnitude of the phasic dopamine discharge (Tobler *et al*., 2005). While dopamine neurotransmission in the ventral striatum plays a significant role during the acquisition of reward learning (Robinson & Berridge, 1993; Di Chiara, 2002), dopaminergic neurotransmission in the dorsal striatum has been associated more with habit learning, but also with attention, executive control and reward learning in both lesion and imaging studies (Alexander & Crutcher, 1990; Everitt & Wolf, 2002; Wickens *et al*., 2003; Kelly *et al*., 2004; Christakou *et al*., 2005; Knutson & Cooper, 2005). In humans, dopaminergic neurotransmission can only be measured indirectly, however, striatal uptake of 6-[^{18}F]fluoro-L-DOPA (FDOPA) measured with positron emission tomography (PET) can be used as a surrogate marker for dopamine synthesis capacity (Firnau *et al*., 1986; Gjedde *et al*., 1991; Cumming & Gjedde, 1998). Unmedicated schizophrenic patients display increased dopamine synthesis capacity (Hietala *et al*., 1995; Lindstrom *et al*., 1999) and phasic dopamine release (Laruelle *et al*., 1996; Breier *et al*., 1997; Abi-Dargham *et al*., 2000), while Parkinson patients show reduced striatal dopamine synthesis capacity (Vingerhoets *et al*., 1996) and low brain activation during processing of reward information (Kunig *et al*., 2000; Goerendt *et al*., 2004). However, so far no human study has directly correlated striatal dopamine synthesis capacity and cerebral activation elicited by rewarding and aversive stimuli.

The ventral striatum, which encompasses the nucleus accumbens, receives direct projections from the anterior cingulate, insula and other parts of the limbic cortex and can modulate activity in the dorsal striatum (Alexander & Crutcher, 1990; Haber *et al*., 2000), while the dorsal (associative) striatum receives direct input from the dorsolateral

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prefrontal cortex (Haber *et al*., 2000). Dopamine-associated activation of the ventral and dorsal striatum may thus modify activity in specific cortical–striatal–thalamic circuits (Alexander & Crutcher, 1990; Cummings, 1998). Animal experiment results suggest that dopamine neurotransmission in the ventral striatum interacts with the attentional response to rewarding or reward-indicating environmental stimuli in the anterior cingulate and limbic cortex (Parkinson *et al*., 2000; Cardinal *et al*., 2001; Christakou *et al*., 2005), whereas in the associative dorsal striatum, dopamine neurotransmission is more associated with processing of rewarding stimuli in the dorsolateral prefrontal cortex and interacts with executive functions such as strategic behaviour planning and working memory (Seamans & Yang, 2004; Christakou *et al*., 2005). However, the relationship between dopamine transmission in the extended striatum and processing of emotional signals is poorly understood in humans (Schultz *et al*., 1997; Haber *et al*., 2000; Cardinal *et al*., 2002).

In order to characterize the association between individual differences in presynaptic dopaminergic function in the ventral and dorsal striatum, and central processing of affectively positive, negative and neutral pictures, we employed a combination of imaging modalities in a group of healthy male volunteers. We hypothesized that dopamine synthesis capacity in the ventral striatum is significantly and positively correlated with individual differences in blood oxygen level-dependent (BOLD) signal change evoked by affectively positive but not negative stimuli in the anterior cingulate, insula and other parts of the limbic cortex with direct anatomical connections to the ventral striatum (Alexander & Crutcher, 1990; Haber *et al*., 2000). To test this hypothesis, we used PET to map the net influx of plasma FDOPA to brain and, in the same subjects, we used functional magnetic resonance imaging (fMRI) to map BOLD signal changes evoked by standardized emotionally laden visual stimuli (Bradley & Lang, 1994). We also tested the hypothesis that, in the dorsal associative striatum, i.e. the central putamen and caudate, high FDOPA net influx is associated with increased processing of affectively positive, but not aversive, stimuli in the dorsolateral prefrontal cortex (Alexander & Crutcher, 1990; Haber *et al*., 2000).

Materials and methods

Subjects and instruments

The local Ethics Committee approved the study according to the Declaration of Helsinki and written informed consent was obtained from all participants after the procedures had been fully explained. Thirteen healthy men (mean age 43.2 ± 9.5, range 32–60 years) were included. Standardized clinical assessment with the temperament and character inventory (TCI; Cloninger *et al*., 1994) and Structured Clinical Interview I and II (First *et al*., 1997, 2001) was performed to exclude axis I psychiatric disorders according to DSM IV and ICD 10. Drug abuse was excluded with urine tests.

Dopamine synthesis capacity measured by PET and FDOPA

We used PET and FDOPA to map the capacity for dopamine synthesis in living brain by calculating the net blood–brain clearance of the tracer (Gjedde, 1988; Martin *et al*., 1989). All subjects were given carbidopa (2.5 mg/kg body weight) orally 60 min before scanning to block extracerebral L-DOPA decarboxylase activity. Subjects reclined on the scanning bed with their eyes closed and their head positioned within the aperture of the ECAT EXACT PET operating in 3-D mode. To correct for tissue attenuation, transmission scans were acquired using a ^{68}Ge rod source prior to FDOPA injection. A dynamic emission recording consisting of 28 frames (4 × 1 min, 3 × 2 min, 3 × 3 min, 15 × 5 min and 3 × 10 min) lasting 120 min was initiated after intravenous administration of 194 ± 27 MBq FDOPA. Arterial blood samples were collected at intervals during the emission recording and the total radioactivity concentration in plasma samples was measured using a well-counter cross-calibrated to the PET. The fraction of intact FDOPA in plasma was measured by HPLC at 5, 10, 15, 20, 30, 45, 60, 90 and 120 min post-injection by reversed-phase HPLC using a Nucleosil 100 RP 18 column (250 × 4 mm).

The continuous arterial FDOPA input function was calculated by bi-exponential fitting of the measured fractions (Gillings *et al*., 2001). Based on the multiple-time graphical analysis (Patlak & Blasberg, 1985) the net influx of FDOPA from plasma to brain (K_{in}^{app}; ml/g/min) was calculated voxel-wise by linear graphical analysis after subtraction of the radioactivity measured in the cerebellum, and using frames recorded in the interval 20–70 min post-injection for the linear analysis (Gjedde, 1988; Martin *et al*., 1989; Cumming & Gjedde, 1998; Kumakura *et al*., 2004). Mean FDOPA net influx was measured from individual datasets by the definition of regions of interest (ROIs): the striatal ROIs were individually defined on high-resolution MRI [T1-weighted image data sets acquired on a Siemens 1.5 T Magnetom Vision magnetic resonance (MR) tomograph (Erlangen, Germany) using a magnetization-prepared rapid gradient echo (MP-RAGE) sequence, 180 images in sagittal orientation with isotropic voxels of 1 × 1 × 1 mm^3]. The ventral striatum ROIs were defined according to Mawlawi *et al*. (2001) on coronal images (three adjacent planes). The ROIs for the associative striatum were placed in the caudate and putamen excluding its most dorsal part on transaxial images (a total of six ROIs on three adjacent planes). All ROIs were superimposed on parametric influx rate constant (Ki) images, which were coregistered to MRI (Fig. 1). The values were averaged for both hemispheres, resulting in one average value for the ventral striatum and one average value for the associative striatum. These mean Ki values were used for the correlational analyses with MRI.

For the voxelwise comparisons summed early emission frames (2–8 min) were coregistered to individual T1-weighted MR images, and normalized to the Montreal Neurological Institute stereotaxic standard brain using an automated coregistration procedure and a 12-parameter affine transformation. After careful inspection of the PET-to-common MR registrations, the individual K_{in}^{app} maps were resampled using the calculated transformation parameters, and then smoothed using a Gaussian filter with isotropic 12-mm full-width at half-maximum (FWHM) prior to further statistical analysis with Statistical Parametric Mapping (SPM99; Friston, 1995).

fMRI

For emotion induction we used affectively negative, positive and neutral pictures. Each category consisted of 18 different pictures. Affective visual stimuli were taken from the International Affective Picture System (IAPS; Bradley & Lang, 1994). These pictures have previously been shown to elicit significant fMRI activation in the prefrontal and anterior cingulate cortex and in the amygdala (Wrase *et al*., 2003; Heinz *et al*., 2005a,b; Smolka *et al*., 2005). All pictures were controlled for arousal and valence according to the standardized rating procedure described by Bradley & Lang (1994). Valence was rated on a scale from 1 (unhappy) to 9 (happy); positive pictures were rated 7.7 ± 0.9, neutral pictures 5.8 ± 1.1 and negative pictures 2.6 ± 2.4. Arousal was rated on a scale from 1 (low) to 9 (high); positive pictures were rated 5.1 ± 1.0, neutral pictures 2.7 ± 1.4 and negative pictures 5.4 ± 2.9. The stimuli were passively viewed (Taylor *et al*., 2003; Wrase *et al*., 2003; Heinz *et al*., 2005b; Smolka *et al*.,

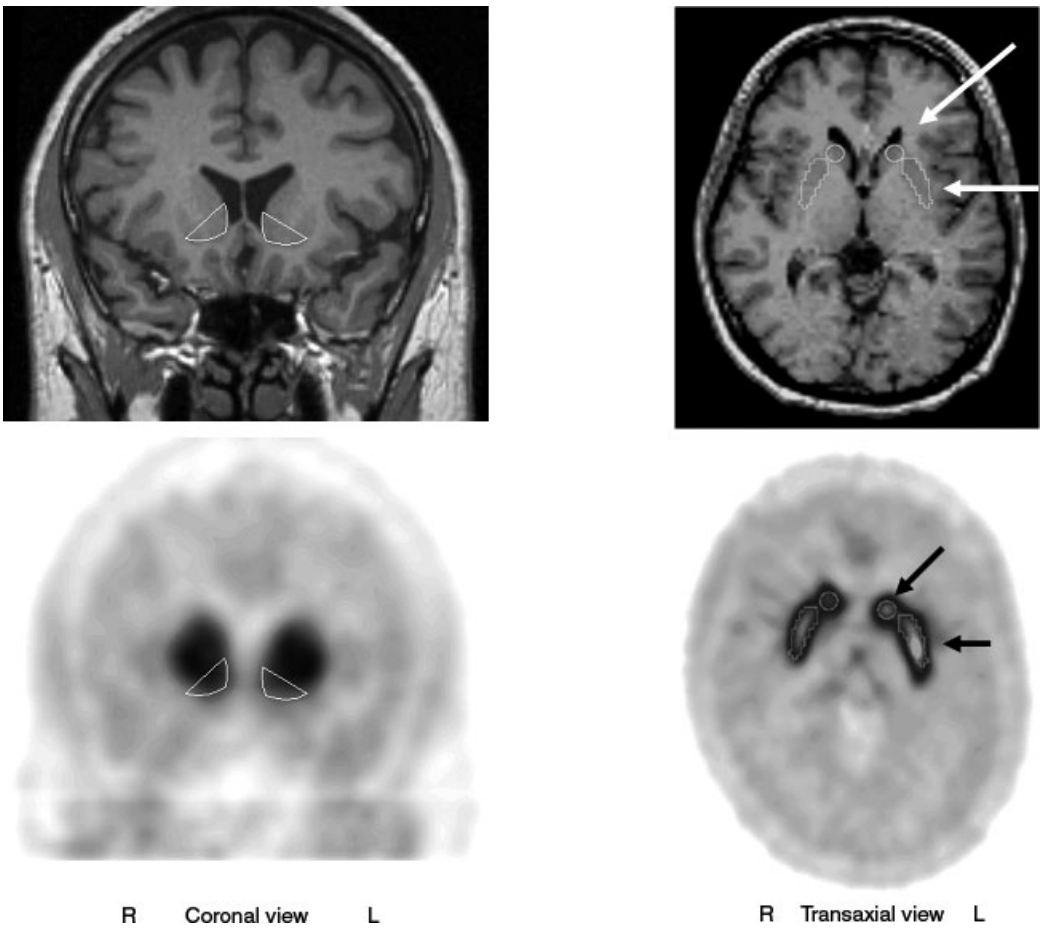


FIG. 1. (Upper left) Ventral striatum ROI defined according to Mawlawi *et al*. (2001) on high-resolution MRI (T1-weighted image; Siemens 1.5 T Magnetom Vision MR tomograph, MP-RAGE sequence, isotropic voxels of 1 × 1 × 1 mm ROIs). (Lower left) Individual ROIs defined on MRI were superimposed to give a composite image (integral FDOPA image between 64 and 94 min post-injection calculated from the original PET dynamic and coregistered to MRI). (Upper right) Caudate and putamen ('dorsal striatal') ROIs were defined on high-resolution MRI. (Right) Transverse image (integral FDOPA image between 64 and 94 min post-injection) illustrating the placement of the ROIs for caudate and putamen (associative striatum).

2005) in an event-related design for 750 ms and were arranged in an individually randomized order for each subject.

To reconstruct the BOLD event-related time-course, it is necessary to sample data points at different peristimulus time points. This was achieved by a random jitter between intertrial interval and acquisition time, resulting in an equal distribution of data points after each single stimulus. The intertrial interval was randomized between three and six acquisition times (i.e. 9.9–19.8 s). During the intertrial interval a fixation condition (fixation cross) was presented.

fMRI scanning was performed with a 1.5 T clinical whole-body tomograph (Magnetom Vision) equipped with a standard quadrature head coil. The automatic Siemens Multiple Axis Projection (MAP) shim was used for shimming. For fMRI, 24 slices were acquired every 3.3 s (4 mm thickness, 1 mm gap) using a standard Echo Planar Imaging (EPI)-Sequence ($3 \times 3 \times 3$ mm^3 voxel size, response time (TR) = 1.8 ms, echo time (TE) = 66 ms, $\alpha = 90°$) with an in-plane resolution of 64 × 64 pixels (field of view 220 mm). fMRI slices were orientated axially parallel to the AC–PC line according to Talairach & Tournoux (1988). A morphological 3-D T1-weighted MP-RAGE image data set ($1 \times 1 \times 1$ mm^3 voxel size, field of view 256 mm, 162 slices, TR = 11.4 ms, TE = 4.4 ms, $\alpha = 12°$) covering the whole head was acquired for anatomical reference.

fMRI data were analysed with SPM99. The structural 3-D data set was coregistered to the first T2* image. The structural image was spatially normalized to a standard template using a 12-parameter affine transformation with additional nonlinear components. A nonlinear transformation was subsequently applied to the T2* data. The functional data were smoothed using an isotropic Gaussian kernel for group analysis (12 mm FWHM). Statistical analysis was performed by modelling the different conditions (positive, negative and neutral pictures; delta functions convolved with a synthetic haemodynamic response function and its time derivative) as explanatory variables within the context of the general linear model on a voxel-by-voxel basis with SPM99. Data were analysed for each subject individually (threshold $P < 0.001$, uncorrected). To detect differences in the BOLD response elicited by affective stimuli, the contrast images [signal change of affective (positive and negative) vs. neutral pictures] of all subjects were included in a second-level random-effects analysis (Table 1; $P < 0.001$ uncorrected).

Statistical analysis of correlations between FDOPA net clearance and central processing of affective stimuli

To detect the association between striatal FDOPA net influx and voxel-wise changes in BOLD signal, the contrast images of all subjects were included in a second-level regression analysis with SPM99. We tested the hypotheses that (i) dopamine synthesis capacity in the ventral

striatum is associated with processing of positive but not negative stimuli in the anterior cingulate, insula and parts of the limbic cortex, and that (ii) dopamine synthesis capacity in the dorsal striatum is associated with processing of emotional stimuli in the dorsolateral prefrontal cortex. In these ROIs with direct projections to the ventral or dorsal striatum (Alexander & Crutcher, 1990; Haber *et al*., 2000), a significance level of $P < 0.001$ uncorrected and a cluster size of > 10 voxels was chosen to assess the association between functional brain activation elicited by affective cues and FDOPA net influx. As FDOPA net blood–brain clearance in the dorsal and ventral striatum were significantly correlated (Spearman's $R = 0.94$, $P < 0.001$), *post hoc* testing was used to assess whether significant correlations between the fMRI BOLD response and FDOPA net influx in the ventral striatum were also observed with FDOPA net influx in the dorsal striatum and vice versa.

Results

fMRI BOLD contrast in emotionally valent pictures

Similarly to previous studies (Wrase *et al*., 2003; Smolka *et al*., 2005), the presentation of affective vs. neutral pictures elicited significant BOLD contrasts in the insula and insular operculum and the frontal, limbic, temporal an occipital cortex (Table 1).

Correlations between PET measures in the ventral striatum and functional activation elicited by affective visual stimuli

The mean magnitude of the FDOPA net blood–brain clearance or influx (K_{in}^{app}) among the 13 subjects was 0.0088 ± 0.0021 mL/g/min in the bilateral ventral striatum and 0.0115 ± 0.0023 mL/g/min in the bilateral dorsal striatum. The magnitude of K_{in}^{app} in the ventral striatum was significantly and positively correlated with the BOLD response elicited by positive vs. neutral stimuli in the left anterior cingulate cortex [Brodmann's area (BA)24, *x*,*y*,*z* coordinates: −18,−10,39; $t = 5.0$, $R = 0.83$, $P < 0.001$, cluster size ≥ 10 voxels] and in the right insular operculum (*x*,*y*,*z* coordinates: 39,−5,22; $t = 5.1$, $R = 0.84$, $P < 0.001$, cluster size ≥ 10 voxels) (Table 2, Fig. 2). *Post hoc* testing showed no significant correlations between FDOPA net influx in the dorsal striatum and the BOLD response in the left anterior cingulate cortex (*x*,*y*,*z*: −18,−10,39; $t = 3.6$, $R = 0.79$, $P < 0.005$ for cluster size ≥ 10 voxels) or in the right insular operculum (*x*,*y*,*z*: 39,5,22; $t = 3.1$, $R = 0.7$, $P = 0.005$ for cluster size ≥ 10 voxels; Table 2).

TABLE 1. FMRI BOLD response contrast elicited by affective visual stimuli in 13 healthy persons

				Talairach coordinates				
Lobe	Location	BA	Side	*x*	*y*	*z*	*t*-value	*P*-value
Frontal	Middle frontal gyrus	6	Left	−30	−3	58	4.35	< 0.001
Frontal	Inferior frontal gyrus	9	Left	−39	3	27	5.18	< 0.001
Frontal	Medial frontal gyrus	10	Left	−3	53	11	4.38	< 0.001
Frontal	Middle frontal gyrus	11	Right	30	37	−17	4.49	< 0.001
Occipital	Cuneus	18	Left	−3	−86	24	5.92	< 0.001
Occipital	Middle temporal gyrus	19	Right	54	−63	14	4.53	< 0.001
Temporal	Fusiform gyrus	20	Right	37	−36	−18	4.32	< 0.001
Temporal	Superior temporal gyrus	22	Left	−54	−58	14	5.68	< 0.001
Temporal	Middle temporal gyrus	22	Right	59	−44	5	4.27	< 0.001
Limbic	Posterior cingulate	29	Left	−3	−46	11	5.19	< 0.001
Limbic	Posterior cingulate	29	Right	3	−49	11	5.0	< 0.001
Limbic	Posterior cingulate	30	Right	24	−55	14	5.65	< 0.001
Limbic	Parahippocampal	34	Left	−18	−12	−15	3.86	< 0.001
Temporal	Fusiform gyrus	37	Right	48	−62	−10	4.27	< 0.001
Temporal	Middle temporal gyrus	39	Left	−45	−72	26	6.23	< 0.001
Temporal	Middle temporal gyrus	39	Right	56	−58	11	4.44	< 0.001
Frontal	Inferior frontal gyrus	45	Right	56	30	7	5.98	< 0.001
Frontal	Inferior fontal gyrus	47	Left	−36	26	−14	4.63	< 0.001
Fontal	Inferior frontal gyrus	47	Right	48	32	−4	4.16	< 0.001
Insula			Right	36	10	16	3.45	< 0.001
	Lingual gyrus		Right	12	−73	1	3.70	< 0.001
	Lingual gyrus		Left	−21	−73	1	3.78	< 0.001

TABLE 2. Correlations between L-DOPA dopamine synthesis capacity in the ventral striatum and fMRI BOLD response elicited by affective visual stimuli in 13 healthy male volunteers

				Talairach coordinates				
Lobe	Location	BA	Side	*x*	*y*	*z*	*t*-value	*P*-value
Positive vs. neutral pictures: positive correlation								
Limbic	Anterior cingulate gyrus	24	Left	−18	−10	39	5.0	< 0.001
	Insular operculum		Right	39	−5	22	5.1	< 0.001
Positive vs. neutral pictures: no significant negative correlation								
Negative vs. neutral pictures: no significant negative or negative correlation								

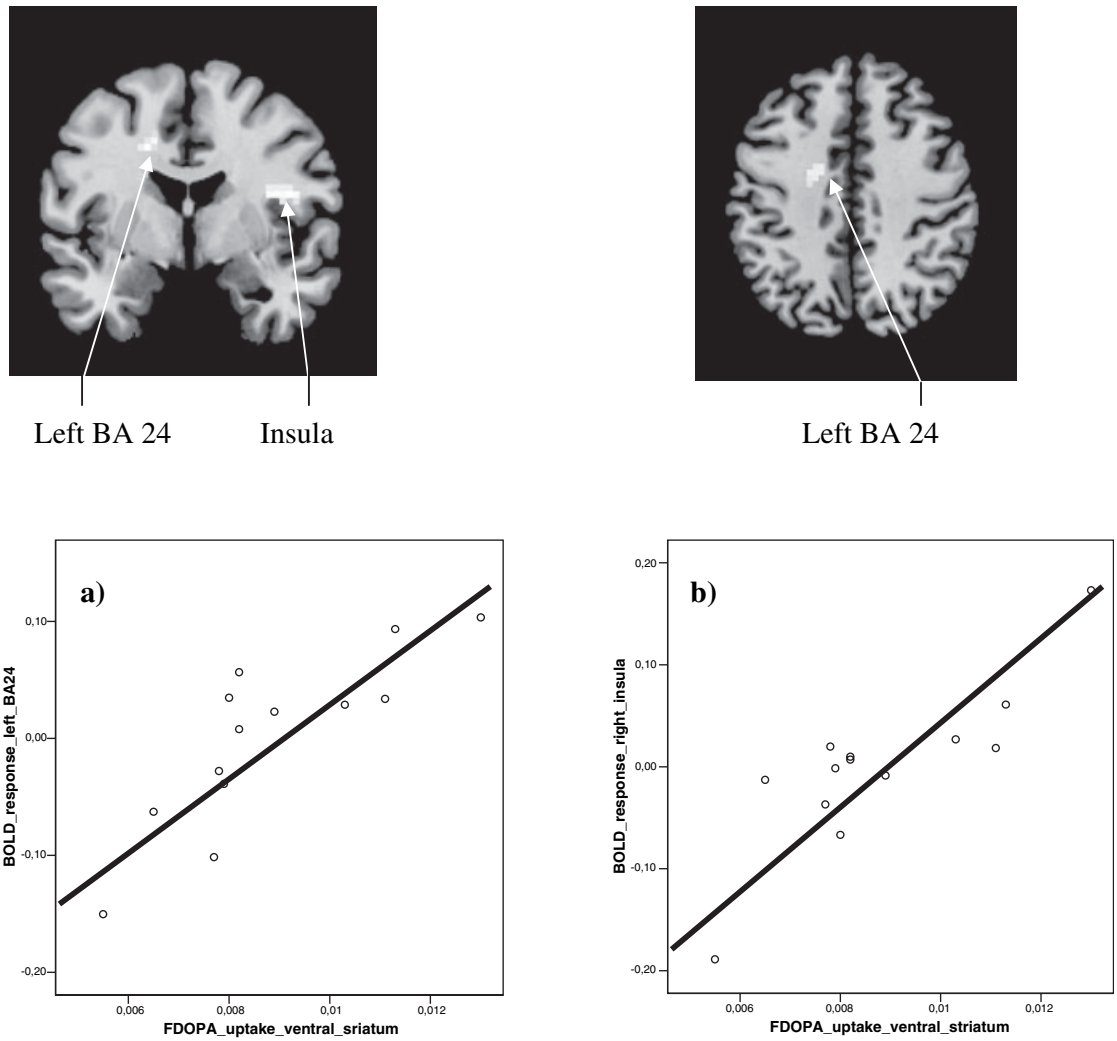


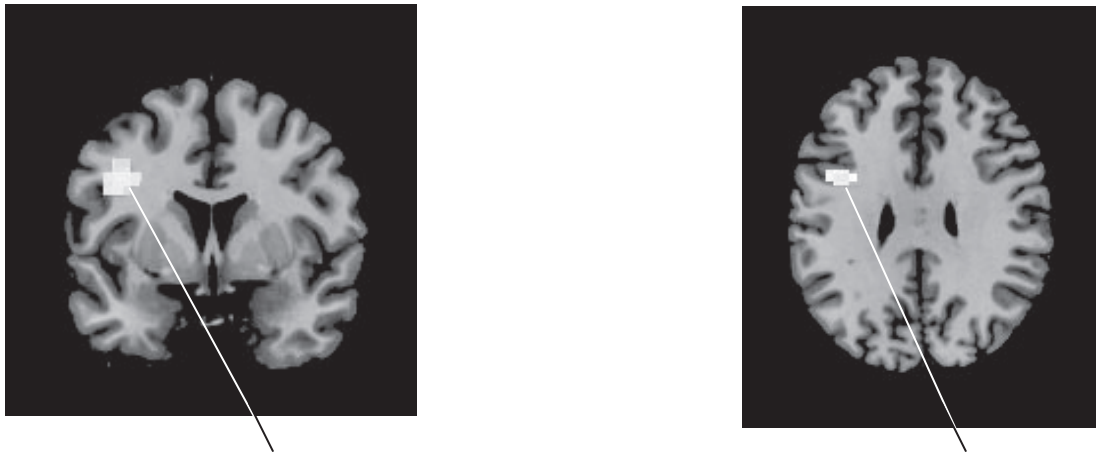
FIG. 2. (Upper half) Positive correlation between the magnitude of FDOPA net influx (K_{in}^{app}, ml/g/min) in the bilateral ventral striatum and the BOLD response measured with fMRI in anatomically closely linked brain areas (Haber *et al*., 2000) during the presentation of positive vs. neutral visual stimuli in a group of 13 healthy male volunteers (for illustrative purposes: $P < 0.001$ uncorrected). (Lower half) Plots of the correlations between the magnitude of FDOPA net influx (K_{in}^{app}, ml/g/min) in bilateral ventral striatum and the BOLD response elicited by positive vs. neutral stimuli in (a) the left anterior cingulate cortex (*x*,*y*,*z*: −18,−10,39, BA24; $R = 0.83$), and (b) the right insular operculum (*x*,*y*,*z*: 39,−5,22; $R = 0.84$).

TABLE 3. Correlation between PET measures in the dorsal striatum and fMRI BOLD responses elicited by affective visual stimuli in 13 healthy persons

				Talairach coordinates				
Lobe	Location	BA	Side	*x*	*y*	*z*	*t*-value	*P*-value
Positive vs. neutral pictures: positive correlation								
Frontal	Inferior frontal gyrus	9	Left	−42	4	27	5.3	< 0.001
Frontal	Middle frontal gyrus	6	Right	42	5	41	5.3	< 0.001
Positive vs. neutral pictures: no significant negative correlation								
Negative vs. neutral pictures, confirmatory analysis: positive correlation								
Frontal	Superior frontal gyrus	9	Left	−9	48	31	5.6	< 0.001
Negative vs. neutral pictures, confirmatory analysis: no significant negative correlation								

Correlations between PET measures in the dorsal striatum and functional activation elicited by affective visual stimuli

The magnitude of K_{in}^{app} in the dorsal striatum was significantly and positively correlated with the BOLD response elicited by positive vs. neutral stimuli in the left dorsolateral prefrontal cortex (BA9, *x*,*y*,*z*: −42,4,27; $t = 5.3$, $R = 0.85$, $P < 0.001$, cluster size ≥ 10 voxels) and right premotor cortex (BA6, *x*,*y*,*z*: 42,5,41; $t = 5.3$, $R = 0.85$, $P < 0.001$, cluster size ≥ 10 voxels) (Table 3, Fig. 3). For negative vs. neutral stimuli, a significant correlation was found between K_{in}^{app} in the dorsal striatum and the BOLD response in the left dorsolateral



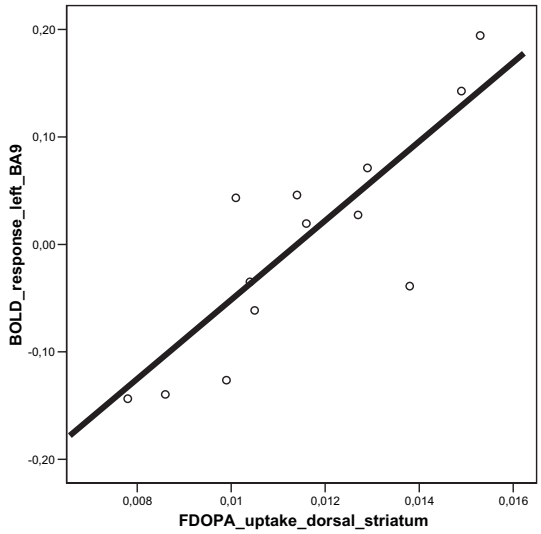


FIG. 3. (Upper half) Positive correlation between the magnitude of FDOPA net influx (K_{in}^{app}, ml/g/min) in the bilateral dorsal striatum and the BOLD response in anatomically closely linked brain areas (Haber *et al*., 2000) measured with fMRI during the presentation of positive vs. neutral visual stimuli in a group of 13 healthy male volunteers (for illustrative purposes: $P < 0.001$ uncorrected). (Lower half) Plot of the correlation between the magnitude of FDOPA net influx (K_{in}^{app}, ml/g/min) in bilateral dorsal striatum and the BOLD response elicited by positive vs. neutral stimuli in the left inferior frontal gyrus (*x*,*y*,*z*: −42,4,27, BA9; $R = 0.85$).

prefrontal cortex (BA9, *x*,*y*,*z*: −9,48,31; $t = 5.6$, $R = 0.86$, $P < 0.001$, cluster size ≥ 10 voxels; Table 3).

Post hoc testing revealed a significant correlation between the BOLD response elicited by positive vs. neutral cues in the left dorsolateral prefrontal cortex (BA9, *x*,*y*,*z*: −39,4,25; $t = 5.3$, $R = 0.85$, $P < 0.001$, cluster size ≥ 10 voxels) as well as in the right premotor cortex (BA6, *x*,*y*,*z*: 30,−1,42; $t = 4.7$, $R = 0.82$, $P < 0.001$, cluster size ≥ 10 voxels) and FDOPA net influx in the ventral striatum.

Discussion

This study shows that the net blood–brain influx of FDOPA (K_{in}^{app}) in the ventral striatum was positively correlated with processing of affectively positive but not negative stimuli in the anterior cingulate cortex and insular operculum. In the dorsal striatum, the magnitude of K_{in}^{app} was positively correlated with processing of positive stimuli in the left dorsolateral prefrontal and the right premotor cortex. To our knowledge, this is the first *in vivo* study in humans that confirms an association between dopamine transmission in divisions of the striatum with emotional processing in the anterior cingulate cortex and other specific cortical regions.

The net influx of FDOPA in arterial blood to brain (K_{in}^{app}, ml/g/min) is a macro parameter, properly defined in terms of the unidirectional clearance of FDOPA across the blood–brain barrier (K_1^D, ml/g/min), the fractional rate constant for diffusion of FDOPA back to blood (k_2^D, min^{-1}), and the fractional rate constant for the decarboxylation of FDOPA *in situ* (k_3^D, min^{-1}; Hoshi *et al*., 1993; Cumming & Gjedde, 1998). While tyrosine hydroxylase, the penultimate step for dopamine synthesis, is frequently presented as the sole rate-limiting step for catecholamine synthesis, we have shown that DOPA decarboxylase activity determines the fraction of DOPA in

brain to be trapped as dopamine rather than exported back to circulation (Gjedde *et al*., 1993); the uncommitted nature of DOPA synthesis has been revealed in studies of [^{3}H]tyrosine metabolism in brain of living rats (Cumming *et al*., 1998). Thus, pharmacological modulation of DOPA decarboxylase activity in brain of living rats (Cumming *et al*., 1995) and modulation of FDOPA net influx in brain of healthy humans (Vernalaken *et al*., 2006) are consequently indicators of altered dopamine synthesis in brain.

Striatal FDOPA net influx may interact with tonic rather than phasic dopamine release (Grace, 1991). Meyer-Lindenberg *et al*. (2002) observed that high striatal FDOPA influx was inversely correlated with the prefrontal fMRI BOLD response elicited during performance of a working memory task. In our study and the study of Meyer-Lindenberg *et al*. (2002), the observed correlations between striatal FDOPA influx and the cortical fMRI BOLD response do not necessarily imply causation; it is conceivable that individual differences in striatal and cortical dopamine tone are in some way related so that, e.g., FDOPA net influx in the ventral striatum reflects dopamine synthesis and release in the anterior cingulate cortex. In the prefrontal cortex, dopamine transporters are less numerous than in the striatum, and cortical dopamine concentrations are strongly affected by catechol-O-methyltransferase (COMT), a major enzyme in dopamine catabolism. The COMT val^{158}met genotype has been associated with the fMRI BOLD response elicited by working memory tasks (Meyer-Lindenberg *et al*., 2005) and the presentation of affective stimuli (Smolka *et al*., 2005). It has been suggested that high tonic dopamine release in the striatum of COMT Met carriers is associated with increased cortical dopamine D1 receptor stimulation, a reduced capacity to update contents of working memory and a sustained execution of prepotent response sets (Bilder *et al*., 2004). In our study, the observed positive correlations between striatal dopamine uptake capacity and the cortical fMRI BOLD response may thus reflect a tendency to sustain affective responses. However, our sample size is not large enough to assess COMT genotype effects; these could be addressed by future research.

The anterior cingulate cortex directly projects to the ventral striatum, including the nucleus accumbens (Alexander & Crutcher, 1990; Cummings, 1998). Our study suggests that dopamine neurotransmission in the ventral striatum may facilitate processing of affectively positive stimuli in a frontocortical–striatal–thalamic circuit that includes the anterior cingulate cortex, the ventral striatum and the thalamus. An unexpected finding of the present study was the high correlation between the magnitude of K_{in}^{app} in the ventral striatum and fMRI activation of the right insular operculum during the presentation of positive vs. neutral pictures. The insula has several subdivisions, some of which are concerned with visceral sensations and thought to mediate the 'gut feelings' of emotive states (Damasio, 1999). A recent study revealed a pathway for 'limbic touch' that directly activates the insula, evoking pleasant feelings of touch and regulating 'emotional, hormonal and affiliative responses to caress-like, skin-to-skin contact between individuals' (Olausson *et al*., 2002). The insula has been implicated in processing of individually relevant emotional cues and of stimuli that are related to the subject's emotional recall (Phan *et al*., 2002). Furthermore, anatomical studies in nonhuman primates revealed direct projections from the insula to the ventral striatum (Haber *et al*., 2000). Activation of the insula during the presentation of affectively positive stimuli may therefore help to place these stimuli in the context of an individual's emotional memory.

As noted above, the dorsolateral prefrontal and the premotor cortex directly project to the associative dorsal striatum (Haber *et al*., 2000). In accordance with these anatomical connections, we observed a positive correlation between the magnitude of K_{in}^{app} in the associative dorsal striatum and the processing of positive and (unexpectedly) negative stimuli in the dorsolateral prefrontal cortex. FDOPA net influx also correlated with processing of positive stimuli in the right premotor cortex. High dopamine synthesis capacity may subserve facilitated dopamine neurotransmission in the dorsal striatum, and thus modulate frontocortical–striatal–thalamic circuits connecting the dorsolateral prefrontal and premotor cortex and the associative dorsal striatum (Alexander & Crutcher, 1990; Cummings, 1998). Our observations suggest that dopamine synthesis capacity in striatal areas associated with habit formation may facilitate processing of salient stimuli in brain areas associated with executive planning and motor control.

Furthermore, we observed a positive correlation between K_{in}^{app} in the ventral striatum and the BOLD response elicited by positive vs. neutral stimuli in the left dorsolateral prefrontal cortex and right premotor cortex. This finding is not easily explained by direct anatomical connections between these parts of the frontal cortex and ventral striatum, but may suggest that dopamine transmission in the ventral striatum modulates the interaction of the anterior cingulate cortex and insula and brain areas involved in executive behaviour control and motor planning (Groenewegen *et al*., 1997; Kerns *et al*., 2004).

Several limitations of our study need to be addressed. First, the present correlation analysis does not indicate causality, as we cannot know whether the striatum drives the cortex or *vice versa*. Second, the sample size was limited and we examined only male subjects to avoid confounding of results by gender differences in the processing of emotional stimuli (Canli *et al*., 2002; Wrase *et al*., 2003). There was a high correlation between the magnitudes of K_{in}^{app} in the dorsal and ventral striatum, and FDOPA net influx in the dorsal striatum was moderately yet not significantly correlated with processing of positive stimuli in the anterior cingulate and insula. Therefore, the failure to observe similar associations between the dorsal and ventral striatum may be a matter of power rather than a true differential pattern, and this question should be addressed in further studies with larger sample sizes. Third, the resolution of our study was limited due to spatial smoothing. The insular correlation focus may well be opercular in nature and the cingulate focus appears to be located lateral to the cingulate, rather than in the sulcus itself. As described by Reimold *et al*. (2006), after smoothing, peaks in t-maps may be considerably displaced towards white matter and the coordinates of the local maximum in the associated contrast images are more precise; within the observed cingulate cluster, the maximum contrast was found in the grey matter at Talairach coordinates (x,y,z: −15,−1,44), which clearly corresponds to the cingulate gyrus. Finally, FDOPA PET net influx is only a surrogate marker for the unknown rate of dopamine synthesis in human brain (Cumming & Gjedde, 1998), as striatal dopamine is not normally derived from blood-borne levodopa. Nevertheless, individual variation in striatal K_{in}^{app} has been associated with behaviourally relevant variables such as alcohol craving in alcoholics (Heinz *et al*., 2005b). The functional state of dopaminergic neurotransmission in the living striatum can further be explored in PET studies combining an assessment of pharmacologically evoked striatal dopamine release (Laruelle *et al*., 1997; Breier *et al*., 1997 Rosa-Neto *et al*., 2005) or the availability of dopamine transporters (Volkow *et al*., 1996) with concomitant assays of FDOPA utilization.

Altogether, the present study revealed significant differences in the correlations between the magnitudes of FDOPA net influx to the ventral and the dorsal striatum with the processing of affective stimuli in the frontal cortex, as indicated by alterations in BOLD signal during stimulus presentation. We found that dopamine synthesis capacity (K_{in}^{app}) in the ventral striatum positively correlated with processing of positive stimuli in brain areas previously associated with attention and

attribution of salience to external cues (Alexander & Crutcher, 1990; Carter *et al*., 1998), while K_{in}^{app} in the dorsal striatum positively correlated with processing of affectively positive stimuli in frontal brain areas associated in previous studies with executive behaviour control (Alexander, 1990; Desposito *et al*., 1995). The present multimodal imaging approach combines the assessment of functional brain activation and neurotransmission, elucidating in part the complex interplay between dopamine and brain activation elicited by emotionally salient stimuli.

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Abbreviations

BA, Brodmann's area; BOLD, blood oxygen level-dependent; FDOPA, 6-[^{18}F]fluoro-L-DOPA; fMRI, functional magnetic resonance imaging; HPLC, high liquid chromatography performance; K_{in}^{app}, net influx of FDOPA from plasma to brain; MP-RAGE, magnetization-prepared rapid gradient echo; MR, magnetic resonance; PET, positron emission tomography; ROI, region of interest.

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