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Relationship of Striatal Dopamine Synthesis Capacity to Age and Cognition

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Past research has demonstrated that performance on frontal lobe-dependent tasks is associated with dopamine system integrity and that various dopamine system deficits occur with aging. The positron emission tomography (PET) radiotracer 6-[^{18}F]fluoro-L-*m*-tyrosine (FMT) is a substrate of the dopamine-synthesizing enzyme, aromatic amino acid decarboxylase (AADC). Studies using 6-[^{18}F]fluorodopa (FDOPA) (another AADC substrate) to measure how striatal PET signal and age relate have had inconsistent outcomes. The varying results occur in part from tracer processing that renders FDOPA signal subject to aspects of postrelease metabolism, which may themselves change with aging. In contrast, FMT remains a purer measure of AADC function. We used partial volume-corrected FMT PET scans to measure age-related striatal dopamine synthesis capacity in 21 older (mean, 66.9) and 16 younger (mean, 22.8) healthy adults. We also investigated how striatal FMT signal related to a cognitive measure of frontal lobe function. Older adults showed significantly greater striatal FMT signal than younger adults. Within the older group, FMT signal in dorsal caudate (DCA) and dorsal putamen was greater with age, suggesting compensation for deficits elsewhere in the dopamine system. In younger adults, FMT signal in DCA was lower with age, likely related to ongoing developmental processes. Younger adults who performed worse on tests of frontal lobe function showed greater FMT signal in right DCA, independent of age effects. Our data suggest that higher striatal FMT signal represents nonoptimal dopamine processing. They further support a relationship between striatal dopamine processing and frontal lobe cognitive function.

Key words: **FMT; PET; normal aging; striatum; cognition; aromatic amino acid decarboxylase; DOPA decarboxylase; caudate; putamen; basal ganglia; prefrontal; upregulation**

Introduction

Performance on frontal lobe-dependent tasks, such as working memory and executive function, relies on the integrity of the striatal dopamine system in normal adults (Bäckman et al., 2000; Erixon-Lindroth et al., 2005; Vernaleken et al., 2007b). Age-related loss of cerebral dopamine system function has been demonstrated in humans and nonhuman primates (Severson et al., 1982; Seeman et al., 1987; Rinne et al., 1990, 1998; Cordes et al., 1994; Kish et al., 1995; Wang et al., 1998; Kaasinen et al., 2000; van Dyck et al., 2002; Collier et al., 2007). Likewise, a decline in frontal lobe-dependent cognitive function is well established with aging (Cohen et al., 1987; De Luca et al., 2003; Gazzaley et al., 2005). Characterizing the relationship between dopamine and frontal lobe function across the adult lifespan is crucial to understanding cognitive aging.

To explore the association between dopamine and frontal lobe-dependent cognitive function with age, we studied older and younger adults using positron emission tomography (PET) scanning using the radiotracer 6-[^{18}F]fluoro-L-*m*-tyrosine (FMT). FMT is a substrate of aromatic amino acid decarboxylase (AADC), which converts levodopa (L-DOPA) to dopamine. Thus, FMT signal represents dopamine synthesis capacity given sufficient substrate.

To date, most PET studies of presynaptic dopamine synthesis have used 6-[^{18}F]fluorodopa (FDOPA), which, like FMT, is a substrate of AADC. Results of studies using FDOPA to measure age-related changes in dopamine synthesis have been inconsistent; some have found decreases in striatal FDOPA signal with age (Martin et al., 1989; Bhatt et al., 1991; Cordes et al., 1994) and some have found no age effect (Sawle et al., 1990; Eidelberg et al., 1993; Ishikawa et al., 1996b). One PET study of nonhuman primates found that FDOPA signal decreased with age, whereas FMT signal increased with age in the same animals (DeJesus et al., 2001). The authors suggested that the disparate results related to differences in what the two tracers measure. Because decarboxylated FDOPA is taken into vesicles and may be released and metabolized further, its signal, particularly at longer scan times, is influenced by both vesicular uptake and postrelease processing (Sossi et al., 2002). In contrast, metabolized FMT in the form of 6-[^{18}F]fluoro-*m*-tyramine is not a good substrate for vesicular transporters (Endres et al., 1997). Because of this, most FMT signal results from tracer that has been metabolized by AADC

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Table 1. Participant characteristics

	Older	Younger
No. of participants	21	16
Age[a,b]	66.9 ± 7.7	22.8 ± 2.8
Males/females	6/15	6/10
Education[a,b]	18.4 ± 2.1	15.8 ± 1.4
Mini-Mental State Exam[a]	29.3 ± 1.0	29.4 ± 0.8
Listening Span test (total recalled)[a,b]	50.7 ± 9.1	60.2 ± 9.0
Digit Span Backward test (total)[a]	9.0 ± 2.8	8.4 ± 3.0
Controlled Oral Word Association (FAS) test (total)[a]	47.4 ± 10.4	49.1 ± 10.2
Category Fluency test (total)[a]	37.7 ± 7.6	39.9 ± 8.6
Stroop C Interference test (no. correct in 1 min)[a,b]	50.4 ± 12.1	64.1 ± 12.8
Wisconsin Card Sort test (% perseverative errors)[a,c]	11.1 ± 7.9	11.6 ± 5.7
Trail Making test (Trails B-A) (s)[a,d]	39.6 ± 38.9	25.7 ± 13.1
Composite frontal lobe function score[a,e,f]	−0.2 ± 0.7	0.3 ± 0.7
Average FMT signal in bilateral DCA	0.022 ± 0.003	0.019 ± 0.002
Bilateral DCA volume (mm^3)	3893 ± 698	4807 ± 921[g]
Bilateral DCA volume as % of intracranial volume	0.31 ± 0.04%	0.36 ± 0.07%[g]
DCA volume asymmetry (right–left) as % of intracranial volume	0.016 ± 0.014%	0.007 ± 0.008%[h]

[a]Demographic features are listed as mean ± SD.

[b]Significant difference between age groups ($p < 0.05$) as determined using a two-tailed Mann–Whitney test.

[c]Score for one younger adult was unavailable.

[d]Scores for two older adults were unavailable.

[e]See text for calculation.

[f]Significant difference between age groups ($p < 0.05$) as determined using a two-tailed unpaired *t* test.

[g]Significant difference between age groups ($p < 0.05$), but no significant correlation with FMT signal in bilateral DCA.

[h]Trend toward significant difference between age groups ($p = 0.06$), but no significant correlation with DCA FMT asymmetry.

and monoamine oxidase-A (MAO-A), and trapped in axon terminals as 6-[^{18}F]fluoro-*m*-hydroxyphenylacetic acid without being released or further processed (Jordan et al., 1997). FMT signal therefore more fully represents the extent of AADC activity (DeJesus et al., 2001). Several past studies have demonstrated age-related changes in enzymes that affect postrelease dopamine processing (Fowler et al., 1980; Saura et al., 1997; Rinne et al., 1998; Harada et al., 2002; van Dyck et al., 2002), potentially affecting the results of FDOPA studies. The *in vivo* relationship between AADC function alone and age has yet to be characterized in humans.

Materials and Methods

Subjects. Included in the study were 21 older (57–85; mean, 66.9) and 16 younger (20–30; mean, 22.8) cognitively intact adults (Table 1). Subjects were recruited via newspaper ads, flyers, and online postings. We excluded volunteers who were current smokers, hypertensive, or taking medications that could affect cognition or FMT signal. We also excluded all who were unable to undergo magnetic resonance imaging (MRI) or PET scanning for safety reasons or who had a history of neurological or psychological disorders, major systemic disease, drug or alcohol abuse, or serious head injury. Each subject underwent a full neuropsychiatric battery including tests of executive function, working memory, language, episodic verbal and spatial memory, motor response, and general cognitive function. All had a Mini Mental State Exam (Folstein et al., 1975) score of at least 26. Each scored low average or better for their age on the Wechsler Memory Scale (WMS) Auditory Immediate (Wechsler, 1987) age-adjusted summed score (which includes WMS Logical Memory Immediate score and WMS Verbal Paired Associates Immediate score), and on the Wechsler Adult Intelligence Digit Span (Wechsler, 1981) age-adjusted summed score (which includes Digit Span Forward and Digit Span Backward). No subject had a Geriatric Depression Rating (21 item) score >10 (Yesavage et al., 1982). All subjects provided written informed consent before enrolling in the study. Of the 21 older subjects in this study, 20 were reported on previously (Landau et al., 2008). Of the subjects included in the previous study, three were excluded from the current study: one whose PET data were unusable as previously reported, one for whom nearly all of the neuropsychological testing scores were unavailable, and one whose structural MRI scan was not useable for the partial volume correction (PVC) analysis performed here.

Frontal lobe function composite score. Past studies have demonstrated that performance on certain tests thought to depend on frontal lobe function, such as working memory (Mehta et al., 2001; Erixon-Lindroth et al., 2005; Alfimova et al., 2007), verbal fluency (Erixon-Lindroth et al., 2005; Alfimova et al., 2007), and executive function (Vernaleken et al., 2007b; Lane et al., 2008), may be modulated by the dopamine system in healthy adults.

Our neuropsychological battery contained seven tests of frontal lobe function: Listening Span (Daneman and Carpenter, 1980) and Digit Span (Wechsler, 1981), which measure working memory; Controlled Oral Word Association (FAS) (Benton and Hamsher, 1989) and Category Fluency, which measure verbal fluency; and Stroop C Interference (Stroop, 1935), Wisconsin Card Sort Test (WCST) (Heaton, 1993), and Trail Making (Trails B-A) (Reitan, 1958), which measure executive function. Trails B-A scores were not available for two older subjects.

To evaluate the relationship between dopamine synthesis capacity and frontal lobe function, we created a composite cognitive score. Using a composite score derived from several similar test scores both reduces measure variability that might be associated with any one score, and eliminates the need to control for multiple comparisons. To identify tests measuring similar aspects of frontal lobe function, we prepared a covariance matrix containing scores on each test across all subjects. Five tests emerged that were highly correlated with at least three of the other test scores using a Pearson correlation ($p < 0.05$): Listening Span total recall, FAS, Category Fluency total, Stroop C Interference, and Trails B-A (Table 1). Scores on these tests were normalized as *Z* scores within the sample. Because a high score on Trails B-A represented worse cognition, whereas a high score on the other four tests represented better cognition, the signs on the *Z* scores for Trails B-A were reversed before the five scores were averaged to create a composite cognitive score. The composite cognitive score was significantly correlated with each of the five established tests of frontal lobe function from which it was derived (R^2 values ranged from 0.54 to 0.64), suggesting that it was a valid measure of frontal lobe-dependent cognitive function. However, although these tests are all thought to measure frontal lobe cognitive function, it is important to note that the tasks are complex and also require abilities such as sensory and motor function that may rely on brain regions other than those thought to subserve the frontal lobe-dependent cognitive function we are trying to measure. Furthermore, the timescale of PET measurements (minutes to hours) is very different from the second to millisecond timescales involved in these cognitive processes.

PET data acquisition. FMT was synthesized at the Lawrence Berkeley National Laboratory as described previously (VanBrocklin et al., 2004). FMT is a well established PET tracer that has been used extensively to study animal models of aging (DeJesus et al., 2001; Eberling et al., 2002) and cognitive function (Cools et al., 2008; Landau et al., 2008), and to measure the effects of gene therapy related to AADC function (Eberling et al., 2008). Details on enzyme specificity, kinetics, and metabolism have been described previously (Srinivasan and Awapara, 1978; DeJesus et al., 1997; Jordan et al., 1997). Radiochemical synthesis for this study produced specific activities of ~1000–2000 mCi/mmol; thus, a typical injection of 3 mCi for a PET imaging experiment would result in a mass dose of the compound of ~3 μmol, which is unlikely to be pharmacologically active.

Subjects underwent PET scanning on a Siemens ECAT EXACT HR PET scanner in three-dimensional acquisition mode with retractable septae. Forty-seven parallel slices (4 mm thick; 3.6 mm in-plane voxel size) were acquired.

Subjects ingested 2.5 mg/kg carbidopa ~60 min before FMT injection. They were positioned on the scanner bed with a pillow and padding to comfortably restrict head motion. After a 10 min transmission scan obtained for attenuation correction, ~2.5–3.0 mCi of FMT were injected as

a bolus into an antecubital vein and a dynamic acquisition sequence in three-dimensional mode was obtained: 4 × 1 min, 3 × 2 min, 3 × 3 min, and 14 × 5 min for a total of 89 min of scan time.

We reconstructed data using an OSEM (ordered subset expectation maximization) algorithm with weighted attenuation, an image size of 256 × 256, and six iterations with 16 subsets. A Gaussian filter with 6 mm full width at half-maximum was applied, with a scatter correction. Images were evaluated for subject motion and adequacy of statistical counts.

MRI scanning. Within 6 months of each PET scan, an MRI scan was obtained using a Varian Unity/Inova whole-body 4.0 T scanner with a TEM send-and-receive head coil (MR Instruments). MPFLASH (magnetization-prepared fast low angle shot) T1-weighted volumetric scans were acquired for each subject (repetition time, 9 ms; echo time, 4.8 ms; field of view, 22.4 × 22.4 × 19.8 cm; matrix size, 256 × 256 × 128; resolution, 0.875 × 0.875 × 1.54 mm) to be used for region of interest (ROI) demarcation and brain matter masking for PVC of the PET data.

MRI analysis. Bias was removed from each MRI scan using the "FSL Automatic Segmentation Tool" (FAST) from version 3.3 of Oxford Centre for Functional MRI of the Brain "(FMRIB) Software Library" (FSL) (Zhang et al., 2001). Nonlinear noise was then reduced using SUSAN ("Smallest Univalue Segment Assimilating Nucleus") of FSL (Smith, 1992). A mask of MRI scan intracranial matter was automatically generated using the BET ("Brain Extraction Tool") of FSL (Smith, 2002). We then used "FSL view" to manually refine individual intracranial masks, which were next applied to the MRI scans to exclude voxels that did not represent brain matter or CSF. FAST was used to segment the skull-stripped brains into brain matter versus CSF. A binary mask of the brain matter alone was created for use in the PVC of the PET data. In addition, we calculated the whole brain matter percentage for each subject, defined as the volume of the brain matter mask divided by the intracranial volume.

PET reference region. Cerebellar masks were drawn in MRI native space on the coronal plane. The masks comprised two-thirds of the slices posterior to the last slice in which the superior cerebellar peduncles stretched superiorly. Including only these most posterior slices ensured that FMT signal from the substantia nigra and ventral tegmental area did not contaminate the reference region. The cerebellum was segmented automatically using FAST to exclude large white matter tracts. To determine whether FMT signal in the cerebellum contributed to our results, for each subject we calculated the average raw FMT cerebellar signal during the first, last, and center PET frames that were included in the final analysis. We compared values at each of the three time points across age groups using a two-tailed Mann–Whitney test. The older and younger groups did not have significantly different cerebellar FMT signal (frame 12, $p = 0.82$; frame 18, $p = 0.61$; frame 24, $p = 0.30$), signifying that choice of reference region did not influence our results.

PET data analysis. To control for between-frame subject motion, we used six parameter (rigid body) realignment algorithms in Statistical Parametric Mapping (SPM2) (Wellcome Department of Cognitive Neurology, University College London, London, UK). Each PET frame was realigned to the summed image of the first 10 frames. We then used SPM2 to realign the individual MRI scans (along with their accompanying cerebellar gray matter masks and their brain matter masks) to their respective summed PET images, which included considerable anatomic detail from early frames. Next, K_i images were generated using a graphical analysis method for irreversible binding (Patlak and Blasberg, 1985). The approach used a simplified reference tissue model (Lammertsma and Hume, 1996), producing a K_i image that was scaled to the volume of distribution in the reference tissue (cerebellum); we used the term K_i for simplicity. Scaled K_i images were created from PET frames corresponding to 24 through 89 min, using the cerebellar gray matter masks as the reference regions.

Partial volume correction. The accuracy of PET tracer measurements depends on the size of the object being measured relative to the effective resolution (point spread function) of the scanner. Apparent isotope concentrations are depressed for smaller items imaged in scanners with lower resolutions (Hoffman et al., 1979), a phenomenon known as partial volume error. These small items include image voxels that are composed partly of brain tissue (where a radiotracer signal is expected), and partly of CSF (where signal is not expected). Because of partial volume errors at brain/nonbrain boundaries, subjects with greater cortical atrophy or larger surface areas bordering on CSF typically demonstrate apparent PET signal attenuation, which may confound radiotracer parameter estimates. Correction for partial volume errors is necessary to render the data comparable (Tanna et al., 1991; Meltzer et al., 1996; Yanase et al., 2005; Park et al., 2006), especially when brain atrophy associated with aging may be present.

Evidence of the need for PVC may be found in several past *in vivo* studies of striatal dopamine synthesis having conflicting results in humans and nonhuman primates. Some of these studies have found age-related decreases in striatal PET signal using FDOPA or [^{11}C]DOPA as a PET tracer (Martin et al., 1989; Bhatt et al., 1991; Cordes et al., 1994; DeJesus et al., 2001; Harada et al., 2002; Ota et al., 2006), whereas others found no age effect (Sawle et al., 1990; Eidelberg et al., 1993; Ishikawa et al., 1996b). Some of these differences seem to be methodological. One PET study evaluated how differences in ROI size can influence the results of the FDOPA signal–age relationship. Specifically, striatal FDOPA signal declined significantly with age when PET-drawn ROIs that encompassed the full striatum were used. Conversely, when "small ROIs" composed of small circles throughout the center of the striatum were used, there was no significant effect of striatal FDOPA signal with age (Vingerhoets et al., 1994). One possible explanation for these contrasting results is that, using full striatal ROIs, there is a greater likelihood of partial voluming, which occurs in voxels that border on CSF or white matter. Such a partial volume effect would depress apparent PET signal more in atrophied brains, in which border voxels would compose a larger percentage of the ROI. Because brain atrophy is frequently associated with age (Raz et al., 1995), using full ROIs that have not been corrected for partial volume effects may result in an atrophy-related apparent decrease of PET signal with age and also may affect signal related to developmental striatal volume changes in young adults (Sowell et al., 1999; Bennett and Baird, 2006).

The current study used full striatal ROIs. However, unlike most previous studies, our FMT PET images were partial volume corrected to adjust for signal loss related to variable structure size. PVC was performed using a two-compartment model as described previously (Meltzer et al., 1999). Briefly, the regionally defined scanner point spread function specific to reconstructed data from our PET scanner was convolved with the binary brain matter mask. The corrected PET scan was then calculated as the observed PET signal divided by the convolved brain matter mask, which represented the percentage contribution of brain matter to signal in each voxel (Meltzer et al., 1999). All FMT signal values referenced in Results and Discussion are partial volume corrected unless otherwise noted.

Regions of interest. Dorsal caudate (DCA) and dorsal putamen (DPUT) were drawn on the individual MRI scans using "FSL view." All were drawn using guidelines outlined previously (Mawlawi et al., 2001). After individual MRI scans were coregistered to the corresponding PET images, an average intensity value for each ROI was calculated using the partial volume-corrected K_i image. This average intensity value represented the partial volume-corrected K_i for that ROI. The volumes of the ROIs also were calculated using FSL and were compared with FMT signal.

Depending on the extent to which variations in FMT signal within a brain region exist, the value from an ROI drawn on PET [as in some previous FMT studies (Cools et al., 2008; Landau et al., 2008)] and one drawn on MRI may be quite different. Conceptually, a PET-drawn ROI is one whose PET intensity has been visually thresholded such that only the strongest signal for each subject is included, whereas MRI-drawn ROIs are blind to PET intensity. As such, a PET-drawn ROI will tend to be smaller and will measure PET peak intensity. PET peak intensity will contribute to signal from an MRI-drawn ROI, but the extent of PET signal within the anatomical region will also contribute to the signal. If the percentage of a region having high PET signal were to change with age (e.g., a greater or lesser proportion of cells in a region contained detectable levels of enzyme activity), only an ROI drawn on MRI would identify that change. Although both methods are valid, they emphasize different aspects of the PET signal. MRI-drawn ROIs are necessary for unbiased

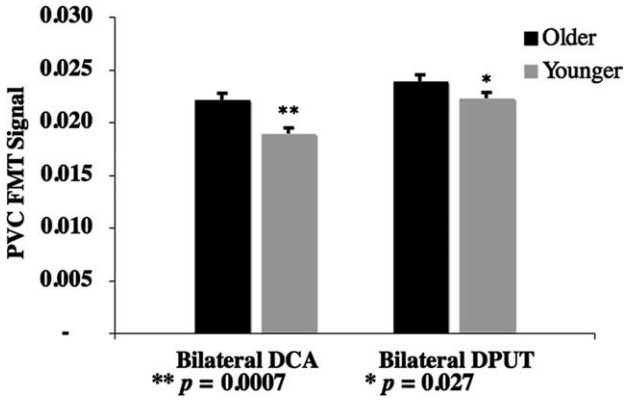

Figure 1. Striatal FMT signal by age. PVC FMT signal in both the bilateral DCA and the bilateral DPUT was significantly greater in older subjects compared with younger subjects (two-tailed Mann–Whitney test) (error bars represent SEM).

results when partial volume correction is performed, as in the current study.

Statistics. For comparisons between two groups or two variables whose data were not normally distributed according to a Jarque–Bera test of normality, we used nonparametric tests: the Spearman ρ rank correlation and the normal approximation of the two-tailed Mann–Whitney test. These tests were used for all comparisons unless otherwise noted. For normally distributed data, we used Pearson correlations or two-tailed unpaired *t* tests. To adjust for age in some comparisons, we used Spearman partial correlations (Schemper 1991). A Spearman partial correlation used here adjusts for age both in the dependent and independent variables in the same way that a Pearson multiple regression would. However, unlike a Pearson multiple regression, this test minimizes the effect of outliers if they exist and is valid even if the data are not normally distributed.

Results

Relationship between FMT signal and age

FMT values were significantly greater in older subjects than in younger subjects in bilateral DCA ($p = 0.0007$) and, to a lesser extent, in bilateral DPUT ($p = 0.027$) (Fig. 1).

This relationship was significant in both brain hemispheres (DCA left, $p = 0.002$; DCA right, $p = 0.001$; DPUT left, $p = 0.028$; DPUT right, $p = 0.036$). Because the relationship between age and K_i in striatum was similar in both hemispheres, for the remainder of this study, we used averaged bilateral K_i values when evaluating the relationship with age.

In addition to between-group striatal FMT signal differences, significant within-group relationships between K_i and age also existed. Specifically, in older adults, K_i in bilateral DCA increased with age (Spearman $\rho = 0.69$; $p = 0.0005$), whereas in younger adults, K_i in bilateral DCA decreased with age ($\rho = -0.76$; $p = 0.0007$) (Fig. 2*A*,*B*). These relationships were significant even when FMT signal was not corrected for partial volume effects ($\rho = 0.59$; $p = 0.005$ in older adults; $\rho = -0.79$; $p = 0.0003$ in younger adults), suggesting that the results were not an artifact of that process.

In older adults, bilateral DPUT ($\rho = 0.47$; $p = 0.032$) was significantly greater with age (Fig. 3); this effect was reduced to a trend when non-PVC FMT signal was used ($\rho = 0.40$; $p = 0.076$). There was no significant relationship between FMT signal in bilateral DPUT and age in the younger group (data not shown).

Relationship between FMT signal and structural volume

To determine whether volume or atrophy of the structures may have contributed to the relationships between age and K_i values,

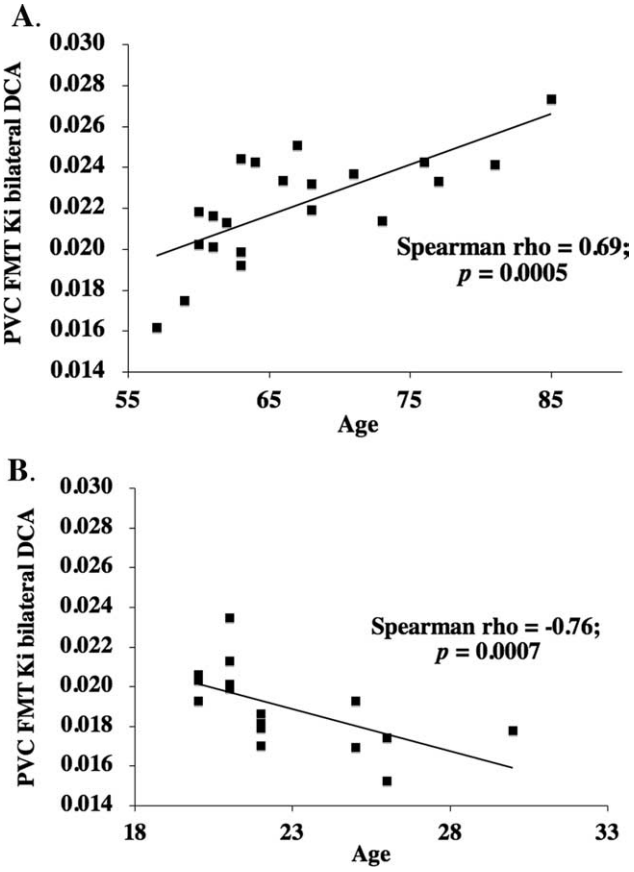

Figure 2. FMT signal in DCA versus age. In the older subjects (***A***), PVC FMT signal in bilateral DCA was higher with increased age, whereas in the younger subjects (***B***), the FMT signal in bilateral DCA was lower with increased age.

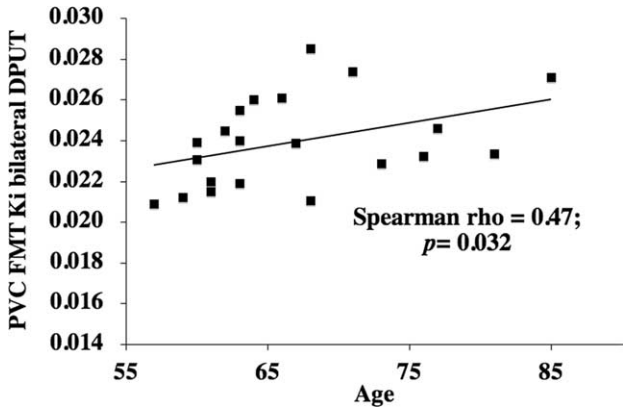

Figure 3. FMT signal in DPUT versus age. In the older subjects, PVC FMT signal in bilateral DPUT was higher with increased age. There was no significant relationship between age and FMT signal in bilateral DPUT in the younger subjects (data not shown).

we examined the relationship between FMT signal and total DCA volume. Total DCA volume was significantly greater in the younger group compared with the older subjects ($p = 0.005$). Total DCA volume as a percentage of intracranial volume, an indication of possible atrophy of that structure, was also larger in younger subjects ($p = 0.025$). However, FMT signal in bilateral DCA was not significantly correlated with either total DCA volume ($\rho = -0.15$; $p = 0.36$), or DCA volume as a percentage of intracranial volume ($\rho = -0.07$; $p = 0.67$), even after controlling for age group using Spearman partial correlation. To provide

additional evidence that our results were independent of ROI volume, we compared the hemispheric asymmetry in DCA volume with the hemispheric asymmetry in DCA K_i in the same subjects. DCA volume asymmetry was not significantly correlated with K_i asymmetry ($\rho = -0.09$; $p = 0.59$), suggesting that our results were independent of structure size and degree of atrophy (Table 1).

Table 2. FMT in right DCA versus cognitive performance in younger adults

	R^2 (full model)	p (full model)	R^2 (partial contribution of FMT to test score)	p (partial contribution of FMT to test score)
Composite frontal lobe function score[a,b]	0.38	0.045	0.38	0.01
Listening Span test (total recalled)	0.02	0.871	0.02	0.61
FAS test (total)[c]	0.31	0.086	0.31	0.03
Category Fluency test (total)[c]	0.36	0.056	0.27	0.04
Stroop C Interference test (timed no. correct)[c]	0.29	0.111	0.23	0.06
Trails B-A (s)[c]	0.31	0.089	0.26	0.04

To further investigate the significant relationship between FMT in right DCA and the composite cognitive scores in younger adults (after adjusting for age), we present above the statistical information for the relationships between FMT in the right DCA and the individual test scores that compose the composite cognitive score. The dependent variable in each Spearman partial correlation was the cognitive test score. FMT in right DCA and age were used as independent variables. For all cognitive scores showing trends or significant relationships, higher FMT was associated with worse test performance.

[a]Higher FMT signal is significantly correlated with a worse cognitive score ($p < 0.05$).

[b]Composed of scores from the five tests listed above (see Materials and Methods).

[c]Trend exists toward higher FMT signal being associated with a worse test score.

Relationship between FMT signal in DCA and cognition

In the younger adults, the composite cognitive score was significantly lower in those having higher FMT signal in right DCA, even after controlling for age using a Spearman partial correlation that included FMT signal and age as independent variables [R^2 (full model) = 0.38; p (full model) = 0.045; R^2 (partial contribution of FMT) = 0.38; p (partial contribution of FMT) = 0.01]. As expected, there was no significant correlation between FMT signal in the control region (right DPUT) and the composite cognitive score [R^2 (full model) = 0.07; p (full model) = 0.60; R^2 (partial contribution of FMT) = 0.07; p (partial contribution of FMT) = 0.32]. To further investigate the significant relationship in DCA, we performed Spearman partial correlations on each of the tests included in the composite cognitive score (Table 2). Although, in the younger adults, FMT signal in right DCA was significantly correlated with that in left DCA ($\rho = 0.51$; $p = 0.04$), the relationship between composite cognitive score and age-adjusted FMT signal in left DCA in younger adults was not significant using the Spearman partial correlation [R^2 (full model) = 0.15; p (full model) = 0.36; R^2 (partial contribution of FMT) = 0.14; p (partial contribution of FMT) = 0.16]. In older adults, the composite cognitive score was not significantly correlated with FMT signal in left DCA [R^2 (full model) = 0.03; p (full model) = 0.75; R^2 (partial contribution of FMT) = 0.03; p (partial contribution of FMT) = 0.49] or right DCA [R^2 (full model) = 0.01; p (full model) = 0.88; R^2 (partial contribution of FMT) = 0.01; p (partial contribution of FMT) = 0.68] after adjusting for age.

Relationship between cognition and brain structure

In the younger group, the composite cognitive score was highest in those subjects having lower (whole brain) brain matter volume as a percentage of intracranial volume ($\rho = -0.55$; $p = 0.03$). Percentage brain matter was not significantly correlated with the composite cognitive score in older subjects.

Discussion

K_i values in bilateral DCA and DPUT were significantly greater with increased age both between age groups and within our older group alone, suggesting an upregulation of AADC function with age. In contrast, past studies using postmortem brain tissue have reported declines in AADC activity with age (Lloyd and Hornykiewicz, 1972; McGeer and McGeer, 1976), but with variable results in part because of susceptibility of AADC activity to postmortem conditions (Kish et al., 1995). Additionally, enzyme activity measured in brain homogenate ignores modulation from distant brain regions. Other postmortem studies found slightly decreased (Kish et al., 1995) or unchanged (Haycock et al., 2003) AADC protein levels (instead of activity) with age. Kish et al. (1995) surmised that mild decreases in AADC levels, given the larger decreases in dopamine noted previously, indicated increased AADC activity in remaining dopaminergic cell terminals. *In vivo* techniques such as PET provide a means for testing this hypothesis.

Two studies have examined how FMT uptake in monkey striatum relates to age. Neither showed between-age group differences in striatal K_i values (DeJesus et al., 2001; Eberling et al., 2002). However, when K_i values were correlated with age as a continuous variable in one study, a significant age-related increase in striatal FMT signal emerged, accompanied by an age-related decrease in striatal FDOPA signal in the same animals (DeJesus et al., 2001).

Because FDOPA, but not FMT, may be taken into vesicles, released, and processed further, it is unsurprising that only FDOPA shows an age-related decrease in striatal signal. At ~90 min after injection, FDOPA deviates from acting as an irreversible tracer (Sossi et al., 2002), but in most FDOPA studies showing an age-related decline in striatal PET signal, scans lasted 120 min (Martin et al., 1989; Bhatt et al., 1991; Vingerhoets et al., 1994; DeJesus et al., 2001). Therefore, noticeable clearance of the tracer and its metabolites from axon terminals was probably underway by the completion of those scans. Past studies have demonstrated age-related decreases in binding to vesicular transporters (Scherman et al., 1989) and dopamine transporters (DATs) (Ishikawa et al., 1996b; Rinne et al., 1998; Harada et al., 2002; van Dyck et al., 2002; Haycock et al., 2003; Tupala et al., 2003), both of which may be reflected in FDOPA PET scans as lower signal. Likewise, research has shown age-related increases in MAO-B activity (Fowler et al., 1980; Saura et al., 1997), which participates in dopamine (and FDOPA) catabolism. Such catabolism may lead to clearance of the resulting metabolites from the brain (DeJesus et al., 2001; Sossi et al., 2002). Therefore, age-related changes in MAO-B activity could also result in decreased FDOPA signal with age, independent of AADC activity. Although FMT metabolites are substrates for MAO-B, the resulting product clears very slowly from the brain and actually comprises most of the tracer signal. Changes in MAO-B activity are therefore not expected to affect FMT signal (DeJesus et al., 2005).

Age-related increases in FMT K_i may seem counterintuitive given the striatal dopamine decreases with age seen in some (Adolfsson et al., 1979; Irwin et al., 1994; Cruz-Muros et al., 2007) but not all (Collier et al., 2007) studies. However, AADC is only one feature of the system that results in available dopamine. Greater age-related catabolism of dopamine by MAO-B (Fowler et al., 1980; Saura et al., 1997) may reduce dopamine in the synaptic cleft, whereas lower DAT activity (Ishikawa et al., 1996b; Rinne et al., 1998; Harada et al., 2002; van Dyck et al., 2002;

Haycock et al., 2003; Tupala et al., 2003) may increase it. Furthermore, in evaluating dopamine synthesis, neither FMT nor FDOPA signal reflects the activity of tyrosine hydroxylase (TH), which converts L-tyrosine to L-DOPA and is the rate-limiting step in dopamine synthesis. L-DOPA is the natural substrate for AADC. Therefore, if L-DOPA levels were to decrease with age, AADC activity also would decline. However, the addition of exogenous AADC substrates (FMT and FDOPA) would mask this effect during scanning. Aging studies of TH levels have been inconclusive, with some (Haycock et al., 2003; Cruz-Muros et al., 2007), but not all (Wolf et al., 1991; Weickert et al., 2007), finding decreases with aging. Because FMT signal measures dopamine synthesis capacity given sufficient substrate, increased FMT uptake could occur in concert with increases or decreases in available dopamine depending on the activity of other dopamine system enzymes.

AADC activity and protein concentrations upregulate in response to declining dopaminergic signaling (Zhu et al., 1992, 1994; Hadjiconstantinou et al., 1993; Ishikawa et al., 1996a; Lee et al., 2000). It is conceivable that (as suggested by our study) such upregulation takes place with aging, reflecting well established age-related decreases in dopamine receptor expression and binding (Severson et al., 1982; Seeman et al., 1987; Suhara et al., 1991; Antonini and Leenders, 1993; Volkow et al., 1996; Ichise et al., 1998; Pohjalainen et al., 1998; Wang et al., 1998; Kaasinen et al., 2000; Weickert et al., 2007), and possible age-related loss of dopaminergic neurons or nerve terminals (Kim et al., 2006; Collier et al., 2007).

Past research supports modulation of striatal dopamine synthesis via available dopamine within both striatum and frontal cortex. Decreased binding of dopamine to D_2 autoreceptors within striatum is associated with increased striatal dopamine synthesis and release (Watanabe et al., 1987; Westerink and de Vries, 1989). Likewise, damage to frontal lobe dopaminergic terminals and reductions in frontal lobe dopamine receptor availability enhance dopamine concentrations in striatum by reducing the inhibition of glutamatergic pathways between frontal cortex and striatum (Pycock et al., 1980; Chéramy et al., 1986; Rosin et al., 1992; Roberts et al., 1994). Our data suggest that increased striatal FMT signal indicates compensation for nonoptimal functioning of the dopamine system within the striatum and functionally connected regions.

In contrast to our older subjects, younger adults showed an age-related decrease in DCA FMT signal. Similarly, previous studies comparing adolescents and younger adults to those >30 have found associations between youth and elevated levels of striatal and frontal lobe dopamine (Wenk et al., 1989; Collier et al., 2007), higher DAT binding (Zelnik et al., 1986; Mozley et al., 1999), greater dopamine receptor binding and expression (Antonini and Leenders, 1993; Weickert et al., 2007), and lower catechol-*O*-methyltransferase (COMT) activity in prefrontal cortex (Tunbridge et al., 2007). Working memory, which relies on dopamine signaling (Cai and Arnsten, 1997; Goldman-Rakic et al., 2000), also does not reach peak ability until late adolescence or early adulthood (De Luca et al., 2003; Luna et al., 2004; Clark et al., 2006). Finally, past research has demonstrated that only frontal and striatal structures showed developmental volume reductions between adolescence and early adulthood (Sowell et al., 1999). Together, these studies suggest that, in young adulthood, the still-developing dopamine system has not yet been honed to provide optimal adult dopamine levels. In younger adults, age and FMT values were not significantly correlated in DPUT, whose major connections, unlike those of DCA, are not to the late-developing prefrontal cortex (Alexander et al., 1986).

In normal adults, performance on certain tests of frontal lobe-dependent cognition may be modulated by the dopamine system endogenously via genotypes (Egan et al., 2001; Mattay et al., 2003; Blasi et al., 2005; Bertolino et al., 2006; Apud et al., 2007; Caldú et al., 2007; Starr et al., 2007; Zhang et al., 2007; Roussos et al., 2008) or exogenously using pharmaceuticals (Roesch-Ely et al., 2005; Gibbs and D'Esposito, 2006; Apud et al., 2007). Past work also has found significant correlations between frontal lobe cognition and FMT, FDOPA, and D_2 receptor binding (Bäckman et al., 2000; Vernaleken et al., 2007b; Cools et al., 2008; Landau et al., 2008). In our study, after controlling for age, younger adults showed lower composite cognitive scores with increased FMT signal in right DCA, which is connected to frontal cortex (Alexander et al., 1986). These results support our hypothesis that increased striatal FMT signal represents nonoptimal brain dopamine levels. It is unclear why these results were unilateral, although asymmetries in the dopaminergic system have been noted (Vernaleken et al., 2007a). As expected, the composite cognitive scores were not significantly correlated with FMT signal in the control region (right DPUT), whose major cortical connections are with the supplementary motor area (Alexander et al., 1986). In older adults, DCA FMT signal was not correlated with composite cognitive scores, although past research found a positive correlation between working memory performance and caudate FMT signal using an overlapping subject pool (Landau et al., 2008). This apparent discrepancy arises from methodological differences: specifically, differences in ROI methods and PVC as well as cognitive tests examined (composite cognitive score currently vs Listening Span and Sternberg accuracy scores previously). Although striatal FMT signal was not significantly correlated with the composite cognitive scores in the older adults, this does not preclude dopamine synthesis capacity from contributing to cognitive ability. Cognitive ability, particularly during aging, is influenced by many factors (including those outside the dopamine system) that may obscure the relationship between FMT signal and cognition in this study. Inclusion of more subjects or use of techniques that measure brain activity (such as functional MRI) during a cognitive task may allow us to link cognition to FMT signal in future studies.

Our results suggest that higher FMT signal indicates nonoptimal dopamine system functioning during development and aging. We hypothesize that age-related modulation of striatal FMT reflects dopamine system deficits both in striatum and the connected frontal cortex. Future FMT studies that include evaluation of COMT effects may elucidate interactions between frontal lobe dopamine levels and striatal dopamine synthesis.

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