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Asymmetry in dopamine $D_{2/3}$ receptors of caudate nucleus is lost with age

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Molecular and functional imaging techniques reveal evidence for lateralization of human cerebral function. Based on animal data, we hypothesized that asymmetry in dopamine neurotransmission declines during normal aging. In order to test this hypothesis, we measured dopamine D2/3 receptor availability with [18F]desmethoxyfallypride-PET (DMFP) in putamen and caudate nucleus (NC) of 21 healthy, right-handed males (24–60 years; 35±10). For volumetric analysis, high-resolution T1-weighted MR-images were obtainedin 18 of the PET-subjects in order to assess possible age-related decreases in NC and putamen volume. The calculated DMFP binding potentials (BP) showed a right-ward asymmetry in NC of young subjects that decreased with age (r=0.577, p=0.006; Pearson correlation; two-tailed). An age-independent analysis showed a right-ward asymmetry in NC of the whole subject group (left: 1.49±0.35; right: 1.65±0.43 [mean±S.D.]; p=0.020). No such side lateralization or age-effects could be found in the putamen. Volumes tended to be asymmetric in the putamen (right: 4.85±0.56 cm^3; left: 4.64 ±0.86 cm^3 [mean±S.D.]; p=0.063), but not in NC. The decline of putamen volume during aging was significant in the right putamen (r = −0.613; p=0.007; Pearson correlation; two-tailed). There were no other significant correlations between striatal volumes and age or BP. Because ventral striatal dopamine neurotransmission is involved in cognitive processes, this loss of physiological asymmetry in NC dopamine transmission during aging might be involved in age-related declines of cognitive performance.

Keywords: Positron emission tomography; Asymmetry; Dopamine receptor; Caudate nucleus; Volumetry

Introduction

The brain of healthy man is considerably asymmetric in both its gross anatomy (in review: Toga and Thompson (2003)) and its functional metabolism. Several morphological studies show the presence of relatively greater volume in the right frontal lobe and the left occipital lobe (Kertesz et al., 1990; LeMay, 1976; Petty, 1999). Moreover, positron emission tomography (PET) studies using ^{18}F-fluorodeoxyglucose (FDG) have demonstrated asymmetric energy metabolism in the basal ganglia and some cortical regions (Kawachi et al., 2002; Willis et al., 2002). Evidence for a functional asymmetry of the human motor system is provided by an effect known as spontaneous turning bias; healthy right-handed men have a marked preference for turning towards their right side (Bracha et al., 1987). Interestingly, this lateralization is inversed in most cases of schizophrenia (Bracha, 1987; Lyon and Satz, 1991). Results from Mohr et al. (2005) suggest that these differences in turning behavior might be related to an underlying lateralization of dopamine transmission. Consistently, patients suffering from schizophrenia show aberrant asymmetry of their gross cerebral anatomy (Crow et al., 1989; Petty, 1999; Raz et al., 1987) and in PET studies of dopamine neurotransmission (Hietala et al., 1999).

Illness-related lateralization of brain morphology can be best understood in the context of effects of normal aging on brain structure (Good et al., 2001; Gunning-Dixon et al., 1998; Kovalev et al., 2003), and upon lateralization of activation during cognitive testing, which also declines in the healthy elderly (Cabeza et al., 1997; Grady et al., 2000). These results suggest that age-related changes of morphological asymmetry might be due in part to an evolving organization of cognition during aging. This scenario implies that neurotransmitter systems that are predominantly involved in cognitive performance should also show lateralization and age-related loss of asymmetry. Dopamine is a key neuro-

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transmitter not only in the extrapyramidal motor system, but is also involved in the expression of motivation, emotion and cognition (Middleton and Strick, 2000) and thus presents itself as a major target for such investigations.

Measurements of $D_{2/3}$ receptor availability in healthy subjects using PET or single photon emission tomography (SPET) have shown a trend towards relatively higher radioligand binding in the right striatum (in review: Larisch et al., 1998). Interestingly, there is also evidence from animal studies of asymmetry in dopamine receptors that decreases with age (Giardino, 1996). However, no previous work has investigated possible differences in the asymmetry of $D_{2/3}$ receptor binding between young and old healthy human subjects. Thus the aim of the present study was to examine if age influences the lateralized distribution of $D_{2/3}$ receptors in the human brain.

To test our hypothesis, we obtained PET recordings using ^{18}F-desmethoxyfallypride (DMFP) as radioligand in a group of healthy subjects. We have previously shown DMFP to be a suitable ligand for quantification of dopamine $D_{2/3}$ receptor availability in human extended striatum (Gründer et al., 2003a; Heinz et al., 2004; Vernaleken et al., 2004) by PET. We also obtained high-resolution, T1-weighted magnetic resonance (MR) images from almost all PET subjects for volumetric analysis of the subjects' caudate nucleus (NC) and putamen. This approach was chosen in order to help distinguish possible age-related changes in dopamine receptor abundance from confounding gray matter changes. The subject group consisted solely of healthy right-handed men, since handedness and gender are known to have major impact on cerebral asymmetry (Shaywitz et al., 1995; Witelson and Kigar, 1992).

Materials and methods

The local ethics committee in Mainz, Germany, and the German radiation safety authorities approved the study. Healthy volunteers were included after having given written informed consent, as required by the Declaration of Helsinki (1991). All PET investigations were performed at the PET Center of the University of Mainz, Germany.

Subjects

The subject group consisted of 21 male right-handed volunteers (range: 24–60 years; mean 35±10). Handedness was assessed by the Edinburgh-handedness inventory. Smoking was allowed. All volunteers were free of any relevant somatic complaint, history of psychiatric diagnosis and centrally acting medication. For screening purposes, subjects underwent a physical and mental state examination, blood and urine analysis (general clinical routine), drug-screening (cannabinoids, opiates, cocaine, methadone, amphetamines), electroencephalography and electrocardiography. Subjects with relevant blood parameter changes, positive drug screening or pathological ECG- or EEG signs were excluded from participation.

Magnet resonance imaging (MRI)

Data acquisition

Structural MRI investigations could be performed in 18 volunteers: three subjects declined to undergo the MRI scan. A T1-weighted, 3D gradient echo MR scan (MPRAGE) with 1.5 mm slice thickness and 128 slices was acquired. The head was positioned in the scanner parallel to the cantho-meatal line. The MR image was re-sliced according to the anterior commissure–posterior commissure (AC–PC) line, which was identified in the mid-sagittal plane.

Data analysis

Segmentation of the putamen and NC was performed according to the method of Szabo et al. (2003), with some modifications. VOIs were positioned (manually) on T1-weighted coronal MPRAGE images which were perpendicular to the AC–PC line: NC and putamen were segmented from their most anterior portions up to that slice in which the most posterior part of the putamen could still be identified. White matter of the internal capsule was excluded from the segmentation, as were the ventral gray structures. Gray matter of the nucleus accumbens and of the anterior perforated substance was delineated from the bottom of the anterior horn to the lateral contour of the putamen, and the point of ascending flexion. Inter-rater reliability ($n=2$) for volumetric analysis in a sub-sample of 16 striatal areas (images of four subjects) was $r=0.980$ ($p<0.0001$) in putamen volumes and $r=0.763$ ($p=0.010$) in NC volumes.

For detection of general aging effects, we additionally performed a normalization of the putamen and caudate nucleus volumes to the individual total intracranial volumes (TIV) according to Brinkman et al. (1981). Striatal volumes then can be expressed as percentage of TIV ([striatal volumes/TIV]*100). The intracranial volume was calculated as described previously by Ferguson et al. (2005).

Positron emission tomography (PET)

Data acquisition

Dynamic emission images were acquired with a Siemens ECAT EXACT whole-body PET scanner. The camera has a field-of-view of 16.2 cm in 47 planes with a plane spacing of 3.375 mm and an axial resolution of 5.4 mm FWHM. Prior to tracer administration, a 20-min-long transmission scan using a ^{68}Ge source was performed for attenuation correction. Emission scanning was initiated immediately after bolus injection of DMFP. The dynamic frame sequence consisted of 28 time frames (4×1 min, 3×2 min, 3×3 min, 15×5 min, 3×10 min) for a total of 124 min. DMFP ((*S*)-*N*-[(1-allyl-2-pyrrolidinyl)methyl]-5-(3-^{18}F-fluoropropyl)-2-methoxybenzamide) was synthesized as previously described (Gründer et al., 2003a). A mean of 208±40 MBq (mean±S.D., range 157 to 308 MBq) DMFP with a specific activity of 314±358 GBq/μmol (mean±S.D.) was intravenously injected as an infusion to a cubital vein over approximately 30 s.

For volume of interest (VOI) based analysis, the PET images were realigned for movement-correction, co-registered with the resliced MRI using the Automatic Image Registration (AIR) algorithm (Woods et al., 1992), and normalized to the space of Talairach and Tournoux (1988) using the MEDx tool. The final PET to Talairach spatial normalization was accomplished by concatenation of the PET to MR and MR to Talairach transformation matrices. A template of polygonal regions of interest (ROI) for cerebellum, putamen and NC was drawn on several planes also using MEDx software. Regions for putamen and NC were drawn in the slices from $z=0$ to +12 mm and for cerebellum, from $z=-28$ to −24 mm. Corresponding ROIs were grouped across the planes to create the VOIs. The volumes predefined in standard space were

3.12 cm^3 for putamen, 1.95 cm^3 for NC and 4.77 cm^3 for cerebellum. For the subsequent compartmental analyses, the cerebellum was chosen as a reference region since it is considered to be nearly devoid of dopamine $D_{2/3}$ receptors. Time activity curves from the template-VOIs were extracted from the spatially normalized dynamic image. The three PET datasets without individual MRI scans were normalized using sum images of the remaining 18 MR-based normalized PET images.

As normalization procedures might hypothetically distort the data especially in the striatum we performed a validation of this method in a subset of 20 VOIs (five subjects) by using an individual PET-to-MRI coregistration approach which has been described in detail by Gründer et al. (2003b). The data analysis for calculation binding potentials (BP) and laterality indices was identical to that of the normalization approach (*v.i.*). We observed high inter-correlations between these methods in binding potentials ($r=0.814$; $p<0.0001$; two-tailed Pearson correlation) and laterality indices ($r=0.825$; $p<0.003$; two-tailed Pearson correlation) as well.

Data analysis

Time activity curves, weighted for total counts, were analyzed using the "Receptor Parametric Mapping" (RPM) software package (Gunn et al., 1997). The specific binding of DMFP was calculated using a two-tissue compartment reference tissue model according to Lammertsma and Hume (1996), in which three free parameters are defined as follows: R_0, the permeability ratio for the initial DMFP clearance in the VOI to that in cerebellum, k_2, the rate constant for transfer from the free compartment to plasma, and BP, the binding potential (k_3/k_4). Parameters were estimated with a non-linear least squares minimization procedure. BP was also estimated using the transient equilibrium method (Farde et al., 1989). The procedure for calculation of DMFP BPs using these two methods has been described in detail by Gründer et al. (2003a).

Statistics

Side-differences for BP and volume were tested using the two-tailed paired *t*-test. For correlation analysis of laterality with age and volumes, we quantified the asymmetry of BP by calculating a lateralization index (Lx) as follows: Lx=(BP[VOI left]−BP[VOI right])/(BP[VOI left]+BP[VOI right]). The laterality index provides a value between −1 and +1 with negative values reflecting a right-ward laterality and positive values reflecting a left-ward laterality. The laterality index for the volumetric investigation was calculated analogously. Correlation analyses were performed using the two-tailed Pearson correlation.

Results

An initial comparison of the methods for BP calculation (SRTM and TE) revealed no significant differences ($t(83)=0.362$; $p=0.718$; two-tailed paired *t*-test) and a high inter-method correlation coefficient ($r=0.949$; $p<0.0001$; two-tailed Pearson correlation). All results mentioned below are according to the SRTM. Individual BP results and laterality indices for NC and putamen are presented in Table 1.

Table 1
Individual [^{18}F]DMFP-BP and volumetry data

Subject	Age	[^{18}F]DMF binding								Volumetry							
		Caudate nucleus				Putamen				Caudate nucleus				Putamen			
		BP left	BP right	BP left–right	Lx	BP left	BP right	BP left–right	Lx	Vol left	Vol right	Vol left–right	Lx	Vol left	Vol right	Vol left–right	Lx
1	24	1.30	1.71	−0.411	−0.136	2.24	1.95	0.286	0.068	4.16	4.24	−0.08	−0.010	5.17	5.38	−0.21	−0.020
2	24	1.99	2.36	−0.367	−0.084	3.04	2.75	0.294	0.051	4.58	4.79	−0.21	−0.022	5.31	5.24	0.07	0.007
3	25	1.72	2.38	−0.657	−0.160	2.92	2.89	0.028	0.005			–	–			–	–
4	25	1.61	1.73	−0.122	−0.037	1.93	2.09	−0.163	−0.041	4.78	4.48	0.30	0.032	5.55	5.66	−0.11	−0.010
5	27	1.11	1.41	−0.303	−0.120	1.99	1.92	0.073	0.019	3.76	3.57	0.19	0.026	4.48	4.90	−0.42	−0.045
6	27	1.59	1.67	−0.082	−0.025	2.01	1.95	0.056	0.014	4.21	4.20	0.01	0.001	4.93	5.06	−0.13	−0.013
7	30	1.32	2.12	−0.800	−0.232	2.65	2.48	0.175	0.034	3.97	4.50	−0.53	−0.063	5.33	5.80	−0.47	−0.042
8	30	1.14	1.55	−0.409	−0.152	1.97	2.14	−0.164	−0.040	3.67	3.77	−0.10	−0.013	5.47	5.20	0.27	0.025
9	30	1.55	1.56	−0.010	−0.003	2.34	2.38	−0.039	−0.008	3.88	3.94	−0.06	−0.008	4.76	4.74	0.02	0.002
10	32	2.02	2.07	−0.050	−0.012	2.90	3.22	−0.320	−0.052	3.97	3.49	0.48	0.064	5.24	5.16	0.08	0.008
11	33	1.08	1.60	−0.522	−0.195	2.09	2.08	0.004	0.001			–	–			–	–
12	36	1.35	1.51	−0.160	−0.056	1.95	2.00	−0.50	−0.013	4.07	3.95	0.12	0.015	4.35	4.58	−0.23	−0.026
13	36	1.97	1.85	0.120	0.031	2.50	2.70	−0.200	−0.038	4.39	4.39	0.00	0.000	5.33	4.98	0.35	0.034
14	37	0.66	0.70	−0.040	−0.029	1.60	2.24	−0.640	−0.167			–	–			–	–
15	38	1.45	1.39	0.060	0.021	1.84	2.02	−0.180	−0.047	5.90	6.51	−0.61	−0.049	1.90	3.69	−1.79	−0.320
16	39	1.83	1.93	−0.109	−0.029	2.53	2.54	−0.012	−0.002	4.01	3.96	0.05	0.006	4.80	5.20	−0.40	−0.049
17	40	1.52	1.36	0.156	0.054	2.30	2.49	−0.195	−0.041	3.27	3.25	0.02	0.003	3.88	4.09	−0.21	−0.026
18	41	1.66	1.85	−0.190	−0.054	2.70	2.32	0.380	0.076	4.61	3.44	1.17	0.145	4.31	4.61	−0.30	−0.034
19	43	1.07	0.78	0.290	0.157	1.29	1.26	0.030	0.012	3.41	3.35	0.06	0.009	4.06	4.22	−0.16	−0.019
20	58	1.76	1.88	−0.119	−0.033	2.56	2.48	0.077	0.015	3.92	3.77	0.15	0.020	4.34	4.35	−0.01	−0.001
21	60	1.55	1.23	0.321	0.116	1.95	1.98	−0.031	−0.008	3.27	3.05	0.22	0.035	4.32	4.48	−0.16	−0.018
Mean	35.0	1.49	1.65	−0.162	−0.047	2.25	2.28	−0.028	−0.008	4.10	4.04	−0.030	0.011	4.64	4.85	−0.212	−0.030
S.D.	9.92	0.35	0.43	0.291	0.097	0.45	0.42	0.226	0.052	0.62	0.78	0.076	0.045	0.86	0.56	0.452	0.076

Individual values of [^{18}F]DMFP binding potential (BP) and basal ganglia volume (Vol) for NC and putamen. Additionally, side differences (left−right) and the laterality index [Lx=(left−right)/(left+right)] are depicted. Dimension of volumes is generally cm^3; values of BPs are estimated using the simplified reference tissue model (SRTM).

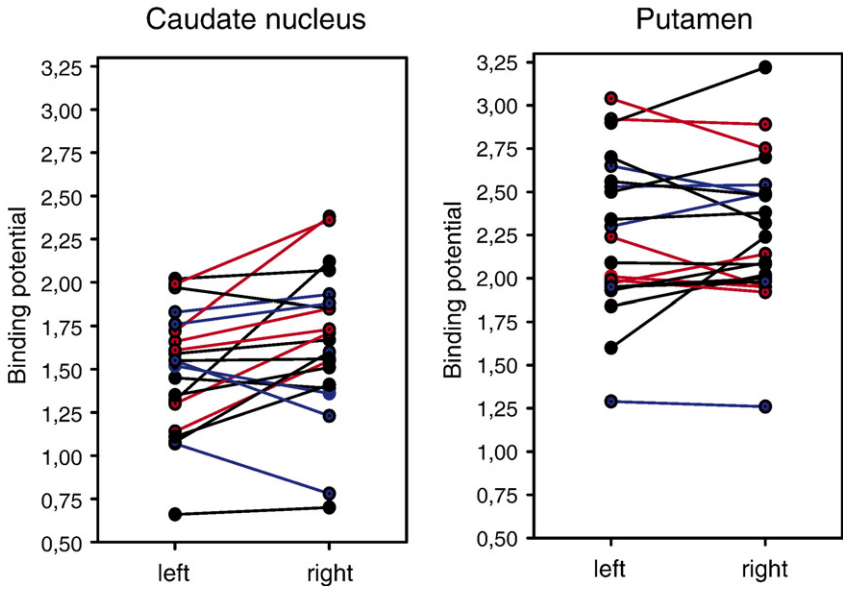

Fig. 1. Individual asymmetry of DMFP binding at $D_{2/3}$ receptors in NC (left) and putamen (right). Red lines and dots represent data of the six youngest subjects; blue lines and dots represent the six eldest subjects. In NC age-independent side differences reached statistical significance ($p=0.019$; paired two-tailed t-test). All binding potentials depicted here are calculated using SRTM.

An age-independent side-difference analysis of striatal BP (BP [VOI left] vs. BP[VOI right]) in all 21 subjects revealed a significant right-ward laterality in the NC ($t(20)=-2.54$; $p=0.020$; paired t-test, two-tailed) but no significant side-differences in the putamen (Table 1 and Fig. 1).

The D_2-laterality index (Lx_{D2}) ranged from −0.232 to 0.157 (mean=−0.047±0.097) in the NC and from −0.167 to 0.076 (mean=−0.008±0.052) in the putamen. In the NC, there was a significant positive linear correlation between the D_2-laterality index (Lx_{D2}) and age ($r=0.577$, $p=0.006$; Pearson correlation; two-tailed) as shown in Fig. 2. We also found significant correlations between age and the uncorrected side-differences between the binding potentials (ΔBP) of the left and right NC ($r=0.581$, $p=0.006$). No equivalent age-related changes were found in the putamen (Lx_{D2}: $r=-0.10$, $p=0.664$; ΔBP: $r=-0.10$, $p=662$) Pearson correlation; two-tailed). The decline of the mean bilateral BP with age was not significant in the NC and the putamen. For illustration of stronger asymmetry in NC of the younger subjects, the mean parametric maps of the six youngest (age: 25.3±1.37) and the six eldest subjects (age: 46.8±9.5) are presented in Fig. 3.

In the volumetric analyses, there was a trend towards a larger volume of the right putamen (right: 4.85±0.56 cm^3; left: 4.64±0.86 cm^3 [mean±S.D.]; $t(17)=-1.99$; $p=0.063$; paired t-test, two-tailed) independent of age effects (Fig. 4), but no evidence was found for side differences in NC volumes (right: 4.04±0.78 cm^3; left: 4.10±0.62 m^3 [mean±S.D.]; $t(17)=0.732$; $p=0.474$; paired t-test, two-tailed). The rate of age-dependent decline in putamen volume was −6.5% per decade in right putamen and −7.3% per decade in left putamen. The decline of putamen volume during aging was significant in the right putamen ($r=-0.613$; $p=0.007$; $n=18$; Pearson correlation, two-tailed) whereas the left putamen

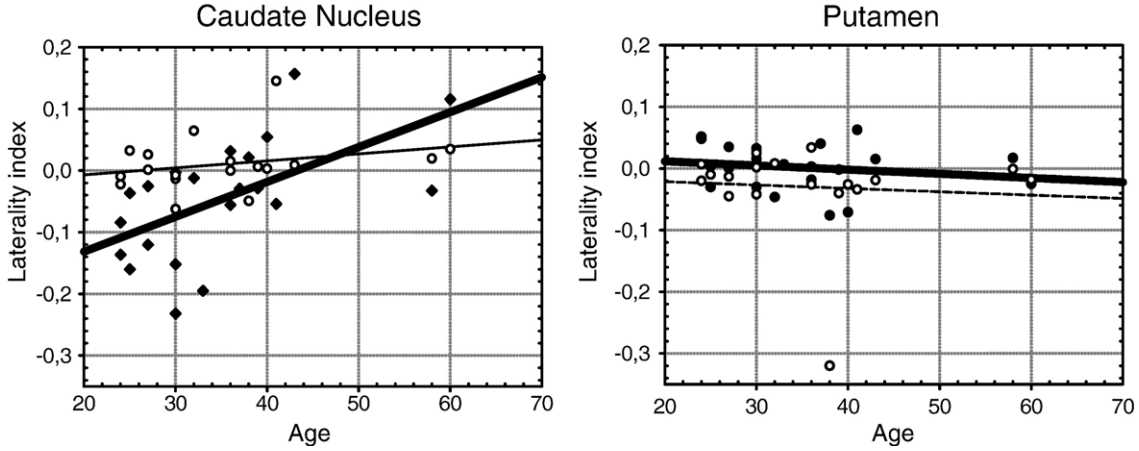

Fig. 2. Scatter plot of individual DMFP binding potentials (♦) and volumes (○) for NC and putamen. Linear regression lines are included (DMFP: solid line/volume: dashed line). In NC DMFP binding correlates significantly with age ($r=0.58$, $p=0.0059$; two-tailed Pearson correlation).

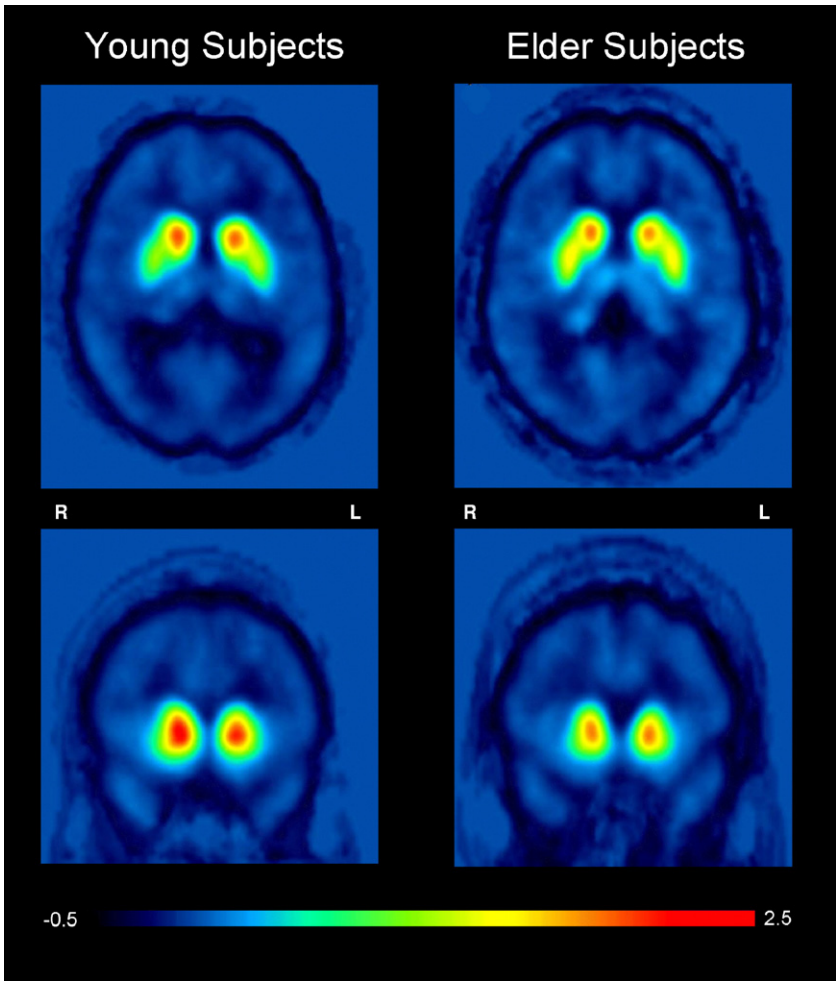

Fig. 3. Transversal (top) and coronar (bottom) planes of summed images derived from the six youngest (left) and the six eldest subjects. Images are parametric maps voxel-wise depicting the DMFP binding potential according the approach of Lammertsma and Hume (1996). All images were transformed into the common stereotaxic space. The left–right orientation is according to radiological convention. The planes are crossing the ventral striatum.

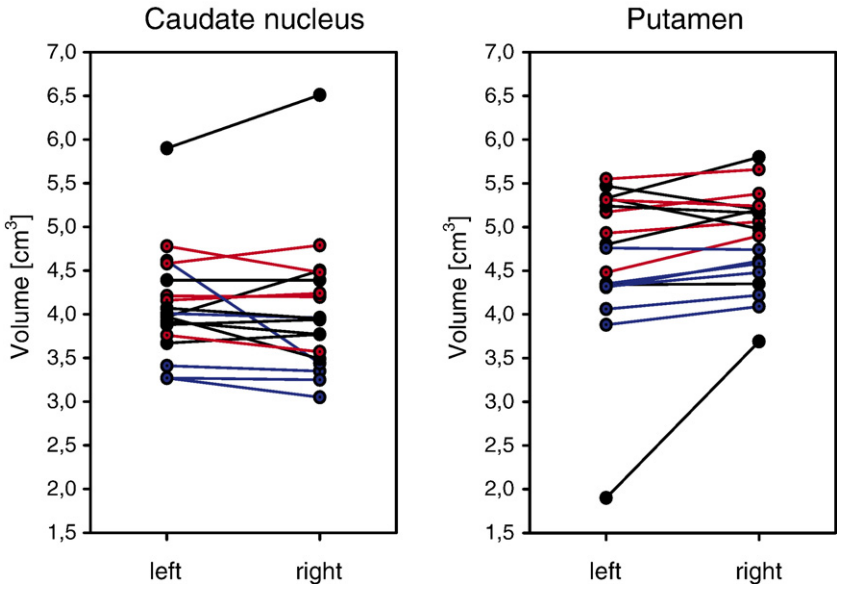

Fig. 4. Individual volumetric asymmetry of NC (left) and putamen (right). Red lines and dots represent data of the six youngest subjects; blue lines and dots represent the six eldest subjects. In putamen there was a trend for age-independent side differences ($p=0.063$; paired two-tailed t-test).

showed only a trend towards declining volumes ($r=-0.432$; $p=0.073$; $n=18$; Pearson correlation, two-tailed). In NC, no statistically significant age effect in volumes was detected. Age related effects on normalized striatal volumes revealed analogous results (left putamen: $r=-0.396$; $p=0.104$; right putamen: $r=-0.521$; $p=0.027$; right and left NC: n.s.; $n=18$; Pearson correlation, two-tailed). The normalized unilateral striatal volumes ranged from 0.20% to 0.41% (0.26±0.047 [mean±S.D.]) in the caudate nucleus and from 0.12% to 0.38% (0.30±0.053 [mean±S.D.]) in the putamen. The volume laterality index (Lx_{Vol}) did not correlate with age in either putamen or NC (caudate nucleus: $r=0.27$, $p=0.28$; putamen: $r=-0.08$, $p=0.77$; Pearson correlation, two-tailed).

Discussion

This investigation is one of the few studies combining molecular imaging and volumetric measurements using structural MRI for the study of age-related changes in dopamine systems.

In support of our hypothesis we found significant right-ward age-independent lateralization in $D_{2/3}$ receptor availability in the NC of healthy men, and also a decrease of this asymmetry with age. The strong right-ward laterality found in the NC of young adult males was reduced and, in some cases, inversed in the older subjects, such that there was a highly positive linear correlation between age and the laterality index in caudate (Fig. 4). The putamen failed to show either age-independent differences or age-related changes in laterality.

There have been several previous investigations assessing possible asymmetries in $D_{2/3}$ receptor availability (Antonini et al., 1993; Farde et al., 1990; Pentilla et al., 2004; Pilowsky et al., 1993). However, clear demonstration of laterality in molecular imaging studies has proven elusive due to several methodological limitations. Specifically, small expected side differences, high variance, small sample sizes, low spatial resolution, and varying analytical methods of PET and SPECT investigations have led to several inconsistent and contrary results. Larisch et al. (1998) have reviewed recently published PET and SPECT results on asymmetric lateralization of dopamine $D_{2/3}$ receptors and emphasized the overall occurrence of a right-sided lateralization of dopamine $D_{2/3}$ receptor availability. However, most of the imaging studies available to Larisch et al. (1998) did not distinguish between putamen and NC structures or their observations were based on very small sample sizes. None of the previous studies considered age as a confounding or covariant factor. Due to these methodological difficulties in earlier studies, we aimed for high accuracy and objectivity in the quantification and analysis of the data. In the present study, we used the SRTM as standard method of calculating the binding potential (BP) of DMFP. This approach has been previously validated for DMFP investigations (Gründer et al., 2003a). Additionally, BPs were calculated using the conventional TE method. TE and SRTM results correlated highly with each other and gave qualitatively and quantitatively similar results. In order to minimize variability, we performed a coregistration of the PET recordings with individual MR images (except in the $n=3$ without MR scans), carried out spatial normalization, and used predefined VOI-templates. Thus, the present findings of a right-ward asymmetry in $D_{2/3}$ availability in an age-independent analysis support the meta-analysis of Larisch et al. (1998).

A key novel finding of the present study is the detection of declining $D_{2/3}$ receptor asymmetry during healthy aging. The fact that right-ward asymmetry was mainly present in younger subjects might have contributed to discrepant results in some previous studies. However, it might be proposed that age related changes in the laterality of $D_{2/3}$ availability could be an experimental artifact caused by side different age-related changes in striatal volumes, with a resultant bias e.g. due to changing partial volume effects; atrophy of striatal structures would thus tend to decrease the apparent BP. Volume changes and volume laterality could hypothetically influence the DMFP BP results by several reasons and not only by partial volume effects. Therefore, we decided not to use partial volume correction but to perform a striatal volumetry in order to observe possible influences in general. Age-related volume shrinkage during aging was previously found to be more rapid in the putamen of the right hemisphere. In NC the left side shows more rapid shrinkage; for both structures this results in a loss of asymmetry during aging (Gunning-Dixon et al., 1998). To correct for possible bias in BP due to volume loss with age, we carefully assessed age-related changes in volumes of the basal ganglia in MR images from the present study group. There were no significant correlations between volume laterality with age or $D_{2/3}$ laterality, suggesting that lateralization of partial volume effects did not contribute importantly to bias in calculation of the $D_{2/3}$-lateralization index. Furthermore, asymmetry in DMFP-binding was detected only in NC of young subjects, whereas volume asymmetry was seen only in the putamen. Considering these arguments, we conclude that the age-related decline of the right>left asymmetry of DMFP binding in NC during aging of healthy subjects reflects an intrinsic change in the availability of post-synaptic dopamine receptors.

The relevance of this age effect on laterality of $D_{2/3}$ receptor availability should be properly discussed in the context of diverse laterality results in morphological and functional observations. Evidence for morphological asymmetry of brain was first reported in the 19th century. Boyd (1861) found the left hemisphere to be slightly heavier than the right, whereas Hrdlicka (1907) found the left hemisphere to be longer than the right, although disparate findings have been reported (Braune, 1891; Gundara and Zivanovic, 1968; Wilde, 1926). The occipital part of the interhemispheric line typically bends to the right, which is known as counterclockwise physiological torque (LeMay, 1976). In a more recent MR imaging study, there was a balanced asymmetry in the horizontal planes with rightward predominance of the temporal lobe and opposite predominance in parietal regions (Falk et al., 1991). Volumetric studies focusing on side-differences in human striatum have reported somewhat inconsistent results (in review: Raz et al., 1995), perhaps reflecting different subject subgroups, accuracy and segmentation methodologies. However, two MR studies of the most outstandingly large populations ($n=104$ and 148, respectively) found a prominent right-ward asymmetry in putamen volume and a smaller left-ward asymmetry in NC of healthy male subjects over all ages (Giedd et al., 1996; Gunning-Dixon et al., 1998). Thus, our volumetric results are in accordance with these investigations.

Several factors may give rise to gross anatomical lateralization, such as fetal orientation, testosterone effects, genetic factors, or environmental influences (Toga and Thompson, 2003). Left-handedness and female gender are associated with less physiological torque than typically occurs in right-handed males (Shaywitz et al., 1995; Witelson and Kigar, 1992). These data suggest that lateralization is not an incidental finding, but mirrors differences in cerebral development due to complex factors. Consequently, in the

present study of right-handed male subjects, we have avoided confounds due to gender and cerebral dominance differences.

Molecular imaging results provided more insight into lateralization processes. As mentioned above, PET and SPET investigations of post-synaptic dopamine $D_{2/3}$ receptors have generally shown asymmetric lateralization of binding sites favoring the right side (Larisch et al., 1998). Likewise, PET studies with the presynaptic tracer 6-^{18}F-fluoro-L-DOPA (FDOPA) revealed a right-sided higher dopamine synthesis capacity, predominantly in the NC (Hietala et al., 1999); dopamine transporters showed a similar laterality (Laakso et al., 2000). Additionally, in some animal investigations an asymmetry of dopaminergic transmission was observed. Cumming et al. (2003) reported asymmetry of ^{11}C-raclopride binding in the caudate and putamen of healthy young female Landrace pigs. Furthermore, enhanced vulnerability of ^{11}C-raclopride binding to nicotine-evoked dopamine release was reported in the left ventral striatum of these pigs, perhaps indicating functional lateralization in response to a pharmacological challenge.

Previous investigations of turning behavior might help to interpret these lateralization results. Thus, schizophrenic males consistently turned left, whereas an age-matched group of patients with affective disorders turned right (Lyon and Satz, 1991). In a group of patients with schizophrenia, delusional intensity correlated significantly with tendency to turn left (Bracha et al., 1993). Furthermore, sub-clinical magical ideation scores in control subjects correlated with left-turning bias in control subjects. The authors considered magical ideation, although sub-clinical, to be a "soft-sign" for functional hyperactivity of dopamine systems on the right side of the body (Mohr et al., 2005). Conversely, in the same study, subjects with higher score for "physical anhedonia", a clinical expression of dopaminergic hypoactivity, showed increasing right-turning behavior.

The right-ward asymmetry of $D_{2/3}$ receptor binding in healthy young adults could reflect differences in maximal binding capacity (B_{max}) and/or apparent affinity, which is a function of competition from endogenous dopamine. In the turning model, spontaneous rotation can be interpreted to indicate a relatively greater dopamine transmission on the side contralateral to turning. According to these results, the right-ward asymmetry of $D_{2/3}$ receptor availability in healthy young adults could thus be a consequence of relatively lower endogenous dopamine concentrations on that side. With respect to cognitive functions, a recent FDOPA-PET study showed a positive correlation between striatal FDOPA uptake and "prefrontal" cognitive performance even in healthy men (Vernaleken et al., 2005). Given the finding of right frontal predominance in morphometric studies cited above, and the particular functional relationship between dopaminergic transmission in the NC and the dorsolateral prefrontal cortex (Meyer-Lindenberg et al., 2002; Roberts et al., 1994; Vernaleken et al., 2005), we propose that an asymmetry in the striatal dopamine transmission system of healthy young males is present that might be linked to the cortico-striatal organization of cognitive performance. This linkage, if true, would support the hypothesis that the increasing complexity of mammalian brains demands more effective structures in cognitive processing to be provided by more specialized brain areas within each hemisphere and less bilateral processing (Toga and Thompson, 2003).

In this scenario, the present detection of an age-related decrease of asymmetry in $D_{2/3}$ receptor availability in NC would predict changes in the pattern of cognitive processing during the human life span. Whereas similar age-related changes in the dopaminergic system have previously been reported only in rats (Giardino, 1996), some earlier morphological and functional investigations in humans reported age-related changes of cortical asymmetry. Using voxel-based morphometry, Good et al. (2001) and Kovalev et al. (2003) defined regions with increasing asymmetry during aging (inferior frontal gyrus, anterior insula, anterior cingulate, parahippocampal gyrus, retrosplenial cortex, corona radiata) and areas of decreasing laterality (optic radiation, the precentral gyrus, and the angular gyrus). Age-related changes in human striatal volume-laterality were found by Gunning-Dixon et al. (1998).

Results of several functional imaging studies of working memory, episodic retrieval, perception, and inhibitory control indicate substantial lateralization of PFC activations in younger adults that decline in older subjects (Cabeza et al., 1997; Dixit et al., 2000; Grady et al., 2000; Logan et al., 2002; Nielson et al., 2002). Considering these reports, Cabeza (2002) and Dolcos et al. (2002) introduced and described the Hemispheric Asymmetry in Old Adults (HAROLD) model. Several different explanations for the decline of asymmetry were suggested. According to the 'compensatory hypothesis', age-dependent declines in the rate of (cognitive) task performance leads to recruitment of structures of the contralateral hemisphere. Thus, bilateral activation patterns are associated with better task performance in older subjects (Reuter-Lorenz et al., 2000). Conversely, the 'dedifferentiation hypothesis' suggests that the hemispheric differentiation process occurring during childhood reverses after adolescence, resulting in recruitment of or engagement of widespread, task-independent resources. In a recent EEG study of event-related potentials, arithmetic tasks evoked bilateral patterns of activation which revealed a failure of flexibility in problem solving strategies in the older subjects, associated with a decline in lateralization of activity (El Yagoubi et al., 2005). Since dopamine synthesis capacity in striatum is highly correlated with cognitive performance in healthy subjects (Vernaleken et al., 2005) the present findings of age-related loss of $D_{2/3}$ receptor binding asymmetry seems linked to the HAROLD model. This loss of asymmetry might be due to compensatory processes or could be part of a dedifferentiation process. It should be considered that all subjects were free of any obvious cognitive deficits. Also, the age-range extended from 24 to 60 years; a range at which substantial loss of prefrontal performance should not be expected. However, distinguishing compensatory or dedifferentiation effects is beyond the scope of the present study design.

Finally, the present finding of an age-dependent decline in the asymmetry of dopamine $D_{2/3}$ receptors in healthy right-handed males seems relevant in the context of some well-known disturbances of morphological brain asymmetries. Previous investigations have demonstrated that patients suffering from early onset schizophrenia fail to show volumetric asymmetries, whereas patients with later exacerbation show increased laterality in comparison to controls (Maher et al., 1998). This loss of restoration of structural symmetry in schizophrenia with late-onset might suggest that the normal age-related loss of asymmetry reflects a physiological process, the disturbance of which might be associated with an accelerated loss of cognitive functions. As the dopaminergic neurotransmission is implicated in the pathophysiology of schizophrenia, the present results suggest the investigation of $D_{2/3}$ receptor binding in untreated patients suffering from schizophrenia or prodromal states and possible changes of laterality under subsequent treatment or disease progression. Furthermore, asymmetries of $D_{2/3}$ receptors in

extrastriatal regions with lower $D_{2/3}$ receptor density might be investigated by the use of PET-ligands with higher affinity in conjunction with additional neuropsychological characterization of the subjects.

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