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Dopamine Transporters Decrease with Age

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Postmortem studies have documented degeneration of dopamine cells with age, but the changes that occur in healthy aging individuals is less clear. The purpose of this study was to evaluate the extent to which age-induced changes in dopamine transporters occur in subjects with no evidence of motor impairment. **Methods:** We evaluated 23 right-handed healthy volunteers (age range 20–74 yr) using PET and [^{11}C]*d-threo*-methylphenidate. The ratio of the distribution volume for [^{11}C]*d-threo*-methylphenidate in striatum to that in cerebellum was used as model parameter for dopamine transporter availability (Bmax/Kd + 1). **Results:** Dopamine transporter availability was significantly lower in subjects >40 yr of age than in those <40 yr. Estimates of dopamine transporter availability showed a significant negative correlation with age both for the putamen ($r = -0.72$, $p < 0.0001$) and the caudate ($r = -0.74$, $p < 0.0001$). Dopamine transporter availability was higher in the left than in the right putamen but did not differ between the left and right caudate. **Conclusion:** This study documents a 6.6% decrease per decade of life in striatal dopamine transporters of healthy volunteers.

Key Words: PET; dopamine transporters; degeneration

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According to projections by the U.S. Bureau of the Census, the number of individuals 65 yr and older will more than double by the middle of the next century to nearly 79 million. Whereas about 1 in 8 Americans were elderly in 1990, about 1 in 5 could be elderly in the year 2030 (*1*). This progressive increase in the elderly population places a sense of urgency on understanding the neurochemical changes accompanying normal aging. Aging is associated with changes in several neurotransmitters (*2*) as well as changes in specific motor, cognitive and emotional behaviors (*3*). The dopaminergic system appears to be among the most age-sensitive neurotransmitters (*4*). Of the behavioral changes associated with aging, the most conspicuous are those related to motoric function. For example, aging is associated with a higher frequency of dyskinesias (*5–6*) and of mild Parkinson-like motor changes such as rigidity (*7*). Some of these motoric changes may reflect an age related decline in nigrostriatal dopaminergic function (*8*).

Studies in animals as well as postmortem human brain studies, have in general documented a decline in brain dopamine activity with aging (*9,10*). Recently, imaging techniques such as PET and SPECT have enabled the measurement of changes in dopamine parameters as a function of age in living human subjects. Most of these studies have focused on dopamine receptors and have documented a decrease in D2 and D1 receptor density with aging (*11–18*). Changes in dopamine receptors, however, predominantly reflect changes in postsynaptic elements presumably GABAergic, muscarinic and glutamatergic neurons and not changes in dopaminergic neurons. Few studies have been conducted on age-related changes in dopamine neurons in living human subjects. Age changes in the dopamine neurons of living human subjects have been studied, using PET and SPECT tracers, to measure dopamine metabolism and dopamine transporter sites. Studies using [^{18}F]fluoro-DOPA to measure dopamine metabolism have been inconclusive documenting reduced uptake (*19*) as well as no changes (*20,21*). Preliminary studies using [^{11}C]nomifensine (*22*), [^{11}C]cocaine (*23*) and [^{123}I]β-CIT (*24*) as ligands for the

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dopamine transporters have documented decreases in dopamine transporter sites with aging whereas studies using [^{11}C]WIN 35 428 have not (*25*).

This report shows the effects of age on dopamine transporters in 23 normal healthy subjects using [^{11}C]*d-threo*-methylphenidate, a new PET ligand with a higher sensitivity and specificity than that of [^{11}C]nomifensine and [^{11}C]cocaine. We proposed [^{11}C]*d-threo*-methylphenidate, the more active enantiomer of methylphenidate, as a PET ligand for the dopamine transporter (*26*). Carbon-11-*d-threo*-methylphenidate binding is inhibited by drugs that bind to the dopamine transporter, but not by drugs that inhibit the norepinephrine and the serotonin transporters indicating its selectivity for the dopamine transporter (*26*). Carbon-11-*d-threo* methylphenidate binding in the human brain is reversible, highly reproducible and saturable and its kinetics are ideally suited for quantitation (*27*). The results from this study were compared with those previously obtained with PET and [^{11}C]cocaine (*28*).

MATERIALS AND METHODS

Subjects

Twenty-three right-handed healthy volunteers (14 men, 9 women; aged 20–74 yr) were screened for absence of medical, neurological or psychiatric disease. Subjects in need of medication and/or with a past or present history of alcohol or drug use (except for caffeine) were excluded. Prescan tests ensured absence of psychoactive drug use. Informed consent was obtained following the guidelines of the Human Studies Review Committee at Brookhaven National Laboratory.

PET Scan

PET studies were performed with a whole-body, high-resolution PET 6 × 6 × 6.5 mm FWHM, 15 slices. To ensure accurate positioning of subjects in the PET camera, an individually molded headholder was made for all subjects. The head of the subject was positioned in the gantry with the aid of two orthogonal laser lines, one of which was placed parallel to the canthomeatal line and the other parallel to the sagittal plane. A chin-strap device was used to minimize movement of the head during the scan. Prior to [^{11}C]*d-threo*-methylphenidate injection, transmission scans were obtained to correct for attenuation. In preparation for the study, subjects had two catheters implanted, one in an antecubital vein for tracer injection and the other in the radial artery for blood sampling. Dynamic scans were obtained immediately after injection of 4–8 mCi [^{11}C]*d-threo*-methylphenidate (specific activity > 0.4 Ci/μM at time of injection). A series of 20 emission scans was obtained from time of injection up to 84 min (four 15-sec, two 30-sec, four 1-min, four 2-min, five 10-min and one 20-min scan).

Arterial Input Function

Total ^{11}C and unchanged [^{11}C]*d-threo*-methylphenidate in plasma were quantified in arterial plasma samples. Arterial blood was obtained using an automated blood sampling device every 2.5 sec for the first 2 min and then drawn manually every minute from 2–5 min and then at 10, 15, 20, 30, 45 and 90 min.

A solid-phase extraction system developed in our laboratory and implemented by a robot was used to quantify [^{11}C]*d-threo*-methylphenidate in plasma samples taken at 1, 5, 10 and 30 min. Whole blood was collected in centrifuge tubes containing sodium fluoride (1 mg/ml) to inhibit plasma esterases. After centrifugation, aliquots of plasma were counted for total radioactivity. Plasma (0.05 ml–0.4 ml) was mixed with 5 ml water and applied to activated Varian BondElut cyanopropyl cartridges (500 mg). A series of four solvent rinses was used to remove the metabolite fractions (2 × 5 ml deionized water followed by 2 × 50% methanol). The radioactivity remaining on the cartridge represented unchanged tracer. Solid phase analysis was validated by HPLC analysis of plasma. The stability of [^{11}C]*d-threo*-methylphenidate to racemization was assessed using a chiral HPLC system described previously (*26*).

Image Analyses

Regions of interest (ROIs) were drawn on the individual's averaged emission scan obtained by averaging the activity from 10–84 min after injection of the tracer. ROIs for striatum (caudate and putamen) and cerebellum from each subject's averaged images were then projected to his/her corresponding dynamic emission scans. ROIs were obtained in two planes and left and right regions were obtained in each plane. A weighted averaged value was then obtained for the left and right caudate, the left and right putamen and the cerebellum. To compare the current results with those previously obtained with [^{11}C]cocaine, we also computed a striatal measure using the weighted average of left and right caudate and putamen. A detailed description for the procedure has been published (*27*).

Binding of [^{11}C]*d-threo*-methylphenidate was quantified using distribution volumes calculated using a graphical analyses technique for reversible systems (*29*). The ratio of the distribution volume in striatal to that in cerebellum (DV_{ST}/DV_{CB}) which corresponds to $Bmax/K_d + 1$, was used as model parameter of dopamine transporter availability. The distribution volume provides a measure of binding that is a linear function of receptor availability given by:

$$DV = K_1/k_2'(1 + NS + Bmax/Kd'), \quad \text{Eq. 1}$$

for regions containing receptors characterized by an equilibrium dissociation constant Kd′ and free receptor concentration, Bmax. For nonreceptor regions the distribution volume is given by:

$$DV = K_1/k_2'(1 + NS). \quad \text{Eq. 2}$$

In both equations, NS represents the ratio of transfer constants for nonspecific binding, K_1 and k_2' are the plasma to tissue and the tissue to plasma transport constants, respectively. A parameter proportional to Bmax can be obtained from Equation 1 and 2 giving

$$\frac{Bmax/K_d'}{1 + NS} = \frac{DV_{ROI}}{DV_{CB}} - 1. \quad \text{Eq. 3}$$

Equations 1 and 2 are based on classical compartmental analysis in which the effects of cerebral blood flow and capillary permeability are implicitly included in the parameters K_1 and k_2'. The advantage of the distribution volume is that it is easily determined by a graphical technique derived from classical compartmental equations, it is not a function of blood flow (*30*) and it is a more stable measure than the individual kinetic constants determined directly by compartmental analysis, which are sensitive to noise and statistical fluctuations in the data (*31*). The ratio of distribution volume for the striatal to cerebellum eliminates possible differences in the K_1/k_2 ratio between experiments. The distribution volume measures were also used to generate images of the distribution volumes for [^{11}C]*d-threo*-methylphenidate in the brain of a young and an old subject. The graphical technique was used to generate distribution volume images as described previously (*28*).

Subjects were divided into two groups, one with subjects less than 40 yr of age (n = 13; average age 29.4 ± 6.8 yr) and the other with subjects more than 40 yr old (n = 10; average age 61.4 ± 12.7 yr). Differences in estimates of $Bmax/Kd$ ($DV_{ST}/DV_{CB} - 1$) between these two groups of subjects were tested with unpaired

t-tests. Correlation analyses were performed using Pearson product moment correlation analysis between the estimates of Bmax/Kd (caudate and putamen) and age. Estimates of dopamine transporter loss per decade, as assessed by Bmax/Kd were obtained using the values from the regression slopes. For the study with [^{11}C]cocaine measures of Bmax/Kd were obtained by subtracting one from the published DV_{ST}/DV_{CB} measures (*23*).

Differences in dopamine transporter availability between left and right caudate, left and right putamen and the differences between caudate and putamen were tested with paired Student t-tests. The differences in the correlations with age between caudate versus putamen and between left striatum versus right striatum were evaluated using the Olkin and Finn method (*32*).

TABLE 1
Dopamine Transporter Availability (Bmax/Kd Estimates)

Subjects	Right putamen	Left putamen	Right caudate	Left caudate
Younger group <40 yr (n = 13)	1.86 ± 0.24	2.00 ± 0.33	1.77 ± 0.24	1.68 ± 0.19
Older group >40 yr (n = 10)	1.37 ± 0.20‡	1.51 ± 0.33*	1.11 ± 0.30†	1.17 ± 0.35†

Values correspond to means and s.d. (Significant differences between groups * = $p < 0.005$, † $p < 0.001$, ‡ $p < 0.0001$).

RESULTS

Dopamine transporter availability in caudate and putamen was significantly lower in the older group of subjects (Table 1). Figure 1 shows images for the distribution volumes maps of [^{11}C]*d-threo*-methylphenidate in the brain of a 34-yr-old and in the brain of a 68-yr-old.

The correlation between age and the estimates of Bmax/Kd (ratio of the distribution volume in striatum to that in cerebellum-1) was significant both for the caudate ($r = -0.74$, $p < 0.0001$) and putamen ($r = -0.72$, $p < 0.0001$) indicating a decline in the availability of dopamine transporter sites with age. There were no significant differences in the Bmax/Kd correlation with age between caudate versus putamen and between left versus right striatal regions (Table 2). The rate of decline of Bmax/Kd estimates in the striatum was approximately 6.6% per decade and was comparable to that obtained with [^{11}C]cocaine in a group of 26 healthy volunteers (aged 21–63 yr) where the estimated decline corresponded to 7%. Figure 2 shows the regression slopes between age and dopamine transporter availability in striatum for the current study and for the study done with [^{11}C]cocaine (*23*). Table 3 compares the results obtained in this study with those previously published and shows a rate of decline of dopamine transporters that ranges between 6.6%–8.0% per decade for these imaging studies.

Comparisons between left and right striatal regions showed significantly higher values for dopamine transporter availability in the left than in the right putamen. No differences between left and right caudate were noted (Table 2). Measures of dopamine transporter availability were also higher in the putamen than in the caudate (Table 2).

DISCUSSION

The dopamine neurons display a special vulnerability in normal aging. Postmortem studies have documented a decrease of 4.7% per decade in nigrostriatal neurons in the normal human brain (*33*). The results from the present study demonstrate a significant loss of dopamine transporters in caudate and putamen in healthy human volunteers. Within the 20–80 yr decade we observed an average loss of ~40%. This rate of loss is similar to what we observed when we used PET and [^{11}C]cocaine to measure changes of dopamine transporters with aging (7% decline per decade) (*23*). These results are also in agreement with findings previously reported by a PET study employing [^{11}C]nomifensine (*22*) as tracer and by a SPECT study employing [^{123}I]β-CIT (*24*). Though one PET study done with [^{11}C]WIN 35428 failed to show an age-related decline in dopamine transporters, it was done in a very small sample of subjects (*25*). The results from these imaging studies are summarized in Table 3. The imaging studies are also in agreement with human postmortem studies (*34,35*). Though imaging studies do not seem to document a decrease in dopamine metabolism with age (reviewed in ref. 21), such results are not incompatible with an age-related decline in dopamine transporters since studies have shown a compensatory increase in dopamine synthesis when presynaptic dopamine terminals are destroyed (*36*).

This study did not document differences in the rate of decline of dopamine transporters between the caudate and the putamen nor between the left and right striatum. These results are similar

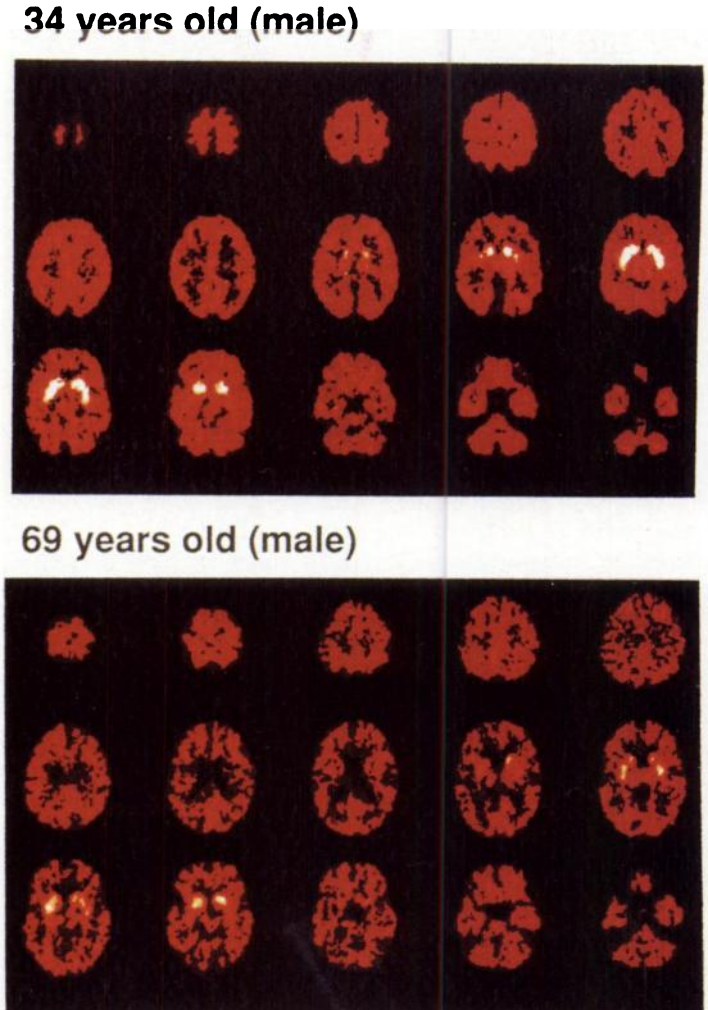

FIGURE 1. Maps of the distribution volume of [^{11}C]*d-threo*-methylphenidate in the brains of a 34-yr-old and a 68-yr-old subject. Notice the significant decreases in the distribution volume in the striatal regions of the older subject when compared to the younger one. Images from the two subjects were normalized with respect to each other. The highest distribution volume pixel values are displayed in yellow and intermediate distribution volume values are displayed in red.

to postmortem data which have shown that the rate of striatal dopamine loss is similar for the caudate than for the putamen (*37*). The results, however, differ from imaging studies in dopamine D2 receptors where it was found that there was a larger decrease in D2 receptors with age in putamen than in caudate (*15*). The rate of striatal D2 decline documented by imaging studies which has been estimated to be 4%–6% per decade (*14*) is similar to the rate of decline for dopamine transporters. The relation between the age related decline in dopamine D2 receptors and the degeneration of dopamine neurons has not been investigated. Such a study is required in order to determine if the decreases in dopamine D2 receptors are primary or whether they represent an adaptation to the age related decline in dopamine neurons.

In this study, the values for the dopamine transporters were higher in the left than in the right putamen, but there were no differences between the left and the right caudate. Asymmetries for the concentration of dopamine D2 receptors were documented in a PET study done with [^{11}C]raclopride which showed higher values for the left than for the right putamen but no asymmetries in the caudate of schizophrenic subjects (*38*). Autoradiographic studies in the rat have also revealed an asymmetric concentration of D2 receptors in striatum (higher in the right than in the left) (*39*). The asymmetric findings from the current study should be interpreted cautiously since slight tilting in the positioning of subjects in the scanner could generate asymmetries. The higher dopamine transporter concentration in the putamen than caudate parallels the D2 receptor findings where a higher concentration for the putamen than for the caudate has also been reported (*38*). Because of the limited spatial resolution of the instrument and the fact that the caudate has a smaller volume in the axial images than the putamen, this finding could reflect the different recovery coefficient for these two regions.

Future imaging work using MRI to corregister the PET images may enable evaluation of the extent to which there is a differential concentration of dopamine transporters between the left and right putamen and between the caudate and putamen. If replicated, the functional significance of the asymmetric findings in dopamine transporter availability and their relation to the dopamine D2 striatal receptor asymmetry would merit further investigation. Coregistration with MRI will also enable correction for possible age-related volumetric changes in striatal regions. This is relevant in that striatal atrophy may be an important confounding element in the analysis of regional tracer binding in normal aging.

The decline in dopamine transporters observed with age could reflect a decrease in presynaptic dopamine terminals and/or a decrease in dopamine transporter availability in a given terminal. The estimates of dopamine transporter cell loss, 6.6% per decade, for the current study with [^{11}C]*d-threo*-methylphenidate and 7% per decade, for the study with [^{11}C]cocaine, are slightly larger than the estimated 4.7% loss per decade of

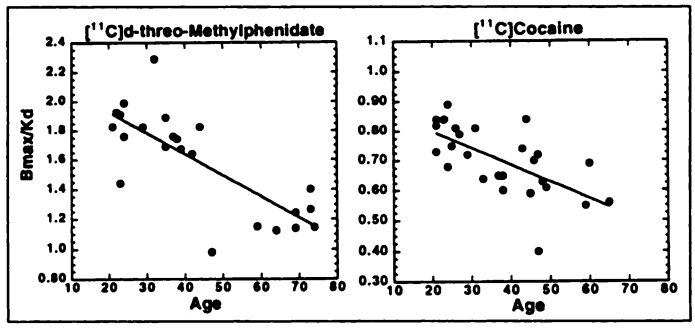

FIGURE 2. Correlation between age and the Bmax/K_d estimates (DV_{ST}/DV_{CB} − 1) obtained in the current study with [^{11}C]*d-threo*-methylphenidate ($r = -0.77$, $p < 0.0001$) and that previously obtained in a different group of subjects with [^{11}C]cocaine ($r = -0.65$ $p < 0.0005$) (*23*). Differences in the scale of the ordinate reflects differences in the range of values for the Bmax/K_d estimates between [^{11}C]*d-threo*-methylphenidate and [^{11}C]cocaine.

nigrostriatal neurons in the normal human brain (*33*). This could reflect the fact that in addition to dopamine cell loss, the decline may also represent reduction of dopamine transporter synthesis as demonstrated by a recent study showing a marked reduction in mRNA for the dopamine transporter with advancing age (*40*). There is evidence that with age there is a decline in dopamine transporters that is larger than that accounted by dopamine cell loss (*40*). One could speculate that with neuronal dopamine loss, the cells may compensate by decreasing dopamine transporter synthesis leading to higher synaptic dopamine concentrations since the dopamine would not be removed as effectively from the synaptic cleft. Preliminary data on rhesus monkeys indicate that dopamine clears slower in the putamen of older than younger animals (*41*). Investigation of the mechanisms regulating the rate of dopamine transporter synthesis may help clarify the decline of dopamine transporters with aging and its functional significance.

Additionally, because dopamine transporters have been found to upregulate or downregulate in response to drugs that change dopamine concentration (*42*), it could be argued that the changes in dopamine transporters could represent adaptations to age related changes in dopamine concentration. This is unlikely since most studies have failed to document a decrease in extracellular dopamine concentration with aging (*37*). Relatively normal extracellular dopamine concentration with aging may reflect an increase in dopamine turnover rate by the remaining dopamine neurons (*37*) and/or changes in the extracellular clearance of dopamine (*41*). In interpreting the functional significance of the decline in dopamine transporters with aging it is useful to compare the magnitude with that observed in patients with Parkinson's disease. We obtained data with [^{11}C]*d-threo*-methylphenidate in only one patient with Parkin-

TABLE 2
Dopamine Transporter Availability (Bmax/K_d Estimates)

Region	Left	Right
Putamen	1.79 ± 0.41	1.65 ± 0.33*
Caudate	1.46 ± 0.37†	1.48 ± 0.42†

Values correspond to means and s.d. *Significant differences between left and right regions ($p < 0.01$); †significant differences between ipsilateral caudate and putamen ($p < 0.0001$).

TABLE 3
Imaging Studies of Dopamine Transporters in Healthy Volunteers

Tracer	Subjects	Age range (yr)	% Decline per decade
[^{11}C]nomifensine (*22*)	7 (6M, 1F)	24–81	na
[^{11}C]cocaine (*23*)	27 (27M)	21–63	7%*
[^{123}I]β-CIT (*24*)	28 (14M, 14F)	18–83	8%
[^{11}C]WIN 35428 (*33*)	10 (5M, 5F)	19–81	none
[^{11}C]*d-threo*-methylphenidate	23 (14M, 9F)	20–74	6.6%*

*Obtained from changes in Bmax/Kd estimates ($DV_{ST}/DV_{CB} - 1$). All studies, except for (*24*), documented an age-related decline in dopamine transporters.

son's disease. In this 58-yr-old L-DOPA responsive woman with a 12-yr history of Parkinson's disease and a Yahr score of 3, the estimates for dopamine transporter availability (Bmax/Kd) in caudate corresponded to 0.37 and those in putamen to 0.14. These values were much lower than those in normal subjects and were 32% for caudate and 10% for putamen of those in the older group of subjects. Future studies will enable us to determine the sensitivity of [^{11}C]*d-threo*-methylphenidate for detecting early stages of Parkinson's disease.

This study replicates previous [^{11}C]*d-threo*-methylphenidate findings obtained with [^{11}C]cocaine as the ligand for the dopamine transporter. Thus, one could question the advantage of one ligand versus the other. This study cannot determine the relative differences in sensitivity of both ligands since that would have required testing the same group of subjects. We have previously described the advantages of [^{11}C]*d-threo*-methylphenidate over those of [^{11}C]cocaine as a dopamine transporter ligand (*27*). Briefly, these include better counting statistics, higher specific-to-nonspecific binding ratios and insensitivity to competition with endogenous dopamine (*43*).

In interpreting the effects of aging on crossover design studies like the current one, it is important to realize that cohort effects can affect the results obtained. Also, the limited sample size of subjects investigated, particularly in the 40–50-yr age range, limits an accurate assessment of the rate of loss of dopamine transporters per decade of life. Longitudinal studies in larger samples will allow controlling for possible cohort effects and will enable better quantification of the rate of dopamine transporter loss throughout the different age decades.

CONCLUSION

This study documents a significant decline in dopamine transporters with age in healthy normal volunteers. Older subjects had 25%–37% lower values than the younger subjects, despite the fact that none of these subjects had evidence of motor impairment. Though it has been estimated that a 50% loss of dopamine neurons and an 80% reduction in striatal dopamine are required for clinical signs of Parkinson's disease to appear (*44*) smaller decrements may lead to more subtle motor derangements. Future studies targeted towards understanding the functional consequences of age-induced dopamine degeneration will enable us to assess its role in the motoric deficits of the elderly. Such studies will also be of value in uncovering the participation of age-related changes in dopamine activity on behaviors that have been directly or indirectly related to the dopamine system such as attention, motivation, drive and mood which are frequently impaired in the elderly.

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Gender Differences in Cerebral Blood Flow as a Function of Cognitive State with PET

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This study explored the role of cognitive states in gender-based differences in brain function. **Methods:** We used the ^{15}O-water bolus method to measure cerebral blood flow (CBF) in 14 young normal volunteers with PET. Each subject was scanned six times, three during different neuropsychological tasks linked to the prefrontal cortex and three others during customized sensorimotor control tasks. The prefrontal tasks were the Wisconsin Card Sorting (WCS) Test, Delayed Alternation task (DA) and Spatial Delayed Response task (DR). **Results:** A significant main influence of sex on global CBF (ml/min/100g) was seen, with higher values in women, as viewed across all six conditions (means: 60.9 versus 53.2, ANOVA $F = 9.35$, $p < 0.01$). Post-hoc contrasts, however, showed that this finding was not uniform in all conditions. Differences between men and women were seen during performance of the frontal lobe tasks, but not during the sensorimotor control tasks. Even within the three frontal lobe tasks, results tended to vary: the differences between the sexes were most significant during the DA and just reached traditional levels of significance during the WCS. Therefore, if we had utilized a single task condition to determine whether men and women have different global CBFs, disparate conclusions would have been reached depending upon the task chosen. **Conclusion:** Although clear sex differences in global CBF can be demonstrated, the cognitive state of the subjects must be controlled and considered when interpreting the differences. Also, variations in the cognitive state might explain some of the discrepancies in gender studies in the rCBF and cerebral glucose metabolism literature.

Key Words: cerebral blood flow; PET; cognitive stimulation; gender differences; frontal lobe

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The search for sexual dimorphism and for gender-based functional differences in the human brain has produced a large amount of research in the neuroscience literature. Several studies have found structural (*1–3*) and electroencephalographic (*4,5*) differences between male and female brains. A considerable amount of research has also arisen from neuropsychological comparisons between the sexes, including observations that men and women have different verbal and/or spatial skills (*6–8*).

Both regional and global differences between the sexes have been reported with functional brain imaging techniques. As for regional patterns, findings in the frontal lobes have been particularly prevalent. Mathew et al. (*9*) found a more robust difference between men and women in frontal areas than in the parietal, temporal, or occipital regions. Azari et al. (*10*) found gender-related differences in interregional correlational patterns of glucose metabolism particularly involving the left frontal lobe, suggesting tighter functional coupling between this and other brain areas in women. Andreason et al. (*11*) reported higher orbitofrontal cerebral glucose metabolism (CMRGlu) values in women, while Rodriguez et al. (*12*) found frontal asymmetry (right > left) in men that was absent in women.

Nevertheless, these findings have been extremely controversial. A majority of previous studies have demonstrated higher global CBF or CMRGlu metabolism in women (*11–16*), but a number of others found no sex-based differences (*10,17–20*). Despite these inconsistencies, there have been no reports of higher brain activity in men than women. Considerable variation exists among these studies as to how measurements were obtained and what functions were measured. Positive findings, however, have emerged regardless of the technique used: with xenon technology (*9,12,15*), SPECT (*14*) and PET (*16*); with measurements of rCBF as well as glucose metabolism; and in studies performed both with subjects at rest (*9,12,14–16*) and during activation (i.e., when subjects were asked to perform motor, sensory or cognitive activities during the scan) (*11,13*). In contrast, studies that have failed to demonstrate gender differences in global brain activity have mainly been performed while subjects were at rest (*10,17,19,20*), a condition which has been demonstrated by some authors to be more variable than when subjects are active (*21*). There has been only one activation study that has failed to delineate global gender differences in brain activity (*18*).

While the explanation for these striking discrepancies in the literature regarding global flow is not entirely clear, a variety of factors have been suggested. Among the more relevant explanations are the possibility that variable brain size of subject groups could add variability to the results (*22*). Moreover, disparate results could be explained by an interaction between subject's age and sex, as evidenced by the fact that differences between men and women occur in younger cohorts only and converge in later years (*14,15,23*). Another potentially crucial source of variation that has not received sufficient attention is the cognitive state of the subjects (*16,20*). The present study, therefore, sought to explore this factor in healthy young men and women by measuring their rCBFs while performing a variety of cognitive tasks. These tasks include some that are traditionally linked to the region most implicated by previous functional brain imaging studies of gender differences—the frontal lobes.

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