The role of the striatal dopamine transporter in cognitive aging

Nina Erixon-Lindroth, Lars Farde, Tarja-Brita Robins Wahlin, Judit Sovago, Christer Halldin, Lars Bäckman

Department of Psychiatry, Department of Clinical Neuroscience, Karolinska Hospital, Box 6401, S-113 82, Stockholm, Sweden
Research and Development Center in Elderly Care, Karolinska Institute, S-113 82, Stockholm, Sweden
Aging Research Center, Division of Geriatric Epidemiology, Neurotec, Karolinska Institute, Stockholm, Sweden
Max Planck Institute for Human Development, Berlin, Germany

Received 22 April 2004; received in revised form 30 August 2004; accepted 1 September 2004

Abstract

We examined the relationship of age-related losses of striatal dopamine transporter (DAT) density to age-related deficits in episodic memory and executive functioning in a group of subjects (n=12) ranging from 34 to 81 years of age. The radioligand [11C]β-CIT-FE was used to determine DAT binding in caudate and putamen. Results showed clear age-related losses of striatal DAT binding from early to late adulthood, and a marked deterioration in episodic memory (word and figure recall, face recognition) and executive functioning (visual working memory, verbal fluency) with advancing age. Most importantly, the age-related cognitive deficits were mediated by reductions in DAT binding, whereas DAT binding added systematic cognitive variance after controlling for age. Further, interindividual differences in DAT binding were related to performance in a test of crystallized intelligence (the Information subtest from the Wechsler Adult Intelligence Scale-Revised) that showed no reliable age variation. These results suggest that DAT binding is a powerful mediator of age-related cognitive changes as well as of cognitive functioning in general. The findings were discussed relative to the view that the frontostriatal network is critically involved in multiple cognitive functions.

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Keywords: Aging; Dopamine transporter; Presynaptic marker; Cognition; Episodic memory; Executive functions; Frontostriatal circuitry

1. Introduction

Research in human brain biochemistry and cognitive neuroscience provides pervasive evidence for the following three propositions: (a) the nigrostriatal dopamine (DA) system declines across the adult life span; (b) many cognitive functions deteriorate with advancing age; and (c) DA is critically implicated in several cognitive functions.

Gradual age-related losses of biochemical markers for dopaminergic neurotransmission have been demonstrated in postmortem studies (Seeman et al., 1987; Allard and Marcusson, 1989; Cortes et al., 1989; Ma...
et al., 1999) as well as in brain-imaging research (Suhara et al., 1991; Van Dyck et al., 1995; Ichise et al., 1998; Rinne et al., 1998). For both pre- and postsynaptic DA markers, the reduction typically ranges from 4% to 10% per decade from the twenties and onwards (for overviews, see Reeves et al., 2002; Bäckman and Farde, 2004). Further, a variety of cognitive functions including episodic memory (Zacks et al., 1999; Bäckman et al., 2001), executive functions (West, 1996; Brébion et al., 1997), and perceptual speed (Salthouse, 1996, 1998) also show gradual performance deterioration over the adult life course (for overviews, see Verhaeghen and Salthouse, 1997; Bäckman et al., 1999).

Multiple sources of evidence suggest that DA plays a role in several cognitive functions. These include clinical observations that individuals with severe alterations of the DA system, such as patients with Huntington’s disease (HD), exhibit impairment across numerous cognitive domains (Brandt and Butters, 1986; Brown and Marsden, 1988). More recently, positron emission tomography (PET) studies have demonstrated sizable relationships between pre- and postsynaptic DA indicators and cognitive performance in HD patients (Bäckman et al., 1997; Lawrence et al., 1998).

Further support for a functional role of DA in cognition has been provided by experimental studies in animals. Lesions in dopaminergic pathways produce deficits across multiple cognitive domains (e.g., memory, attention, inhibitory functions) in rodents and monkeys alike (Simon et al., 1986; Jones and Robbins, 1992; Boussaoud and Kermadi, 1997; Baunez and Robbins, 1999). In humans, pharmacological challenges indicate that dopaminergic agonists may facilitate performance (Luciana et al., 1998; Kimberg and D’Esposito, 2003), whereas dopaminergic antagonists may impair performance (Luciana and Collins, 1997; Ramaekers et al., 1999), in different executive and working-memory tasks.

On the basis of the correlative triad among adult age, DA markers, and cognitive performance, investigators have begun to examine the extent to which age-related cognitive deficits can be accounted for by DA losses. Using PET, Wang et al. (1998) found strong relationships among age, striatal D2 receptor binding, and psychomotor performance. Similar results were obtained in a recent single photon emission computed tomography (SPECT) study examining intercorrelations among age, striatal D2 receptor binding and finger-tapping performance (Yang et al., 2003). Volkow et al. (1998a,b) reported marked age-related losses in D2 receptor binding in the striatum along with age decrements in tasks assessing executive functioning and speed. Importantly, there was a strong relationship between D2 binding and cognitive performance that remained after controlling for age. The findings of Volkow et al. (1998a,b) were corroborated and extended in a study by Bäckman et al. (2000). The latter study revealed marked age-related deterioration in episodic memory and perceptual speed tasks, and a gradual decrease of D2 binding in both striatal structures. The key finding was that statistical control of D2 binding effectively eliminated the influence of age on cognitive performance, whereas the reverse was not true. These results provide further evidence for the view that DA is implicated in age-related cognitive deficits as well as in cognitive functioning in general.

In the studies described above, postsynaptic markers of the DA systems were assessed. It has been suggested that the density of the DA transporter (DAT) is more sensitive than postsynaptic receptor densities as a marker of the activity of the dopaminergic system (Mozley et al., 1999). The DAT is a membrane-bound presynaptic protein that regulates the synaptic concentration of DA at nerve terminals (Giros et al., 1992, 1996). Thus, because DAT activity indirectly regulates the occupancy of DA on D1 and D2 receptor-containing neurons, this protein may serve as a more general marker of the DA system. In a SPECT study, Mozley et al. (2001) reported age-related reductions of the DAT in the striatum along with age-related deficits in verbal episodic memory. Importantly, DAT binding in the striatum was strongly associated with memory performance in both younger and older adults.

Although the available evidence suggests that pre- and postsynaptic DA markers can account for age-related cognitive deficits, the relevant database is still quite limited, with only a handful of published studies. In particular, there is a need to extend previous findings by determining the influence of regional age-related losses in DAT binding on age-related cognitive deficits across several domains of interest.
The main purpose of the current PET study was to provide further knowledge concerning the relationship between age-related DAT losses and age-related cognitive deficits. DAT binding in caudate and putamen was quantified in a sample of healthy persons from early to late adulthood by taking advantage of the selective radioligand \([11C]\)[\(\beta\)-CIT-FE (Farde et al., 2000). The cognitive battery involved tests of episodic memory (word recall, figure recall, face recognition) and executive functions (visuospatial working memory, verbal fluency). These cognitive domains were targeted because of their age sensitivity (West, 1996; Bäckman et al., 2001). In addition, to further examine whether DA is related to cognitive performance independent of age, we included a test of crystallized intelligence (Information) known to be relatively unaffected by normal aging processes (Kausler, 1991; Salthouse, 1991).

On the basis of prior research, we expected an age-related reduction of striatal DAT binding, age-related deficits in episodic memory and executive functioning, but no age differences in crystallized intelligence. Our chief interest, however, was to extend previous findings by determining the relationship of age-related losses in DAT binding to age-related cognitive deficits.

2. Materials and methods

2.1. Subjects

The study was approved by the Ethics and Radiation Safety Committees of the Karolinska Hospital, Stockholm. Written and spoken information about the study was provided to the subjects. All subjects signed written informed consent prior to participation. Twelve subjects (6 women and 6 men) between 34 and 81 years of age participated in the study. All subjects were healthy according to physical examination, blood and urine analysis, and no subject had a history of psychostimulant use or any psychiatric or neurological disorder.

2.2. Cognitive tests

2.2.1. Episodic memory

Three tests of episodic memory were included. The tests were selected to involve variation with regard to the nature of the learning materials (i.e., verbal vs. non-verbal) and the retrieval conditions (i.e., recall vs. recognition).

2.2.1.1. Word recall. A list of 20 words from different taxonomic categories was presented bimodally at a rate of 5 s/word (Wahlin et al., 1995). The words were presented visually in a booklet, and the experimenter read the words aloud simultaneously. Subjects were instructed to remember as many words as possible for a subsequent recall test. Following presentation of the last word in the series, subjects were given an oral free recall test in which the experimenter recorded the responses. Three minutes were allowed for the recall test. No subject reported requiring more time for task completion. The maximum score for this task was 20.

2.2.1.2. Figure recall. Rey–Osterrieth’s Complex Figure (R-OCF) was used to assess figure recall (Rey, 1941; Osterrieth, 1944). Subjects were given a blank sheet of paper and another sheet of paper on which the R-OCF was printed. They were first asked to copy the figure on the blank sheet of paper as accurately as possible, with no time restrictions. Following completion of this task, the experimenter removed both the original and the copied figure. After a retention interval of 4 min during which time the verbal fluency test (see below) was completed, subjects were again given a blank sheet of paper and asked to reproduce the R-OCF from memory. The task was self-paced. The R-OCF was scored according to standardized criteria (Lezak, 1983), and the maximum score was 36.

2.2.1.3. Face recognition. Twenty-four black-and-white pictures portraying unfamiliar faces were presented consecutively in a booklet for purposes of later recognition (Bäckman, 1991). Each picture was presented for 5 s. No faces with unusual hairstyles or jewelry were included. After presentation of the last face, a self-paced yes–no recognition test was given, in which the 24 target faces were presented along with 24 new faces randomly intermixed at a rate of 5 s / face. Subjects responded orally by saying “yes” to the target faces and “no” to the lures, and the experimenter recorded the responses. A standard measure of discrimination accuracy, \(d’\), was used to index face
recognition performance (Hochhaus, 1972). This measure is based on the proportions of hits and false alarms and ranges from -4.64 to 4.64, with chance level being represented as 0.

2.2.2. Executive functioning

Two tests of executive functioning were included, a test of visuospatial working memory under demanding performance conditions and a test of verbal fluency.

2.2.2.1. Visuospatial working memory. The visual working memory test was modeled after the delayed-response task devised by Park and Holzman (1992). Subjects were seated in front of a computer screen. A black circle, the target, was displayed on the screen for 200 ms. The location of the target varied randomly from trial to trial. While the subject kept the target position in mind, a three-digit number (e.g., 282) appeared in the center of the screen. The computer counted down in steps of two, displaying a new number every second. However, for 30% of the trials, the number appearing on the screen did not differ from the preceding number by two units. The subject’s task was to detect such deviations from the typical sequence. The time period of being attentive to the numbers, either 5 or 30 s, was terminated by the appearance of eight empty circles. One of these represented the position where the target had appeared. The subject was asked to drag the marker to the correct position and click to confirm the answer and continue the test. The 5- and 30-s attention spans were both repeated 16 times, randomly distributed.

Performance in the 30-s condition was selected as the outcome variable in the current study. In this condition, a new number was displayed on the computer 480 times. A correct response was registered for trials where subjects did not click the mouse when the computer counted down in steps of two, and for trials where subjects clicked the mouse in case of a deviation from the typical counting-down sequence. The outcome measure was computed by dividing the total number of correct responses with 480, yielding a measure of proportion correct responses.

2.2.2.2. Verbal fluency. The Controlled Oral Association Test (Benton and Hamsher, 1989) was used to assess verbal fluency. In this test, subjects are asked to produce as many words as possible, beginning with the letters F, A, and S, respectively, with the exception of proper names, numbers, and words with the same suffix. One minute was allowed for each letter. Subjects responded orally, and the experimenter recorded the responses. The number of words produced for each letter was combined into an overall verbal fluency score.

2.2.3. Crystallized intelligence

One subtest of crystallized intelligence (Information) from the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981) was included.

2.2.3.1. Information. The Information test involves 29 general knowledge questions (e.g., What is the capital of Italy?, “Which person is associated with the theory of relativity?”). The test was administered according to standard procedures. Questions were answered orally in free-recall format, and the experimenter recorded the responses. The maximum score was 29.

2.3. Brain-imaging procedure

2.3.1. Magnetic resonance imaging

The magnetic resonance imaging (MRI) system used was GE Signa, 1.5 T. T2-weighted and proton-density MR images of the brain were obtained for all subjects. The positioning of the head and the series of sections were the same as in the subsequent PET measurements (see below). A head fixation system with an individual plaster helmet was used in both the MRI and PET measurements to allow the same head positioning in the two imaging modalities (Bergström et al., 1981).

2.3.2. Radiochemistry

The precursor for synthesis of \textsuperscript{[11C]}β-CIT-FE was kindly supplied by Research Biomedicals International (Natick, MA, USA). \textsuperscript{[11C]}β-CIT-FE was prepared by O-methylation of the corresponding free acids with \textsuperscript{[11C]}methyl iodine or \textsuperscript{[11C]}methyl triflate, according to procedures that have been described in detail previously (Halldin et al., 1996; Lundkvist et al., 1998).

2.3.3. PET

The PET examinations were performed using a Siemens ECAT Exact HR 47 in three-dimensional
mode. The reconstructed volume was displayed as 47 sections with a center to center distance of 3.125 mm and a slice thickness of 4 mm. The in-plane and axial resolutions were approximately 3.8 mm and 4.0 mm, full width at half maximum (Weinhard et al., 1994).

In each PET measurement, the subject was placed recumbent with the head in the PET system. A cannula was inserted into the antebrachial vein on both arms. A sterile physiological phosphate buffer solution (pH=7.4) containing \[^{11}\text{C}]\beta\text{-CIT-FE (196–323 MBq)} was injected intravenously as a bolus over 2 s. The specific radioactivity was 300–3299 Ci/mmol (11–122 GBq/\text{A}mol) at the time of injection.

Brain radioactivity was measured in a series of consecutive time frames up to 57 min. The frame sequence consisted of three 1-min frames followed by four 3-min frames and seven 6-min frames.

2.3.4. Image analysis

Regions of interest (ROIs) were drawn on three horizontal MRI sections through the central part of the putamen and the head of the caudate, respectively. The top and bottom of the putamen and caudate were not included, because these parts may be subject to considerable partial-volume effects. Three horizontal sections covering the middle part of the region defined the cerebellum. The ROIs were transferred to the corresponding reconstructed PET images. To obtain regional time–activity curves, average radioactivity in each ROI was calculated for each frame, corrected for decay, and plotted vs. time.

2.3.5. Calculations

The binding potential (BP) reflects the ratio between receptor density (\(B_{\text{max}}\)) and affinity (\(K_d\)). Assuming that \(K_d\) is constant in the population, BP may serve as an index for receptor density. To calculate regional BP values, the simplified reference tissue model (Lammertsma et al., 1996; Gunn et al., 1997) was applied, as described previously (Farde et al., 2000). In this model, the time–activity curve for the cerebellum, a reference region assumed to be devoid of DAT, was used as an indirect approximation of the plasma input function.

3. Results

Summary statistics for all measures of interest are shown in Table 1. As can be seen from the table, the data for both the cognitive parameters and DAT binding were within normal ranges and demonstrated sufficient variability to compute meaningful measures of association.

In relating the three sets of variables, age, DAT binding, and cognitive performance, we first examined the zero-order correlations among these variables. One-tailed product–moment correlations were computed, because previous research unequivocally indicates that (a) age is negatively related to both DAT binding and cognitive performance, and (b) DAT binding is positively related to cognitive performance.

DAT binding decreased as a function of advancing age, with values predicted by the following relationships: \(\text{BP}=6.8006–0.0337\times\text{age}\) for the caudate (\(r=0.65, P<0.02\)); and 6.6316–0.0277\times\text{age}\) for the putamen (\(r=0.70, P<0.01\)). The mean age-related decrease in DAT binding was estimated to be 4.9% per decade for the caudate and 4.2% per decade for the putamen. The observed rates of decline are in good agreement with prior observations (Van Dyck et al., 1995; Rinne et al., 1998). Fig. 1 shows representative PET images of FE-CIT binding to DAT in a younger, a middle-aged, and an older subject.

Further, age was negatively related to performance in the three episodic memory tasks and the two executive tasks. The correlations were \(-0.56, -0.59, -0.53, -0.63, \text{and } -0.38\) for word recall, figure
recall, face recognition, working memory, and word fluency, respectively. Each correlation was significant at \( P < 0.05 \) or better, except for the test for word fluency, which failed to approach conventional significance (\( P < 0.11 \)). As expected, age was unrelated to performance in the Information subtest of the WAIS-R (\( r = 0.27, P > 0.15 \)). Thus, in general, the age–cognition relationships were in precise accord with previous research.

DAT binding in caudate and putamen were strongly related (\( r = 0.60, P < 0.02 \)). Thus, following the analytical strategy of Bäckman et al. (2000), these data were aggregated to form a DAT composite score. The DAT composite was positively related to performance in all cognitive tasks. The correlations were 0.68, 0.70, 0.63, 0.70, 0.55, and 0.56, for word recall, figure recall, face recognition, working memory, word fluency, and Information, respectively (all \( P \)'s < 0.05).

In line with Bäckman et al. (2000), we then conducted hierarchical regression analyses to determine the relative importance of age and DAT binding to performance in the cognitive tasks. Two analyses were performed for each cognitive task variable. The relative variance accounted for by age and DAT binding in each ordinal position reflects the strength of association with the cognitive criterion. The top panel of Table 2 shows that although age made a substantial initial contribution to performance in the episodic memory and executive tasks, DAT binding explained an additional 13–24% of the cognitive variance when entered second. Together, age and DAT binding accounted for between 31% and 55% of the performance variation across the five tasks. Most interestingly, the middle panel of Table 2 shows that initial entry of DAT effectively eliminated the influence of age on cognitive performance. Specifically, although age accounted for between 15 and 40% of the variation in episodic memory and executive function when entered first, it only accounted for 1–9% of the variance following statistical control of DAT.

This pattern of results indicates that DAT may serve as a biochemical marker of age-related deficits in episodic memory and executive function, and that DAT is implicated in cognitive performance irrespective of age. The latter point was substantiated by the results for Information. For this test, DAT accounted for slightly less than one third of the total variation whether entered first or second in the equation, whereas age was unrelated to performance.

To further substantiate these findings, we used an established statistical procedure (Salthouse, 1992) to...
determine the amount of age-related cognitive variance accounted for by statistical control of DAT. This procedure estimates the amount of variation for a particular outcome measure (e.g., episodic memory) associated with an independent variable (e.g., age) that is accounted for by a mediating variable (e.g., DAT). The calculation involves subtracting $R^2$ for the independent variable when entered last in the equation from $R^2$ for the independent variable when entered first in the equation, and dividing this by the latter $R^2$ estimate. The values in the bottom panel of Table 2 clearly indicate that DAT accounted for a substantial portion of the age-related cognitive variation.

4. Discussion

The present results demonstrate a correlative triad among adult age, in vivo DAT binding in the striatum, and performance in tasks assessing episodic memory and executive function. In this way, we extend similar findings from previous PET studies on postsynaptic markers of dopaminergic neurotransmission (Volkow et al., 1998a,b; Wang et al., 1998; Bäckman et al., 2000) and a SPECT study on the presynaptic DAT marker (Mozley et al., 2001). It is noteworthy that remarkably strong and consistent findings have been obtained in research on DA and cognitive aging, although the relevant studies involve relatively few participants and thus have limited statistical power.

The current data further corroborate earlier observations by indicating that the effects of aging on cognitive performance were mediated by DAT binding, whereas the reverse was not true. The result that DAT binding is related to cognitive performance over and above age was strengthened by the fact that DAT binding was associated with performance on the Information subtest from the WAIS-R, for which no age-related differences were observed. Of particular consequence, the relationship of DAT binding to cognitive performance was quite uniform, with correlations ranging from 0.55 to 0.70 across the six cognitive tasks. This strikingly similar size of associations was observed although there was variation both across (i.e., episodic memory, executive functioning, crystallized intelligence) and within (e.g., word recall vs. face recognition in episodic memory; working memory vs. verbal fluency in executive functioning) task domains. This pattern of results suggests a rather general role of the DA system in cognitive functioning.

The latter point is interesting to view in light of neurocomputational models in which DA is hypothesized to facilitate switching between different targets both within and across neural networks (e.g., Beninger, 1983; Oades, 1985; Servan-Schreiber et al., 1998; Li et al., 2001). By enhancing the neural signal relative to background noise (e.g., Cohen and Servan-Schreiber, 1992; Sawaguchi et al., 1988), DA is assumed to promote the firing frequency of innervated neurons (e.g., Daniel et al., 1991; Luciana et al., 1998). Obviously, the global influence of DAT binding on cognitive performance observed in the present research is consistent with these assertions.
The age-related DAT loss observed in this study is in good agreement with previous PET studies of DAT (Van Dyck et al., 1995; Rinne et al., 1998) as well as related studies targeting D₁ (Suhara et al., 1991; Wang et al., 1998) and D₂ (Nordström et al., 1992; Ichise et al., 1998) receptor densities. The similar aging patterns observed for pre- and postsynaptic DA markers are interesting to consider in view of research that has specifically targeted the relationship between these markers. Replicating and extending animal studies (e.g., Irwin et al., 1994; Hebert and Gerhardt, 1998), Volkow et al. (1998a,b) found a sizable relationship between D₂ receptor binding and DAT binding in the striatum. Importantly, this association remained after partialing out the age-related variance. This suggests that the expression of receptors and transporters may reflect functional demands on dopaminergic pathways. Indeed, work on DAT knockout mice has shown a reduction of D₂ receptor mRNA in postsynaptic medium spiny neurons (Gainetdinov et al., 1999).

Given that loss of DAT may initially result in increased DA, one possibility is that increased DA levels lead to functional down-regulation of receptors in these neurons, thereby contributing to the decline in postsynaptic receptor densities with advancing age (e.g., Sakata et al., 1992; Zhang et al., 1995; Shinkai et al., 1997).

Age-related losses of brain protein concentrations may reflect decrease in neuronal number (Fearnley and Lees, 1991; Snow et al., 1993), decrease in the number of synapses per neuron (Gopnick et al., 1999), and decreased expression of receptor proteins per cell (Mesco et al., 1993). Although there is empirical support for all these mechanisms, evidence suggests that the age-related decrease in DAT mRNA exceeds the extent of neuronal loss. Accordingly, age-related changes in DAT have been largely attributed to losses of DAT mRNA rather than to a decreased number of neurons or nerve terminals (De Keyser et al., 1990). The age-related decrease in DAT mRNA is an interesting observation in view of the fact that mRNA for the enzyme tyrosine hydroxylase (TH), which converts tyrosine to the DA precursor DOPA is but marginally affected by aging (e.g., Joyce, 2001). Thus, rather than suggesting a general age-related biochemical failure of DA neurons, the evidence indicates that these neurons selectively down-regulate the expression of DAT with advancing age.

Given that the current study and related research indicate a strong relationship between striatal DA function and cognitive aging, it is important to note that the striatum is topographically organized with abundant reciprocal connections to the neocortex (Graybiel and Ragsdale, 1979; Crosson, 1992) and the thalamus (Dom et al., 1976; Jayarman, 1984). Alterations in any one component of the frontostriatal network may lead to functional and eventually structural changes in other components (Cummings, 1993; Wise et al., 1996). Toward this end, it has been stressed that a declining nigrostriatal DA system may lead to impoverished inputs to the frontal lobes, thereby reducing the executive capacity of working memory (Prull et al., 1999). Relatively, a deficient DA-frontal mechanism has been proposed to underlie age-related changes in context processing, resulting in age decrements across several cognitive domains including attention, inhibition, and working memory (Braver et al., 2001).

Further, structural imaging evidence indicates gradual age-related morphological changes in the frontal cortex and the striatum of about the same magnitude across the adult life span (Good et al., 2001; Raz et al., 2003; Raz, 2004). Functional imaging evidence demonstrates under-recruitment of task-relevant frontal regions during episodic memory (Grady et al., 1995; Stebbins et al., 2002) and working memory (Rypma and D’Esposito, 2000; Rypma et al., 2001) performance with advancing age. Underscoring the interrelatedness between striatal and frontal regions, Volkow et al. (2000) demonstrated a strong relationship between D₂ binding and frontal and cingulate metabolism that was independent of age. Finally, there is PET evidence that the size of the age-related loss for frontal and other extrastriatal DA markers mimics that observed for striatal DA markers (Suhara et al., 1991; Inoue et al., 2001; Kaasinen et al., 2000). Thus, the current finding of a strong link between age-related losses of striatal DAT binding and age-related cognitive deficits may best be interpreted to reflect general age-related alterations in the frontostriatal circuitry, rather than dopaminergic down-regulation in the striatum, per se. This contention does not exclude the possibility that DAT may serve as an excellent biological marker of cognitive aging in a wider sense including the entire frontostriatal circuitry.
Acknowledgments

This research was supported by grants to Lars Bäckman from the Swedish Research Council and the Bank of Sweden Tercentenary Foundation, and to Lars Farde from the Swedish Research Council. Nina Erixon-Lindroth was supported by a graduate stipend from the Swedish Foundation for Strategic Research. We are grateful to Kjerstin Lind and Hans Olsson for their assistance in the PET experiments, and to Alan Baddeley and Arne Öhman for their contributions in modifying the visual working memory test.

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