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Striatal dopamine transporters correlate with simple reaction time in elderly subjects

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Abstract

The decline in motor performance that accompanies advanced age has unclear neurobiological substrates but may relate, in part, to degeneration of the nigrostriatal dopamine system. This research tested the hypothesis that striatal dopamine transporter (DAT) availability in healthy elderly individuals was related to measures of motor performance. Thirty-six healthy volunteers (18 male, 18 female) who ranged in age from 68 to 88 (75.4±4.9 years) received a neuropsychological evaluation that included two primary motor measures (tested with dominant hand): 1) Simple Reaction Time (SRT); and 2) Finger Tapping (FT). Subjects underwent SPECT scanning with [^{123}I]2ß-carbomethoxy-3ß-(4-iodophenyl)tropane ([^{123}I]ß-CIT) for measurement of striatal DAT availability. A ratio of specific to nondisplaceable brain uptake (i.e., V_3''=[striatal −occipital]/occipital), a measure proportional to the binding potential (B_{max}/K_D), was derived. SRT was significantly correlated with striatal DAT availability with or without controlling for the contribution of age. However, contrary to hypothesis, FT was not correlated with striatal DAT availability. Comparison measures, including episodic memory and general intelligence, were also unrelated to striatal DAT availability. These results demonstrate that a loss of nigrostriatal dopaminergic function likely contributes to slowing of reaction speed with advancing age.

Keywords

aging; simple reaction time; finger tapping; dopamine transporter; dopamine; [^{123}I]ß-CIT; SPECT

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1. Introduction

Healthy aging is associated with a decline in motor performance, including slowing of reaction time and motor speed [14,16,20,32]. Previous authors have speculated that these motoric changes may be attributable to age-related degeneration of the nigrostriatal dopamine system [26]. In recent years, several elements of this neural system have been probed for age-related changes. Most studies of dopamine receptor binding with aging have been conducted with D_1 and D_2 receptors whose location is primarily postsynaptic [10,27,35,38]. Presynaptic markers are uniquely valuable, however, as they provide direct information about the nigrostriatal cells. *In vitro* studies of presynaptic elements have shown deterioration with age, including reduction in the number of neurons in the substantia nigra [26] and striatal dopamine content [7,21], both of which demonstrate an age-dependent reduction of approximately 50% over the adult lifespan. Another presynaptic marker located on the terminals of dopaminergic neuronal projections is the dopamine transporter (DAT), which functions to remove dopamine from the synapse back into the terminal for storage or metabolism. The concentration of striatal DATs shows a decline with age of 65% to 75% over the adult lifespan, or approximately 9% per decade [2,10,53].

With the advent of functional brain imaging methodologies—specifically, Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT)—it has become possible to study the aging of neural systems in living subjects. Aging effects on striatal DATs have received considerable attention with PET and SPECT studies [43,44,46,47], which collectively have confirmed a robust decline with age (of 6.6 to 8% per decade) [44]. However, there have been few attempts to relate striatal DATs to motor or cognitive performance in healthy elderly subjects [28] (detailed in Discussion section 4.1).

Such correlational research requires the selection of motor tasks sensitive to the degree of nigrostriatal degeneration that occurs with normal aging. Whereas, early animal studies held that a depletion of nigrostriatal dopamine in the order of 85-95% was necessary to produce chronic impairment in most motor tests [33,37], more specialized tasks were subsequently shown to have sensitivity to much smaller lesions [8,40]. Simple Reaction Time (the time interval from the presentation of a stimulus until a response is initiated; SRT) performance in rats has been observed to be highly sensitive to small (10-25%) dopamine depletions in striatum when the animal is required to react with maximal speed [40]. Moreover, interresponse time on a self-directed lever-pressing task [36] has been shown to be sensitive to small depletions (mean=29%) in ventrolateral striatum [8]. In humans, SRT exhibits well-documented aging effects [14,16], and the Finger Tapping (FT) [34] task—which contains some common features with rodent self-directed lever-pressing paradigms—also shows slowing with age [20,32,34].

This research aimed to test the hypothesis that striatal DAT availability by [^{123}I]2ß-carbomethoxy-3ß-(4-iodophenyl)tropane ([^{123}I]ß-CIT) SPECT in healthy elderly individuals is related to performance on two motor tasks: SRT and FT. The specificity of this relationship was examined by two comparison measures: 1) episodic memory (California Verbal Learning Test, CVLT) [11,31]; and 2) general intelligence. Following the completion of this study, a report emerged that in patients with Parkinson's disease (PD) striatal DAT availability correlated with learning strategy on the CVLT [3]. Specifically, this study found a correlation with internally generated, semantic learning strategy versus externally guided, serial learning strategy. We therefore performed a *post-hoc* exploratory analysis of this correlation in healthy elderly subjects.

2. Methods

2.1. Human subjects

Previous investigators that have used neuroimaging to relate dopaminergic markers to neuropsychological function have examined subjects across a broad age range [6,28,48,49]. In the present study we adopted a different strategy, electing instead to study healthy elderly subjects spanning a narrow age range such that the variance in motor and SPECT measures due to age was small.

The study population consisted of 36 healthy volunteers (18 male, 18 female; 100% Caucasian) who ranged in age from 68 to 88 (75.4±4.9) years. There were similar age distributions for males (75.2±4.6) and females (75.6±5.3). Educational level ranged from 9 to 20 years (14.0±3.1). All subjects, except one, were right handed. Subjects underwent a clinical examination by a research geropsychiatrist (CHvD) and a neurologist (KLM) to exclude any neurological or psychiatric disease, alcohol or substance abuse. Screening procedures included a medical history, physical and neurological examination, EKG, serum chemistries, thyroid function studies, CBC, urinalysis, and urine toxicology screen. Subjects were also assessed with the Folstein Mini-Mental State Examination (MMSE) [13], the Hamilton Rating Scale for Depression (Ham-D) [19], and a structural MRI scan of the brain (including axial T1, coronal T2, and sagittal 3D spoiled gradient echo sequences). Subjects were excluded for significant cognitive impairment as evidenced by MMSE<26. In order to exclude clinical depression as a cause of psychomotor slowing, subjects were required to have a Ham-D<13. All of the brain MRI scans were read by a neuroradiologist and were considered normal with respect to subject age. Subjects were also excluded for visual or auditory impairment sufficient to compromise evaluation and testing. No subject was taking psychotropic medications or drugs known to affect the brain dopamine system. All subjects gave written informed consent to the research protocol approved by the Yale Human Investigation Committee and conducted in accordance with the 1964 Declaration of Helsinki.

2.2. Neuropsychological evaluation

Subjects received a neuropsychological evaluation that included the two primary motor measures—SRT and FT—as well as the CVLT [11] and the Wechsler Adult Intelligence Scale-Revised (WAIS-R) [50] (33 subjects only). Insofar as possible, subjects were tested with motor measures and CVLT on days of SPECT scanning (all but two subjects), with WAIS-R performed on a separate day.

Simple Reaction Time (SRT)—The SRT task was performed using a key press apparatus with computer interface. Subjects were instructed to respond as quickly as possible to a visual stimulus (presented on a computer monitor) by pressing a single microswitch key (temporal resolution=1 ms) with the index finger of the dominant hand. Subjects rested the dominant hand on the key press apparatus with index finger over the microswitch key and sat approximately 70 cm from the computer monitor on which stimuli (and performance feedback) were presented. In each trial, a fixation mark ("+") appeared at the center of the screen for 1000 ms. The fixation mark then disappeared and, after a pseudorandomly selected duration (500, 750, or 1000 ms), the target character "O" appeared and remained visible until the subject performed the key press. There were a total of 5 blocks of 18 trials. After each block, the subject received a rest period during which performance feedback was displayed (i.e., the subject's median SRT for that block in ms, followed by the exhortation "Can you go even faster?"). The subject chose when to end the rest period and begin the next block with the instruction "Press button to continue." SRT

values<100 ms were considered anticipations and not included in the analysis. Median key press latencies were used as final measures of SRT.

Finger Tapping (FT)—This task employed the same key press apparatus and computer described for SRT. However, the computer monitor did not provide stimuli but only performance feedback. Subjects were instructed to press a single microswitch key with the index finger of the dominant hand as many times as possible in 10 s. Subjects performed the task in five separate blocks at 30 s intervals during the testing session. After each 10 s block, the subject received a 20 s rest period during which performance feedback was displayed (i.e., the subject's total number of taps for the previous block, followed by the exhortation "Can you go even faster?"). Key presses/10 s were averaged for the five blocks. FT performance was also evaluated with the nondominant hand (always following dominant hand) and analyzed in one *post-hoc* analysis (See Results).

Comparison Tasks—The CVLT is a word list-learning test, designed to measure explicit memory for episodic information [11]. It also offers a framework for identifying internal versus external learning strategies [3,5]. The test is composed so that the words (shopping list items) can be regrouped semantically, i.e., according to the hidden categories of which the list is comprised, or can be repeated serially, by relying on the fixed sequence in which the words are read over five trials [3]. In this study, the Total Recall score (range 0-80), which is the sum of trials 1 through 5, was taken as a measure of recall memory. The %Discriminability score was used as a measure of recognition memory. The WAIS-R [50] provided an additional comparison task hypothesized to be relatively unrelated to nigrostriatal dopaminergic function and also permitted characterization of the sample with regard to general intelligence.

2.3. SPECT Imaging

All subjects received 0.6 g potassium iodide (SSKI solution) in the 24 h prior to tracer administration. They then received an injection of [^{123}I]ß-CIT (5.9±0.4 mCi; specific activity>5,000 Ci/mmol) on day 1, followed 21.1±1.2 h later by a 24 min scan with a Picker (Cleveland, OH) PRISM 3000XP SPECT camera equipped with a low energy, high resolution (LEHR) fanbeam collimator (128×128 matrix, 120° angular range, 3° angular step, 40 steps, 36 s per step, 15.5 cm radius of rotation). In this configuration, the PRISM 3000 acquires images at a reconstructed full-width at half-maximum resolution of 12.3 mm as determined by an ^{123}I point source in water. Previous studies have demonstrated that [^{123}I]ß-CIT reaches equilibrium binding in the brain by 18-24 h, yielding a simple unitless ratio of regional radioactivities (V_3''=specific/nondisplaceable binding=[striatal−occipital]/occipital) proportional to the binding potential (B_{max}/K_D) [25,43]. Prior to scanning, four or five fiducial markers filled with 5 μCi of $Na^{99m}TcO_4$ were attached to the skin along the canthomeatal plane to identify this plane during image analysis.

Images were reconstructed from photopeak counts (159±16 keV) using standard filtered backprojection methods (Butterworth, power 10, cutoff 0.24 cm^{-1}) and displayed as a 128×128×64 matrix with a voxel size of 2.07×2.07×3.56 mm (15.25 mm^3). Subsequent image analysis was performed by an operator who was unaware of subject demographics. SPECT data were reoriented to correct for deviations from the canthomeatal plane, as identified by the fiducial markers. Eight contiguous transaxial slices with the highest uptakes in striatum were identified from a reconstructed midsagittal image and digitally summed to yield a transaxial slice 28.5 mm thick. Attenuation correction was performed using a Chang zero order method (attenuation coefficient μ=0.15 cm^{-1}) within an ellipse drawn around the skull. Standard region of interest (ROI) templates (previously published [45]) for left and right caudate (424 voxels or 6.5 mL each), left and right putamen (824 voxels or 12.6 mL

each), and occipital cortex (7912 voxels or 120.6 mL) were positioned on the summed slice. The caudate and putamen show volumetric effects of both age and sex [18]. To minimize partial volume effects, smaller ROIs for caudate and putamen (96 voxels or 1.5 mL each—well below actual volumes, which are approximately 3.4 mL for caudate and 4.2 mL for putamen [18]), as previously published [39]) were also analyzed. V_3'' for striatum and striatal subregions (caudate and putamen) was computed without conversion of SPECT cpm to absolute units of radioactivity as $[(\text{cpm/voxel})_{\text{striatum}} - (\text{cpm/voxel})_{\text{occipital}})]/(\text{cpm/voxel})_{\text{occipital}}$.

2.4. Statistical analysis

We hypothesized that the primary motor measures (SRT and FT, tested with dominant hand) would be correlated (Pearson's ***r***) with striatal V_3'' (and thus applied a Bonferroni correction for two planned comparisons $\alpha=0.05/2=0.025$). We planned *a priori* to partial out the contribution of age, which has been shown in numerous studies to be associated with both striatal DAT levels [23,29,42,43,44,46,47,52] and SRT [16] and FT performance [20,32,34]. For the FT task, we also planned to partial out the variance due to sex, based on prior evidence [20]. To examine the specificity of a relationship between striatal V_3'' and either SRT or FT, we also performed additional correlations with comparison tasks in two categories: 1) age-sensitive tasks not hypothesized to correlate with nigrostriatal dopaminergic function (CVLT: Total Recall, Recognition %Discriminability, partialing for the contribution of age) [11,31]; and 2) general intelligence (WAIS-R: FSIQ) [50].

As previously mentioned, a *post-hoc* exploratory analysis was also conducted to determine whether striatal DAT availability was correlated with semantic versus serial learning strategy [3]—as identified by the CVLT. Semantic and Serial Gradients were derived from the semantic and serial clustering ratios (ratio first trial up to ratio 5th trial) provided by the computerized CVLT scoring program [15]: a ratio of 1 indicates a chance clustering performance controlled for the total number of recalled words, and a ratio greater or less than 1 indicates above or below chance clustering performance, respectively. The "Semantic Gradient" [3,5] was calculated as 0.2(semantic ratio trial 5 − semantic ratio trial 1) + 0.1(semantic ratio trial 4 − semantic ratio trial 2), and the "Serial Gradient" as 0.2(serial ratio trial 5 − serial ratio trial 1) + 0.1(serial ratio trial 4 − serial ratio trial 2). The Semantic and Serial Gradients were correlated with striatal V_3'' using partial correlations, controlling for the contribution of age.

As explained in the Results section, additional *post-hoc* analyses were conducted to examine the relationship between striatal DAT availability and: 1) intra-individual variability of SRT and FT performance (i.e., the ratio of the interquartile difference to the median), 2) temporal patterns of FT performance [9], including response initiation time (RIT) and response duration time (RDT), and 3) the laterality of SRT and FT performance (i.e., in relation to left versus right striatal DAT availability).

All statistical analyses utilized the SPSS (SPSS Inc., Chicago, IL) software package and employed two-tailed tests of significance.

3. Results

Demographic and neuropsychological data are displayed in Table 1. MMSE scores for these subjects ranged from 26 to 30 (29.0±1.2), indicating no significant cognitive impairment. Ham-D scores ranged from 0 to 8 (3.2±2.2), indicating no significant depressive symptoms. As expected, male subjects had significantly faster FT (Males: 54.9±6.0, Females: 49.8±5.0; ***t***=2.76, df=34, P=0.009). However, several unexpected sex differences (all favoring females) were also observed in this sample. Female subjects performed significantly better on CVLT

Total Recall (Males: 45.3±12.0, Females 54.8±8.4, ***t***=2.73, df=34, P=0.01) and Recognition %Discriminability (Males: 91.7±6.0%, Females 95.6±4.4%, ***t***=2.22, df=34, P=0.034). Females also had higher VIQ (Males: 112±12, Females 127±15, ***t***=3.14, df=31 P=0.004) and FSIQ (Males: 115±14, Females 127±13, ***t***=2.67, df=31 P=0.012).

Among the neuropsychological measures only FT was correlated with age (***r***=−.34, df=36, P=.043), whereas no significant correlations with age were observed for SRT (***r***=.19, df=36, P=.27), CVLT Total Recall: (***r***=−.10, df=36, P=.58), Recognition %Discriminability: (***r***=−.01, df=36, P=.98), Semantic Gradient: (***r***=−.08, df=36, P=.67), Serial Gradient: (***r***=−.004, df=36, P=.98), VIQ (***r***=.09, df=33, P=.60), PIQ (***r***=−.18, df=33, P=.32), or FSIQ (***r***=−.02, df=33, P=.91). However, subsequent analyses nonetheless corrected for age per the *a priori* statistical plan. Furthermore, additional partial correlations were added *a posteriori* to correct for sex for those measures observed to have significant sex effects (FT, CVLT Total Recall, Recognition %Discriminability, VIQ, and FSIQ).

Striatal DAT availability (V_3'', range 3.7 to 7.6; 5.1±1.0) was uncorrelated with age in this restricted age range (***r***=−.03, df=36, P=.87). Comparisons between left and right hemispheres showed no significant difference in V_3'' between left (5.12±1.01) and right (5.13±0.99) striatum (***t***=.04, df=35, P=.97, paired t-test). However, V_3'' was significantly higher in the left (5.19±1.04) than in the right (5.01±1.03) caudate (***t***=2.87, df=35, P=.007, paired t-test) but showed a reverse trend in the right (5.19±0.99) compared to the left (5.10±1.03) putamen (***t***=2.02, df=35, P=.051, paired t-test).

3.1. Relationship between striatal DAT availability (V_3'') and neuropsychological measures

Table 2 displays the overall results of correlations between neuropsychological test results and striatal DAT availability (V_3'').

Simple Reaction Time (SRT)—Fig. 1 displays the values of SRT versus striatal DAT availability (V_3'') as measured by [^{123}I]ß-CIT and SPECT in healthy elderly subjects (N=36). The simple zero-order correlation between SRT and V_3'' was significant (***r***=−.40, df=36, P=.016), as was the partial correlation after controlling for age ($\boldsymbol{r}_{SRT,V3''|AGE}$=−.40, df=33, P=.017). A *post-hoc* analysis of striatal subregions showed that this partial correlation was true for both caudate ($\boldsymbol{r}_{SRT,V3''|AGE}$=−.39, df=33, P=.020) and putamen ($\boldsymbol{r}_{SRT,V3''|AGE}$=−.40, df=33, P=.019). However, this partial correlation failed to show laterality: when only the right-handed subjects (n=35) were considered, SRT (with the right hand) was equally correlated with left ($\boldsymbol{r}_{SRT,V3''|AGE}$=−.39, df=32, P=.021) and right ($\boldsymbol{r}_{SRT,V3''|AGE}$=−.39, df=32, P=.022) striatum. A *post-hoc* analysis of smaller ROIs was also significant ($\boldsymbol{r}_{SRT,V3''|AGE}$=−.38, df=33, P=.024), suggesting that the partial correlation between SRT and striatal DAT availability was not accounted for by volume differences in the corpus striatum. Interestingly, the intra-individual variability of SRT performance (as measured by the ratio of the interquartile difference to the median SRT) was also inversely correlated with striatal DAT availability (***r***=−.34, df=36, P=.046).

Finger Tapping (FT)—Fig. 2 displays the values of FT performance (dominant hand) versus striatal DAT availability (V_3'') in this sample. The simple zero-order correlation between FT and V_3'' was not significant (***r***=.04, df=36, P=.81); nor were the partial correlations after controlling for age ($\boldsymbol{r}_{FT,V3''|AGE}$=.03, df=33, P=.85) or age and sex ($\boldsymbol{r}_{FT,V3''|AGE,SEX}$=.15, df=32,P=.40). Examination of laterality did not alter the results: when only the right-handed subjects (n=35) were considered, FT with the right hand was uncorrelated with left striatum ($\boldsymbol{r}_{FT,V3''|AGE,SEX}$=.13, df=31,P=.47), and FT with the left hand was uncorrelated with the right striatum ($\boldsymbol{r}_{FT,V3''|AGE,SEX}$=.14, df=31,P=.44).

The intra-individual variability of FT performance (as measured by the ratio of the interquartile difference to the median inter-tap time in ms) was also uncorrelated with striatal DAT availability (***r***=−.25, df=36, P=.14). A *post-hoc* analysis of temporal patterns of FT performance [9] showed that striatal DAT availability was uncorrelated with both the median response initiation time (RIT; time from offset of one finger tap until the onset of next tap; ***r***=−.10, df=36, P=.55) and the median response duration time (RDT; time from onset of one finger tap until offset of same tap; ***r***=−.10, df=36, P=.58).

Episodic Memory (CVLT)—Similarly, the simple zero-order correlation between Total Recall and V_3'' was not significant (***r***=.27, df=36, P=.11), nor were the partial correlations after controlling for age ($r_{RECALL,V3''|AGE}$=.27, df=33, P=.11), or age and sex ($r_{RECALL,V3''|AGE,SEX}$=.20, df=32,P=.25). The simple zero-order correlation between Recognition %Discriminability and V_3'' was not significant (***r***=−.01, df=36, P=.94), nor were the partial correlations after controlling for age ($r_{RECOGNITION,V3''|AGE}$=−.01, df=33, P=.94), or age and sex ($r_{RECOGNITION,V3''|AGE,SEX}$=−.10, df=32, P=.57). A *post-hoc* analysis of semantic vs. serial learning strategy showed that the simple zero-order correlation between the Semantic Gradient and V_3'' was not significant (***r***=.18, df=35, P=.29), nor was the partial correlation after controlling for age ($r_{SEMANTIC\ GRADIENT,V3''|AGE}$=.18, df=32, P=.31). The simple zero-order correlation between the Serial Gradient and V_3'' was not significant (***r***=−.07, df=35, P=.68), nor was the partial correlation after controlling for age ($r_{SERIAL\ GRADIENT,V3''|AGE}$=−.07, df=32, P=.68).

WAIS-R—The simple zero-order correlation between WAIS-R FSIQ and V_3'' was not significant (***r***=−.05, df=33, P=.79), nor was the partial correlation after controlling for sex ($r_{FSIQ,V3''|SEX}$=.02, df=30, P=.93). Correlations controlling for age were not conducted, since WAIS-R FSIQ is already age-normed.

4. Discussion

In this study, performance on one of two motor tasks—SRT, but not FT—was significantly correlated with striatal DAT availability (V_3'') as measured by [^{123}I]ß-CIT and SPECT, with or without controlling for the contribution of age. None of the comparison measures—episodic memory, general intelligence—showed a significant correlation with DAT concentrations. *Post-hoc* analyses suggested that CVLT learning strategy was also uncorrelated with striatal DAT availability.

4.1. Dopamine Imaging in Relation to Neuropsychological Function

The relationship between neuropsychological measures and striatal DAT binding has been examined in one previous neuroimaging study, which differed from the present investigation by enrolling subjects across a wide age range (66 subjects, aged 18-75). Using [^{99m}Tc]TRODAT-1 and SPECT, Mozley et al [28] observed that in female subjects, specific tracer uptake in the caudate and putamen was correlated with performance on the Stroop test, thumb-finger sequencing, and the Grooved Pegboard test. Specific uptake for putamen only was correlated with FT performance in the left hand only. None of these correlations was significant for male subjects. However, these analyses did not partial out the confounding contribution of age, thus leaving unclear the relationship between striatal DAT binding and neuropsychological variables.

Three other neuroimaging studies have examined the relationship between neuropsychological function and dopamine receptors. Wang et al [49] related motor function and D_1 binding using [^{11}C]SCH-23390 and PET in 21 healthy subjects (aged 22-74). They observed a correlation between Purdue Pegboard Test score and D_1 binding potential in

caudate and putamen but also did not control for the effect of age. Two groups have examined the relationship between neuropsychological measures and D_2 binding in healthy subjects. Volkow et al [48] studied 30 subjects (aged 24-86) with [^{11}C]raclopride and PET and a neuropsychological test battery. After appropriately partialing out the contribution of age, they reported significant correlations between D_2 availability in caudate and FT, Stroop interference score, and Symbol-Digit Modalities Test. For the putamen only the partial correlation with FT was significant. Bäckman et al [6] studied 11 healthy subjects (aged 21-68) with [^{11}C]raclopride and PET and a neuropsychological test battery. They observed residual effects of D_2 binding after controlling for age on tests of perceptual speed (Dots and Trailmaking A) and episodic memory (Word Recognition and Face Recognition).

To examine the relationship between striatal DAT availability and neuropsychological function, we studied an elderly cohort spanning a narrow age range. This strategy differs from that of all four of the studies discussed above, which examined broad age ranges [6,28,48,49]. Either subject sampling strategy is appropriate to detect effects that are present across the lifespan. However, a narrow age range might provide greater sensitivity for effects that develop only in old age, e.g., if neurochemical losses must cross a critical threshold before function is altered. Given the strong aging effects of many dopaminergic elements and neuropsychological measures, analyses spanning broad age ranges require control for the confounding effect of age—either by partial correlations [48] or multiple regression analysis [6]—to avoid spurious associations.

4.2. Relationship to Other Preclinical and Clinical Studies

Simple Reaction Time (SRT)—Our observation that SRT was correlated with striatal DAT availability accords with a number of preclinical and clinical findings. Animal lesion studies have demonstrated that SRT performance in rats is highly sensitive to small (10-25%) dopamine depletions in striatum when the animal is required to react with maximal speed [40]. In humans, healthy aging is associated with striatal DAT reductions that are at least 50%, as shown by both *in vitro* homogenate binding studies [2,10,53] and *in vivo* radioligand studies [43,44,46,47], and these reductions are commensurate with age-related reductions in the number of dopaminergic cell bodies in the pars compacta of the substantia nigra (SNc) [26]. Thus, the nigrostriatal dopaminergic “lesion” of normal aging is sufficient to contribute to some of the observed aging effects [14,16] in SRT performance. Moreover, the fact that SRT is slowed in relatively asymptomatic individuals with MPTP-induced parkinsonism [41] supports the notion that this task is sensitive to the selective destruction of nigrostriatal dopaminergic neurons, even of subclinical proportions.

Finger Tapping (FT)—Our failure to find a significant correlation between FT and striatal DAT availability is somewhat at odds with a number of preclinical and clinical findings. Animal lesion studies have demonstrated that interresponse time on a self-directed lever-pressing task [36] is sensitive to small depletions (mean=29%) in ventrolateral striatum [8]. However, human FT may differ from such a rodent task in both important motivational respects (as animals are trained to a fixed reward schedule) and anatomical requirements (as animals utilize a whole limb rather than a single digit). Nonetheless, FT is slowed in healthy elderly individuals [20,32,34], and Volkow et al [48] observed FT to be strongly correlated with striatal D_2 availability in another *in vivo* imaging study. Divergent results between our study and that of Volkow et al may be attributable to the difference between presynaptic and postsynaptic markers (and specifically to the fact that a subset of striatal D_2 receptors are located on corticostriatal terminals [12]). They may also be due to the dissimilar age ranges of the two subject samples.

Episodic Memory (CVLT)—The use of an episodic memory test (CVLT) as a comparison task—hypothesized to be unrelated to striatal DAT availability—warrants comment. Volkow et al [48] also employed episodic memory measures as control tasks ("dopamine-insensitive") in their neuropsychological study of striatal D_2 receptors. These investigators indeed found no correlation between D_2 availability and performance on the Wechsler Memory Scale-Revised or the Benton Visual Retention Test. However, Bäckman et al [6] observed residual effects of striatal D_2 binding after controlling for age on tests of episodic memory (Word Recognition and Face Recognition). While the striatum is clearly implicated in procedural memory, its role in episodic memory is unestablished, despite isolated case reports of impairment in memory and executive functions with focal damage to neostriatum in some [51] but not other [22] studies.

In PD patients, Berger et al observed a robust inverse correlation between striatal DAT binding and the externally guided, serial learning strategy as well as a significant positive correlation between caudate DAT activity and the internally generated, semantic learning strategy [3]. Our failure to detect a significant correlation between striatal DAT availability and CVLT learning strategy in our healthy elderly subjects may be a consequence of inadequate statistical power. Alternatively, it may reflect the qualitative difference between the disease process of PD and the normal aging of the nigrostriatal dopaminergic system that has been suggested by previous postmortem [24] and neuroimaging [44] studies.

4.3. Limitations

Certain limitations of the present study deserve mention. First, the superior education and IQ of the subject cohort is common in studies of healthy aging [48] but may limit the generalizability of the findings. Second, information was not systematically obtained from subjects regarding their full employment history and daily motor activities—factors that may have influenced their motor performance or striatal DAT availability. Third, the neuropsychological battery omitted tasks of prefrontal executive function, as included in some of the previously discussed studies [28,48]. Such tasks may have been interesting in light of the fact that DAT availability in caudate may measure dopaminergic innervation of the caudate, modulating frontostriatal circuits [1]. Fourth, the present investigation was restricted to elderly subjects and therefore cannot ascertain the age-specificity of the results. Future research in young controls would be necessary to determine if DAT availability is correlated with SRT across the age spectrum. Finally, it is unclear to what extent a measure of nigrostriatal dopaminergic function is directly implicated in SRT, or serves as a surrogate for dopamine function more broadly. Aging involves generalized losses of dopamine in subcortical and cortical structures, including premotor cortices [17], which may also contribute to slowing of SRT. Cortical DATs are difficult to quantitate with [^{123}I]ß-CIT because cortical areas have low ratios of specific-to-nonspecific tracer uptake.

4.4. Conclusion

Our results have significant conceptual implications for the decline in motor performance that accompanies advancing age. They suggest that even the modest nigrostriatal dopaminergic "lesion" of healthy aging has functional consequences. They thus provide further contrary evidence for the older doctrine—derived from both autopsy studies of PD [4] and early animal lesion studies [33]—that a depletion of striatal dopamine in excess of 80% was necessary for functional impairment to occur. Kish et al [24] have extrapolated that, in normal aging, this threshold would only be reached at about the age of 110 years. Our results demonstrate, on the contrary, that among healthy subjects of retirement age with no clinical evidence of PD, diminished nigrostriatal dopaminergic function is associated with slowing of reaction speed. It remains to be seen whether motor performance in normal elderly subjects can be enhanced with therapeutic interventions. Speeding of SRT in normal

elderly humans by levodopa treatment has not been observed to be statistically significant [30]. However additional testing using dopaminergic therapies aimed at post-synaptic sites (e.g., D_1 or D_2 dopamine receptors) is certainly warranted.

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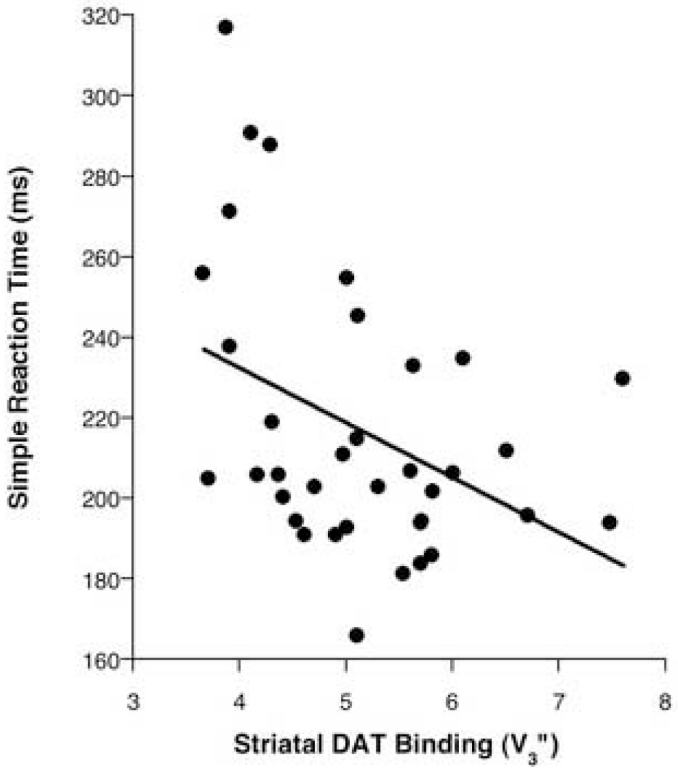

FIGURE 1.

Simple Reaction Time (SRT) versus striatal dopamine transporter (DAT) availability (V_3'') as measured by [^{123}I]ß-CIT and SPECT in healthy elderly subjects (N=36). SRT represents the median speed (in ms) with which subjects responded to a visual stimulus (presented on a computer monitor) by pressing a single microswitch key with the index finger of the dominant hand. SRT showed a significant inverse correlation with V_3'' either with (P=.016) or without (P=.017) controlling for age.

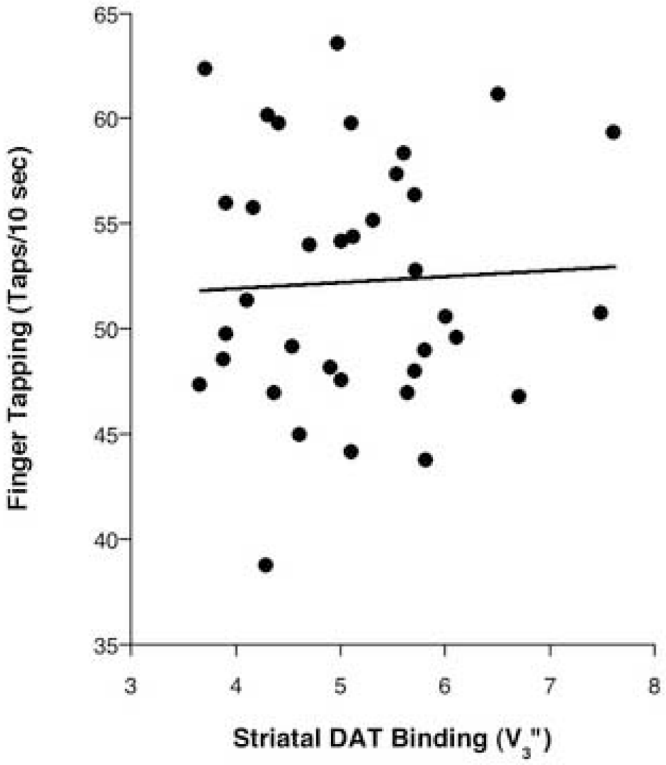

FIGURE 2.

Finger Tapping (FT) versus striatal dopamine transporter (DAT) availability (V_3'') as measured by [^{123}I]ß-CIT and SPECT in healthy elderly subjects (N=36). FT represents the number of key presses per 10 s with the index finger of the dominant hand, averaged across five trials. FT was not significantly correlated with V_3''.

Table 1

Subject Characteristics

Variable	Mean	SD
Demographics		
Age	75.4	± 4.9
Gender	18M, 18F	
Handedness	35R, 1L	
Education (yrs)	14.0	± 3.1
Neuropsychological		
MMSE	29.0	± 1.2
Hamilton Depression Scale	3.1	± 2.2
Verbal IQ (n=33)	119.2	± 15.0
Performance IQ (n=33)	118.3	± 12.8
Full Scale IQ (n=33)	120.9	± 14.7
CVLT - Total Recall	50.1	± 11.3
CVLT - Recognition Memory	93.6%	± 5.6%
Simple Reaction Time (ms)	217.3	± 34.0
Finger Tapping (per 10 s)	52.3	± 6.0

MMSE = Mini-Mental State Examination, CVLT = California Verbal Learning Test

Table 2

Correlations of Neuropsychological Test Results with Striatal DAT Availability in 36 Healthy Elderly Subjects

Task	r	p	$r_{\|age}$	$p_{\|age}$	$r_{\|age,sex}$	$p_{\|age,sex}$
Motor						
Simple Reaction Time	**−.40**	**0.016***	**−.40**	**0.017***		
Finger Tapping	.04	.81	.03	.85	.15	.40
Episodic Memory						
CVLT - Total Recall	.27	.11	.27	.11	.20	.25
CVLT - Recognition Memory	−.01	.94	−.01	.94	−.10	.57
CVLT - Semantic Gradient	.18	.29	.18	.31		
CVLT - Serial Gradient	−.07	.68	−.07	.68		
Intelligence						
Verbal IQ (n=33)	−.09	.64				
Performance IQ (n=33)	−.03	.88				
Full Scale IQ (n=33)	−.05	.79				

All correlations are with striatal DAT availability (V3″). r=zero-order Pearson's correlation. $r_{|age}$=partial correlation, controlling for age. $r_{|age,sex}$=partial correlation, controlling for age and sex (displayed only for tasks that differed by sex). CVLT=California Verbal Learning Test