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Dopamine D1 Receptor Associations within and between Dopaminergic Pathways in Younger and Elderly Adults: Links to Cognitive Performance

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Age-related dopamine (DA) losses have been extensively demonstrated for the D2 receptor subtype. Comparatively little is known about adult age changes regarding D1 receptors. In this study, we demonstrate marked age-related D1 receptor losses in striatal, limbic, and cortical areas using positron emission tomography and the radioligand [^{11}C]SCH23390 in humans. Interregional correlations of binding potential (BP) values were high for areas within DA pathways in younger and elderly adults alike. Furthermore, interregional correlations in D1 BP between DA pathways were uniformly high in younger adults, indicating that D1 receptor densities in striatal, limbic, and cortical areas are not regulated independently, despite dopaminergic innervation from different midbrain areas. For elderly adults, between-pathway correlations of D1 receptor densities were preserved only between mesolimbic and mesocortical areas, whereas striatal BPs were weakly related to those in limbic and neocortical regions. Importantly, weak between-pathway correlations in elderly adults were found only for the slower half of the sample when BP was estimated during a cognitive interference task. These results suggest that D1 receptor densities in different pathways are not regulated independently in younger adults, but segregate in older age, and that this segregation of D1 receptor systems may be related to age-related cognitive slowing.

Keywords: aging, cognition, D1 receptors, dopamine, PET

Introduction

Dopamine (DA) plays an important role in modulating motor and cognitive functions, and during the last decade, DA losses with advancing age have emerged as an important mediator of age-related changes in motor and cognitive performance (Volkow, Gur, et al. 1998; Wang et al. 1998; Bäckman et al. 2000, 2006, 2009, 2010; Erixon-Lindroth et al. 2005; Reeves et al. 2005; Karlsson et al. 2009; Fischer et al. 2010; Morcom et al. 2010). DA is synthesized in the midbrain; it densely innervates the striatum and, to a lesser degree, limbic and cortical areas via separate pathways. Dopaminergic projections from the substantia nigra (SN) reach the associative (largely the caudate) and sensorimotor (largely the putamen) part of the striatum via the nigrostriatal pathway. The ventral tegmental area (VTA) provides dopaminergic input to the ventral striatum (VST; largely the nucleus accumbens) and the limbic system via the mesolimbic pathway and to the lateral prefrontal cortex and other neocortical areas via the mesocortical pathway. The 2 main DA receptor types expressed in the human brain are D1-like (D1 and D5; henceforth referred to as D1 receptors) and D2-like (D2, D3, and D4; henceforth referred to as D2 receptors). D1 receptors are more abundant than D2 receptors in neocortical areas, particularly in prefrontal regions, and there is evidence that the cortical D1 receptor system plays a key role in executive functioning, working memory, attention, and inhibition, which depend on frontal lobe integrity (Lidow et al. 1991; Hall et al. 1994; Williams and Goldman-Rakic 1995; Müller et al. 1998; Ito et al. 2008; Takahashi et al. 2008; Bäckman et al. 2009; Karlsson et al. 2009; McNab et al. 2009).

Human molecular imaging studies have consistently found an age-related decrease of D2 receptor markers in the magnitude of 5–10% per decade, starting in early adulthood (e.g., Antonini et al. 1993; Rinne et al. 1993; Wang et al. 1995; Wong et al. 1997; Pohjalainen et al. 1998; Volkow, Wang, et al. 1998; Bäckman et al. 2000; Ishibashi et al. 2009). Less is known about age-related losses of D1 receptors, with only 2 published studies. However, similar to D2 receptors, these studies suggest losses of D1 receptor densities in the striatum of around 8% per decade (Suhara et al. 1991; Wang et al. 1998) and losses in prefrontal cortex (Suhara et al. 1991) and occipital cortex (Wang et al. 1998) of similar magnitude.

Although age-related DA receptor losses throughout the brain have been relatively well documented, to our knowledge, no previous study has examined interregional correlations of DA receptor densities in elderly adults. Thus, it remains unknown whether individual differences in DA receptor losses are consistent across different brain areas. Two recent positron emission tomography (PET) studies in middle-aged adults reported weak interregional correlations between striatal and cortical D2 receptor densities (Cervenka et al. 2010; Zald et al. 2010). These findings suggest that different dopaminergic systems are anatomically and functionally distinct. However, D2 receptors are largely confined to the striatum and it is difficult to assess D2 receptor densities in the striatum and neocortex with the same radioligand (Slifstein et al. 2010). Therefore, weak correlations of extrastriatal and striatal D2 receptors may be due to the use of different ligands in striatum and extrastriatal areas (Cervenka et al. 2010) and due to low measurement reliability in extrastriatal regions (Zald et al. 2010).

Moreover, although different areas of the midbrain innervate striatal and neocortical/limbic areas, separate DA pathways do not work in isolation (e.g., Haber et al. 2000; Düzel et al. 2009), making it unlikely that receptor densities in striatum and cortex are regulated completely independently. Rodent and monkey studies have identified dopaminergic projections from the VST to the associative and sensorimotor parts of the striatum via the midbrain (Nauta et al. 1978; Somogyi et al. 1981). Accordingly, in addition to reciprocal DA projections between midbrain and striatum, efferent projections of the VST

reach both the VTA and the SN (Fig. 1). This striato-midbrain-striatal circuitry forms a "spiral" loop, which connects the frontal cortex to motor areas (for reviews, see Joel and Weiner 2000; Haber and Knutson 2010).

Therefore, it might be expected that intact striato-midbrain-striatal projections lead to balanced (i.e., correlated) DA functions across nigrostriatal, mesolimbic, and mesocortical areas in younger adults, even though DA innervation originates from different areas in the midbrain. However, when there are DA losses in striatum and midbrain, such as in older age (Fearnley and Lees 1991; Snow et al. 1993), projections between pathways may be altered. On this view, correlations among areas within the nigrostriatal, mesolimbic, and mesocortical pathway are expected to be positive regardless of age, as they are innervated from the same midbrain area, but correlations among DA receptor densities between pathways may be reduced in elderly compared with younger adults.

Integrity of dopaminergic striato-midbrain-striatal projections is thought to be critical to effective integration of emotional, cognitive, and motor functions (Haber et al. 2000; Belin and Everitt 2008). Therefore, segregation of D1 systems could contribute to impaired cognitive performance in aging. Specifically, in task situations that require an effective integration of cognitive processing and motor speed, the elderly may be at a disadvantage as DA levels in mesocortical and mesolimbic areas, which are associated with cognitive processing, may be regulated relatively independently from those in the nigrostriatal pathway, which are related to motor functioning (i.e., show weaker associations). An example of such a situation is cognitive interference resolution, which refers to the speed with which a target is correctly discriminated from incongruent, or interfering, distracters. Cognitive interference resolution involves prefrontal areas but also poses demands on the motor system, as participants are required to indicate their responses by pressing a button as fast as possible.

In the present study, 20 younger and 20 elderly adults underwent 2 PET measurements with the D1 receptor ligand [^{11}C]SCH23390, one during rest and one while performing a cognitive interference task. For the resting state PET measurement, the key objectives were to determine whether 1) the expected mean loss of D1 receptors in older age generalizes across different DA pathways and brain regions and 2) relationships between D1 receptor availability within and between DA pathways change with age. D1 receptor densities were estimated for regions part of the nigrostriatal pathway (sensorimotor striatum [SMS] and associative striatum [AST]) and the mesocortical/limbic pathways (VST, medial temporal lobe [MTL], orbitofrontal cortex [OFC], anterior cingulate cortex [ACC], medial prefrontal cortex [MPFC], dorsolateral prefrontal cortex [DLPFC] and parietal cortex [PC].

During cognitive task performance, participants performed the multisource interference task (MSIT), which taxes interference resolution and involves the frontal cortices, particularly the DLPFC and the ACC (Bush et al. 2003), and where reaction time (RT) differences between control and interference trials constitute the primary behavioral outcome measure. Provided that high interregional D1 receptor associations between frontal areas and sensorimotor striatum reflect a well functioning integration of cognitive and motor functions, we predict that high-interregional relationships of D1 receptor densities between frontal cortex and sensorimotor striatum are linked to response speed during cognitive interference resolution.

Materials and Methods

Participants

Twenty younger (mean = 25.20, standard deviation [SD] = 2.21, 10 females) and 20 elderly (mean = 70.35, SD = 3.12, 10 females) right-handed adults took part in the study. All participants reported to be nonsmokers and free from previous or present drug or alcohol abuse and significant medical conditions, such as neuropsychiatric disorders or brain damage. Women were not on hormone replacement therapy. The study was approved by the Ethics and Radiation Safety Committees at the Karolinska Hospital, Stockholm, Sweden.

Procedure

Participants took part in 2 separate PET measurements, both acquired in the afternoon, but not necessarily on the same day (10 younger and 13 elderly participants performed the measurements on the same day). During the first data acquisition, participants were instructed to rest. During the second PET measurement, participants performed the MSIT. After completion of the study, participants were paid 4000 SEK.

MSIT

During the MSIT measurement, participants viewed combinations of 3 digits (0, 1, 2, and 3) in the center of a computer screen (Fig. 2). Each combination consisted of 1 digit that was different from the other 2 digits (e.g., 211), and participants were instructed to identify the digit that was different as fast as possible via a corresponding button press. Responses were given via a keypad with 3 buttons: 1, 2, and 3, from left to right. For control trials, the target was always congruent with the position (e.g., the digit 1 was in the first position), in a larger font size than the 2 distracters, and the distracters were always 0s (e.g., 100). For

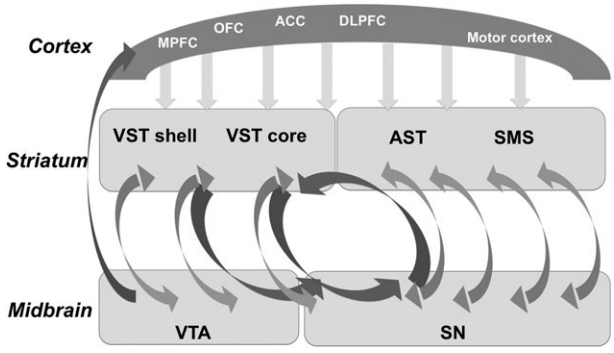

Figure 1. Schematic illustration of corticostriatal projections and spiral striato-midbrain-striatal pathways. Adopted by permission from MacMillan Publishers Ltd: Neuropsychopharmacology, Haber and Knutson (2010).

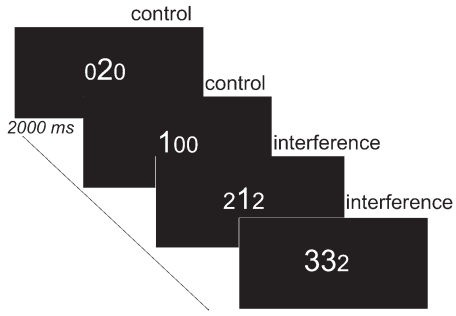

Figure 2. The Multisource Interference Task (Bush et al. 2003). Participants are instructed to indicate the digit that is different from the other 2 as fast and accurately as possible.

interference trials, the target was different from the corresponding position, and distracters were other digits that could be either larger or smaller than the target (e.g., 211 or 232). Each trial was presented for 2000 ms and control and interference trials were alternated in blocks of 24 trials. There were 16 blocks in total, with a 90 s break after block 4 and 8.

Positron Emission Tomography and Magnetic Resonance Imaging

The PET measurements were performed with an ECAT Exact HR 47 system (CTI/Siemens) run in 3D mode and with a transaxial resolution of 3.8 mm full width at half maximum at the central field of view and 4.5 mm radially at 20 cm from the center. Following a transmission measurement of 10 min with 3 rotating 68Ge–68Ga sources, 300 MBq of [^{11}C]SCH23390 (Halldin et al. 1986) was injected into the left antecubital vein as a rapid bolus injection. Emission data were recorded over a period of 51 min in 13 time frames of increasing duration. A T1-weighted magnetic resonance image (MRI) with a voxel size of 1.02 × 1.02 × 1.00 mm was acquired on a 1.5 T GE Signa Scanner and coregistered to the summated PET image. The anatomical MRI was then segmented into gray matter, white matter, and cerebrospinal fluid, and the segmented gray matter regions of interest (ROIs) were used to obtain time activity curves (TACs) from the PET image for each hemisphere and collapsed across hemispheres.

For TAC generation, radioactivity was plotted versus time and corrected for decay. There were no age-related differences in the general shape or time of peak of the TACs (see Supplementary Fig. 1). D1 receptor availability was measured by the binding potential (BP) of [^{11}C]SCH23390 defined as the ratio at equilibrium of specifically bound radioligand to that of nondisplaceable radioligand in tissue (Innis et al. 2007) and calculated using the simplified reference tissue model, with the cerebellum as reference region (Lammertsma and Hume 1996). PET data were corrected for partial-volume effects (Meltzer et al. 1990). All parameters and procedures were identical for both PET measurements.

ROIs

ROIs were manually delineated on each individual's coregistered MRI using the Human Brain Atlas software (Roland et al. 1994). Based on our a priori hypotheses about interregional correlations among areas within known dopaminergic pathways, we selected ROIs from previously published reviews on the dopaminergic system (Lewis and Sesack 1997; Vallone et al. 2000; Nieoullon and Coquerel 2003; Pierce and Kumaresan 2006; Haber and Knutson 2010). We delineated the dorsal areas of the striatum (AST and SMS) in the nigrostriatal pathway and VST, MPFC, OFC, ACC, MTL, DLPFC and PC in the mesocortical/limbic pathways.

Boundaries for all ROIs were based on previously published reports (Abi-Dargham et al. 2002; Cervenka et al. 2008, 2010) and an MRI-based atlas (Tamraz and Comair 2005). Briefly, the striatum was functionally divided into precommissural putamen and dorsal caudate nucleus (AST), postcommissural dorsal putamen (SMS), and the ventral portion of the striatal complex (VST). In the frontal lobe, we indentified the DLPFC as the medial inferior and lateral part of superior frontal gyrus, the MPFC as the medial part of superior frontal gyrus, and the OFC inferior to MPFC and bound laterally by the DLPFC. The ACC was defined as the anterior part of the cingulate, inferior to cingulate sulcus, and superior to corpus callosum, and the MTL was delineated as hippocampus and amygdala. The PC was posteriorly bound by the parieto-occipital sulcus, inferiorly by the cingulate sulcus, and anteriorly by the central sulcus. All 9 ROIs were delineated separately for each hemisphere.

Statistics

Resting State Measurement

All statistics were conducted using the BP estimates for ROIs collapsed across hemispheres, as there were significant resting state interhemispheric correlations (Ps < 0.05) for all ROIs in both age groups (with the exception of the MTL in elderly adults, $r = 0.36$, $P = 0.12$). The mean and SD of BP were calculated separately for each age group, and ROI and age differences in regional BPs were compared using a 2 (Age) × 2 (Sex) × 9 (ROI) ANOVA (sex was included as a factor in order to account for potential sex differences in BP). Post hoc independent t-tests and Cohen's d as a measure of effect size were computed to explore potential interactions.

For the analysis of interregional correlations within and between dopaminergic pathways, Pearson product–moment correlation coefficients were calculated among BPs for areas in the nigrostriatal, mesolimbic, and mesocortical pathways. The binomial distribution was used to test our hypothesis that correlation coefficients for between-pathway correlations were higher for younger than for elderly adults. The 28 correlation coefficients (14 between-pathway correlations in 2 groups) were ranked and divided into high and low. The binomial distribution is defined as

$$p\left(X\right) = C_X^N p^X q^{(N-X)} = \frac{N!}{X!(N-X)!} p^X q^{(N-X)}$$

where $p(X)$ is the probability of X high correlations occurring in one group, N is the number of correlations in one group, p is the probability of a high correlation on any one correlation, $q = 1 - p$, and C_X^N is the number of combinations of N taken X at a time (Howell 2009).

The BP values portrayed in Figure 5 were standardized in z-score metric within age groups to enable comparability of individual ROI profiles between age groups. For the MSIT measurement, mean accuracy and mean RT for accurate responses were calculated separately for control and interference trials. The difference in RT between correct interference and control trials ($RT_{interference} - RT_{control}$) was used in all further analyses, with a larger score indicating a greater interference effect. Interregional correlations among mean BP values during the MSIT measurement were restricted to task-relevant areas, which were DLPFC, ACC, and SMS according to previous functional MRI studies (e.g., Bush et al. 2003) and our a priori hypotheses. Because of region-specific hypotheses, the difference in correlation strength between groups were here compared using Fisher's r with z-transformed scores, and probability levels were adjusted for 1-tailed tests.

Results

Resting State BP across Age

As can be seen in Figure 3, mean BP during the rest measurement in both age groups was highest in the striatal ROIs ($mean_{younger} = 1.49$, SD = 0.25; $mean_{elderly} = 1.16$, SD = 0.15), followed by the frontal and parietal ROIs ($mean_{younger} = 0.53$, SD = 0.04; $mean_{elderly} = 0.41$, SD = 0.04), and finally the MTL ROI ($mean_{younger} = 0.23$, SD = 0.10; $mean_{elderly} = 0.20$, SD = 0.06). Elderly adults had on average 20.95% (SD = 3.61) lower BP values than younger adults, which translate into a mean overall D1 receptor loss of around 5% per decade. An Age × Sex × ROI ANOVA showed a main effect of Age ($F_{1,36} = 22.55$, $P < 0.001$) and a main effect of ROI ($F_{2.24,80.64} = 677.41$, $P < 0.001$, with degrees of freedom corrected using Greenhouse–Geisser estimates of sphericity). We also observed a significant Age × ROI interaction ($F_{2.24,80.64} = 12.38$, $P < 0.001$), reflecting that the effect of Age differed across ROIs (Fig. 3). t-Tests revealed that there was no age group difference in BP for the MTL ($t < 1$, $d < 0.2$) but strong age effects for all other ROIs (ts > 2.14, ds > 0.80). We found no significant main effect or any interaction effects involving Sex (Fs < 1).

Interregional Correlations of Resting State BP

Correlations among D1 BPs in the 9 selected ROIs by age group are shown in Figure 4. For younger adults, D1 receptor densities were highly correlated among areas within the nigrostriatal, mesolimbic, and mesocortical pathways (rs > 0.61, Ps < 0.01). Moreover, younger adults showed moderate to

strong between-pathway correlations for all 3 DA circuitries (rs > 0.51, Ps < 0.05), with the exception of PC × SMS, where there was a nonsignificant trend (r = 0.40, P = 0.08). These patterns suggest that D1 receptor densities in separate pathways are not regulated independently in early adulthood.

For elderly adults, BPs in ROIs within the nigrostriatal and mesocortical pathways were also highly correlated (rs > 0.77, Ps < 0.01). Correlations within the mesolimbic system were high among corticolimbic areas (ACC, OFC, MPFC; rs > 0.69, Ps < 0.01) and moderate for the VST and MTL with corticolimbic areas (rs > 0.47, Ps < 0.05, with the exception of $r_{VST \times ACC}$ = 0.42, P = 0.07 and $r_{MTL \times OFC}$ = 0.37, P = 0.11).

Significant interregional correlations among the ROIs in the mesolimbic and in the mesocortical pathways were also present in elderly adults (with the exception of the VST). However, elderly adults showed weak correlations of the nigrostriatal ROIs to both the mesolimbic and the mesocortical ROIs (rs < 0.40, Ps > 0.05, except $r_{AST \times DLPFC}$ = 0.46, P < 0.05), suggesting that elderly adults had weaker between-pathway correlations compared with younger adults. We used the binomial distribution to estimate the probability of the difference in between-pathway correlations for younger and elderly adults. The ranking of the 28 coefficients for the between-pathway correlations (highlighted in red in Fig. 4) showed that 13 of the 14 highest correlation coefficients were found in the younger group. According to

$$p(13) = \frac{14!}{13!1!}(0.5)^{13}(0.5)^{1} = 0.00085$$

the probability of having 13 of the highest 14 correlations in the younger group purely by chance is less than 0.001.

This pattern is of importance for the interpretation of the global mean D1 receptor density differences we report above. The lack of interregional relationships of the nigrostriatal to the mesocortical and mesolimbic pathways in elderly adults suggests that there are individual differences in the rate of age-related decline in the different DA pathways.

This observation is illustrated in Figure 5, showing standardized BP values for the nigrostriatal and mesocortical/limbic ROIs, for which within-pathway correlations were high in both age groups (Ps < 0.01). Figure 5 shows that younger adults are more consistently either above or below the mean BP for their age group than elderly adults. Elderly adults are more variable in that they may show low D1 BP relative to their age group in the nigrostriatal system but have relatively high D1 receptor densities in the mesocortical/limbic ROIs relative to the group mean and vice versa.

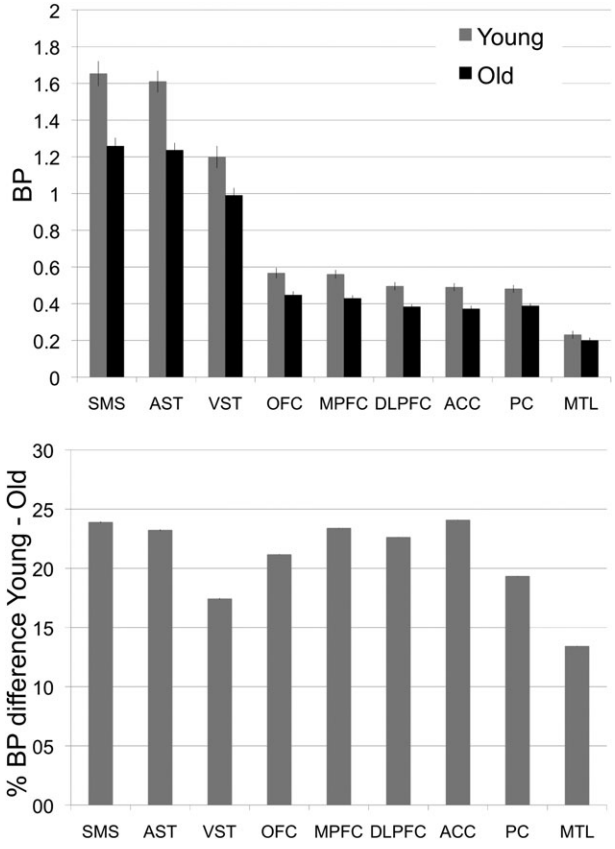

Figure 3. Mean BP with standard errors across age group and region (top) and % decrease in BP for elderly compared with younger adults (bottom).

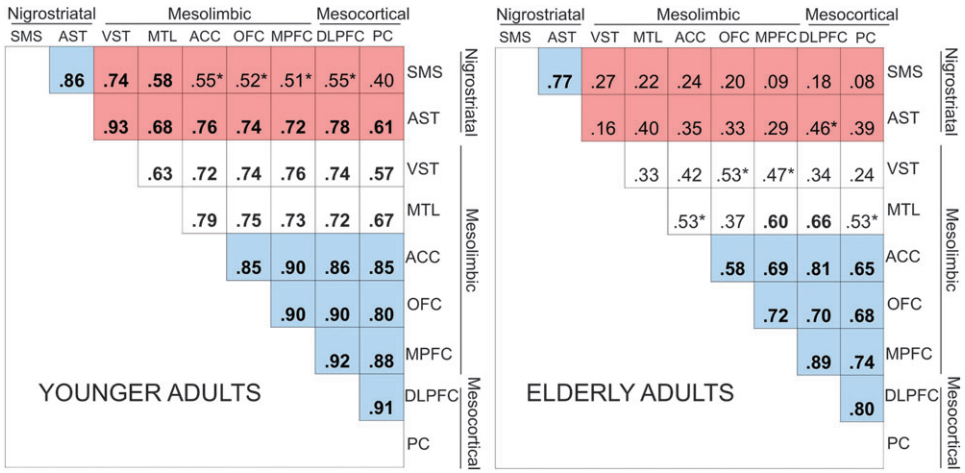

Figure 4. Bold correlation coefficients significant at $P < 0.01$, *Correlation coefficients significant at $P < 0.05$. Blue areas highlight high within-pathway correlations among nigrostriatal areas and among mesocortical/limbic areas in both age groups. Red areas highlight high between-pathway correlations in younger adults but low correlations in elderly adults.

Interregional Correlations of BP during Cognitive Task Performance

One younger adult was excluded from the MSIT analyses because of failure in response recording. In addition, one younger and one elderly adult were excluded from the MSIT analyses as they had very high error rates of 98.44% and 44.27%, respectively, for the interference trials. All remaining participants (18 younger, 19 elderly) performed the task accurately (mean error rate: younger = 3.63%, elderly = 7.99%). The difference in RT between correct interference and control trials was significantly larger for elderly adults (mean = 399.63 ms, SD = 95.94) than for younger adults (mean = 337.78 ms, SD = 84.86; $t_{35} = 2.07$, $P < 0.05$; Fig. 6).

For both younger and elderly adults, BP estimates during MSIT performance were significantly correlated with BP estimates in the same ROI during rest ($rs_{younger} > 0.61$, $Ps < 0.01$; $rs_{elderly} > 0.47$, $Ps < 0.05$).

As described above, our analysis of interregional correlations during MSIT performance was focused on task-relevant ROIs (SMS, ACC, and DLPFC), as demonstrated in previous functional-magnetic resonance imaging (fMRI) studies (Bush et al. 2003). Nevertheless, to serve as an analog to Figure 4, correlational tables including BPs during MSIT performance for all 9 ROIs are presented separately for younger and elderly adults in Supplementary Figure 2. Interregional correlations among the task-relevant ROIs during the MSIT mirrored closely those during rest: There were high correlations between the 2 areas within the mesocortical/limbic system (DLPFC and ACC) for both age groups ($r_{younger} = 0.79$, $r_{elderly} = 0.82$, $Ps < 0.01$; $z = -0.09$, $P > 0.40$) but significantly lower correlations for elderly, compared with younger, adults between SMS and ACC ($r_{younger} = 0.84$, $P < 0.01$; $r_{elderly} = 0.23$, $P = 0.30$; $z = 1.86$, $P < 0.05$; Fig. 7*A*) and between SMS and DLPFC ($r_{younger} = 0.79$, $P < 0.01$; $r_{elderly} = 0.23$, $P = 0.30$; $z = 1.70$, $P < 0.05$; Fig. 7*A*). There were no significant correlations between BP in any of the 3 task-relevant ROIs (DLPFC, ACC, and SMS) and MSIT performance in either age group ($Ps > 0.10$).

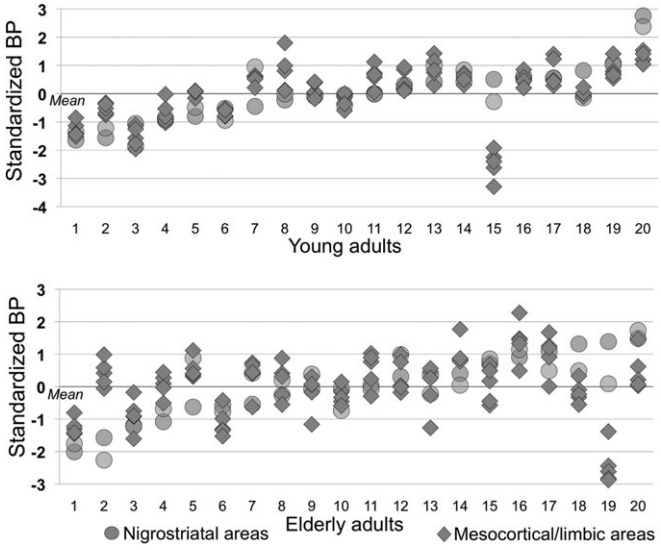

Figure 5. Individual *z*-score-standardized BP values for nigrostriatal (AST and SMS) and mesocortical/limbic ROIs (ACC, OFC, MPFC, DLPFC, and PC) in younger and elderly adults.

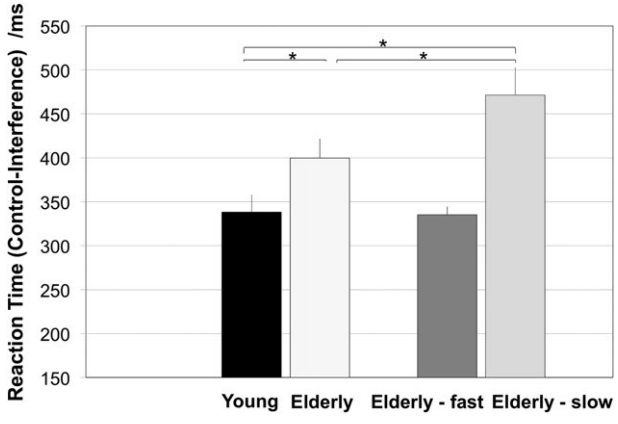

Figure 6. Behavioral performance during the MSIT by age group and performance level (fast vs. slow) for the elderly adults. Bars reflect mean RT (with standard errors) for interference control items. *Significant at $P < 0.05$.

A median split of the elderly sample based on $RT_{interference-control}$ (median = 373.05 ms) showed that the faster half of the elderly group performed as well as younger adults ($mean_{elderly\ fast} = 335.11$, SD = 29.73; $t < 1$). By contrast, the slower half of the elderly group ($mean_{elderly\ slow} = 471.32$, SD = 93.44) was significantly slower than both the younger adults ($t_{25} = 3.73$, $P < 0.01$) and the faster elderly adults ($t_{17} = 4.38$, $P < 0.01$; Fig. 6). Critically, like younger adults, faster elderly adults exhibited high correlations of SMS with ACC and DLPFC ($r_{SMS \times ACC} = 0.49$, $P < 0.05$; $r_{SMS \times DLPFC} = 0.70$, $P < 0.05$), whereas slower elderly adults showed low correlations ($r_{SMS \times ACC} = -0.01$, $P > 0.90$; $r_{SMS \times DLPFC} = -0.25$, $P > 0.30$; Fig. 7*B*). The difference in correlational strength between fast and slow elderly adults was significant for the association between SMS and DLPFC ($z = 2.44$, $P < 0.05$). However, the difference in correlation between SMS and ACC failed to reach conventional significance ($z = 1.19$, $P = 0.12$) likely due to the small sample sizes. Nevertheless, this pattern among D1 receptors suggests that the lower between-pathway correlations in elderly adults were driven by the slower subgroup, whereas elderly adults who performed as well as younger adults had patterns of interregional relationships that were similar to the younger adults. Within-pathway correlations (ACC × DLPFC) were high in younger ($r = 0.75$, $P < 0.01$), fast elderly ($r = 0.85$, $P < 0.01$), and slow elderly adults ($r = 0.91$, $P < 0.01$), and there was no significant difference in mean BP in any of the ROIs between slow and fast elderly adults ($ts < 1.7$, $Ps > 0.10$). This further suggests that fast interference resolution in aging is linked to high between-pathway correlations, but not to mean D1 receptor densities in frontal cortex and sensorimotor striatum, or to within-pathway associations.

Lastly, in order to establish whether the performance-related difference in between-pathway correlations reflected a more general compared with a task-specific pattern, we applied the subgrouping between fast and slow elderly adults to the rest PET data. As during MSIT performance, the fast elderly adults showed significant correlations between ACC and SMS ($r = 0.57$, $P < 0.05$), DLPFC and SMS ($r = 0.65$, $P < 0.05$), and DLPFC and ACC ($r = 0.57$, $P < 0.05$). For the slow elderly adults, ACC and DLPFC were significantly correlated ($r = 0.90$, $P < 0.01$) but neither ACC nor DLPFC BP correlated with SMS BP ($r_{ACC \times SMS} = 0.07$, $P < 0.80$; $r_{DLPFC \times SMS} = 0.10$, $P < 0.80$). The difference in correlation coefficients between fast and slow elderly adults was at trend level ($z_{DLPFC \times SMS} = 1.47$, $P = 0.07$; $z_{ACC \times SMS} = 1.3$, $P = 0.10$), indicating that the finding of lower

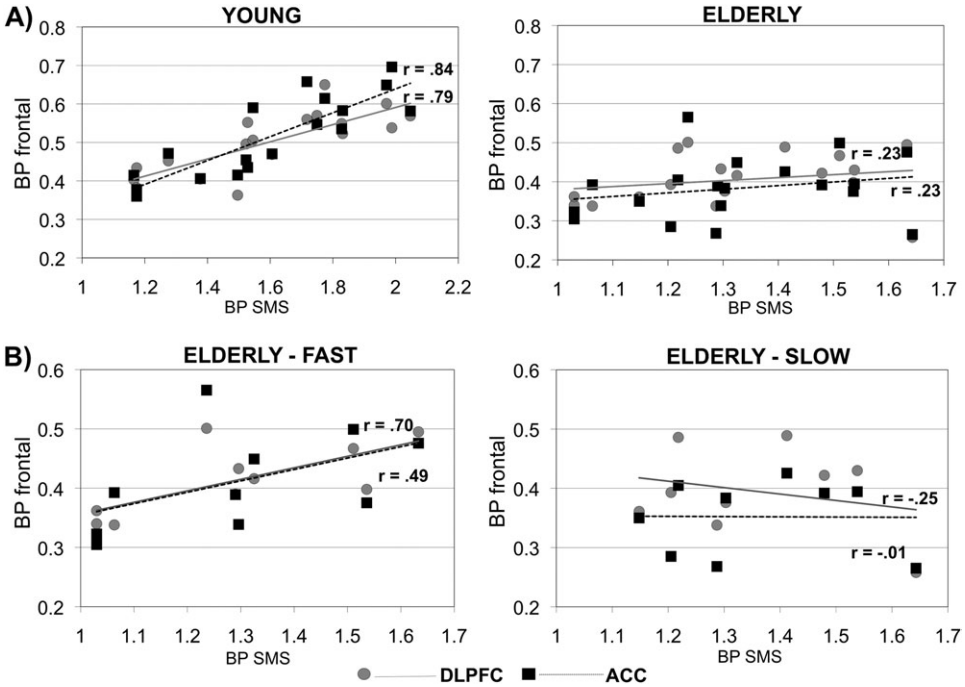

Figure 7. Correlations of D1 BP in sensorimotor striatum (BP SMS) with D1 BP in frontal areas (DLPFC and ACC) during performance of the MSIT by age group (*A*) and performance level (fast vs. slow) for the elderly adults (*B*).

between-pathway correlations in the slow elderly adults may not be task-specific but rather reflects a more general segregation of DA pathways in this group.

Discussion

This study replicates earlier reports of decreased D1 receptor densities in striatum and frontal cortex in aging (Suhara et al. 1991; Wang et al. 1998) and extends these observations showing that age-related D1 receptor losses of around 5% per decade are also found in different striatal compartments, the limbic system (with the exception of the MTL), and in different subregions in frontal cortex as well as in parietal cortex. These results are comparable with reports on D2 receptor losses in striatal, limbic, and cortical areas (e.g., Kaasinen et al. 2000; Ishibashi et al. 2009) and indicate that there are pronounced age-related losses of both receptor subtypes throughout the human brain. The lack of age-related differences in MTL D1 BP should be treated with caution, given the paucity of D1 receptors in this brain region (Ito et al. 2008; Takahashi et al. 2008), potentially resulting in poor measurement reliability.

The current finding of high interregional correlations within DA pathways for both age groups likely reflects common dopaminergic innervations from the midbrain. Mesocortical and mesolimbic areas receive DA input from the VTA, whereas the AST and SMS receive input from the SN. Relatedly, we found high correlations for the mesolimbic and mesocortical areas for both younger and elderly adults, presumably because they are innervated from a common midbrain area.

Between-pathway correlations of the nigrostriatal to the mesolimbic and mesocortical pathways were also high in younger adults, suggesting that D1 receptor densities in these circuitries are not regulated independently. This finding is in agreement with the notion that different DA pathways are connected via striato-midbrain-striatal pathways (for reviews, see Joel and Weiner 2000; Haber and Knutson 2010). Accordingly, only projections from the shell of the VST terminate in the VTA to form a closed reciprocal loop, whereas corticolimbic areas project widely to both VTA and SN via the striatum, forming a spiral striato-midbrain-striatal loop (Fig. 1).

For elderly adults, we found low between-pathway correlations for the nigrostriatal pathway with both the mesolimbic and the mesocortical pathways. The fact that we found low between-pathway correlations, but high within-pathway correlations in elderly adults, indicates that the absence of between-pathway correlations is not due to lower measurement reliability. Rather, the results show that there are individual differences in D1 receptor losses in different DA pathways, such that some elderly adults have relatively more pronounced losses in areas innervated by the VTA compared with areas innervated by the SN and vice versa. This pattern suggests that projections between the VTA pathways and the SN pathway via spiral midbrain connections may be compromised in aging. This notion is further supported by the fact that the strength of the correlations between VST and cortical areas in elderly adults maps well onto the topography of their efferent projections to the midbrain: MPFC (r = 0.47) and OFC (r = 0.53) project to areas in the VTA directly adjacent to the efferent connections of the VST, whereas ACC (r = 0.42), DLFPC (r = 0.34), and PC (r = 0.24) project to increasingly ventral areas of the midbrain (Fig. 1).

In a second PET measurement, we examined the relation between interregional D1 receptor associations and cognitive performance. According to our interpretation that low between-pathway correlations in elderly adults reflect more segregated DA systems, we predicted that weak associations between task-relevant areas are linked to increased response times during a cognitive interference task. As good MSIT

performance requires accurate interference resolution, mediated by frontal areas, as well as fast motor responses, drawing on the SMS circuitry, we focused here on interactions among D1 BP in ACC, DLPFC, and SMS. The pattern observed during the resting state PET measurement, with high within-pathway correlations for both age groups, but weak between-pathway correlations for elderly adults, was also present during cognitive task performance. There were high correlations between frontal areas in both age groups but weaker associations of the SMS with frontal areas in the elderly adults. Importantly, a median-split analysis of the older sample revealed that those elderly adults who performed as well as the younger also showed similarly high correlations between D1 BP in frontal areas and SMS. By contrast, the low-performing elderly subgroup showed weak BP associations for these regions. The within-pathway correlation between ACC and DLPFC was comparably high in younger adults, fast elderly adults, and slow elderly adults. This pattern indicates that the poor performers in the elderly sample drove the age-related reductions in between-pathway correlations and suggests that weak between-pathway links among task-relevant areas are related to slower cognitive performance. Importantly, we also found that the absence of correlations of SMS to ACC and DLPFC in the slow elderly adults was present during the rest PET scan as well. This observation suggests that reduced between-pathway correlations in low-performing elderly adults were not specific to the MSIT task but reflect a more general segregation of DA pathways in this group.

The idea that a more "youth like" brain is linked to higher cognitive performance in aging was recently put forward in an fMRI study (Nagel et al. 2009). Nagel et al. found that elderly and younger adults who showed similar levels of performance in a working-memory task also showed similar levels of brain activation in frontoparietal cortex, whereas elderly adults who performed worse than younger adults showed reduced frontoparietal responsivity. The dominant focus on group averages in the cognitive neuroscience of aging hides the heterogeneity of brain and cognition that is particularly prevalent in older age. This focus also hides the notable degree of invariance in brain characteristics that promote successful performance across age. Documenting this heterogeneity in relation to brain (e.g., interregional associations of D1 BP, and blood oxygen level–dependent [BOLD] responsivity) and cognition might facilitate detection of mechanisms that promote positive cognitive outcomes in elderly age. On a similar note, Andrews-Hanna et al. (2007) have shown that aging was associated with a reduction in coordinated (i.e., correlated) activity between neuronal systems. Most interestingly, reduced correlations between anterior and posterior regions could be linked to altered white matter integrity, as well as to poorer executive functioning, processing speed, and episodic memory. Our study may indicate that such "disconnections" between neuronal systems (O'Sullivan et al. 2001) extend also to the DA system. On the basis of recent reports of a relation between DA activity and BOLD responsivity during working memory and episodic memory (Schott et al. 2008; Bäckman et al. 2009; Landau et al. 2009; Nyberg et al. 2009), an interesting avenue for future research would be to explore the hypothesis that a more segregated DA system (i.e., reduced between-pathway correlations) in older age contributes to compromised functional brain activation. Moreover, protocols combining different imaging modalities such as PET, fMRI, and diffusion tensor imaging could be employed for a multimodal exploration of a cascade model of cognitive decline in aging, in which age-related changes in DA functions may play a key role.

To our knowledge, only 2 previous PET studies have reported interregional correlations of DA BP for striatal and extrastriatal regions (Cervenka et al. 2010; Zald et al. 2010). Both studies included middle-aged adults and focused on D2 BP. High correlations within extrastriatal regions were found, although the relationships of extrastriatal areas to striatum were weak. However, comparability between these results and the present data is hampered by the facts that Cervenka et al. used different ligands for striatal and extrastriatal D2 receptors, and that measurement reliability of extrastriatal D2 receptors is low (Slifstein et al. 2010). That said, there is evidence that D1 and D2 receptors have opposing effects on neural signaling, are weakly colocalized and differentially expressed (for a review, see Smith and Villalba 2008), and play differential roles in human cognition (e.g., Takahashi et al. 2008). Therefore, it is conceivable that previous reports of a weak association between striatal and extrastriatal D2 receptors along with strong positive associations between corresponding D1 receptors in the present study reflect a true difference in D1 and D2 receptor expression. However, future research is needed to identify more precisely the mechanisms that link striato-midbrain-striatal functions to DA receptor availability and to differences in D1 and D2 receptor expression.

Some caveats should be noted. First, while PET studies have proven valuable to our understanding of the human DA system, there are methodological limitations when compared with the more detailed information gained by, for example, single cell recordings in animals or staining techniques. We interpret our data in light of previous descriptions of the DA system and suggest that a reduction in correlations between pathways could be accounted for by midbrain DA cell losses. However, regulation of D1 receptor densities and their effects on cognition are likely much more complex than any single PET study could address. For example, although we describe the DA system in terms of a subdivision into nigrostriatal, mesolimbic, and mesocortical pathways, there is animal evidence for some overlap between these projections. Williams and Goldman-Rakic (1998) reported that frontal areas in the primate brain also receive DA projections from the SN, indicating that the separation of the DA system into distinct pathways (Fig. 1) is an oversimplification. This may further suggest that communication between pathways could also be partly influenced by diffuse projections to the frontal cortex. However, to date these projections are not well described in primates, and their functional significance is not clear. Moreover, the slow and fast elderly adults were indistinguishable in DLPFC BP, and DLPFC BP was unrelated to MSIT performance. Such associations might have been expected if the DLPFC played a key role in mediating between-pathway correlations.

Another potential concern arises from studies showing significant [^{11}C]SCH23390 binding to serotonin 5-HT2A receptors in the neocortex (e.g., Ekelund et al. 2007), whereas the striatum is largely devoid of 5-HT2A receptors in the human brain (Ito et al. 1998; Hall et al. 2000). In addition, strong age-related 5-HT2A losses have been found for the neocortex (Sheline et al. 2002; Versijpt et al. 2003; Adams et al. 2004). It may therefore be argued that the segregation between pathways in elderly adults partially reflects cortical 5-HT2A losses and not only changes in the D1 receptor systems. However,

several observations may provide indirect support for the view that the confounding effects of cortical 5-HT2A binding are most likely small: 1) Mean age differences and associated variances did not differ between cortical and subcortical ROIs which would not have been the case if 2 receptors with different age effects represent the cortical regions; 2) Striatal and cortical BPs in younger adults were highly correlated, making it unlikely that BPs in striatum and neocortex represent different receptors (i.e., striatal BPs reflecting D1 receptor densities only but cortical BPs being significantly confounded by 5-HT2A binding); and 3) We found no differences between fast and slow elderly adults in mean BPs for both ACC and DLPFC, which would have been expected if cortical 5-HT2A losses mediated the segregation of pathways.

Lastly, although our sample sizes are relatively large for PET studies, they are small for statistical inference. One of the key observations in our study is that of weaker correlations of the nigrostriatal pathway to the mesolimbic and mesocortical pathways in elderly, when compared with younger adults. We provided statistical support for this conclusion by estimating the probability for the observation that 13 of the 14 highest correlations (out of 28 correlation coefficients) were found in the younger group. This approach builds upon our a priori hypothesis but ignores direct comparisons of single correlation coefficient pairs between age groups. Alternatively, the correlation coefficients could have been compared directly using Fisher's r with z-transformed scores or by estimating the overlap between confidence intervals for each pair of correlations. However, both of these approaches would entail at least 14 different comparisons, which requires multiple comparison adjustments of the significance level in addition to power issues associated with small sample sizes. In the absence of region-specific hypotheses, but on the basis of the more general hypotheses concerning relations between pathways, we argue that it is justified to use the binomial distribution to test for differences between pathways. That said, 1-tailed Fisher's r to z-transformed scores were used to estimate the difference between correlation coefficients, when a priori hypotheses had been formulated concerning specific regions, that is, for BP associations during the MSIT.

In summary, this study is the first to report striatal and extrastriatal D1 receptor associations in younger and elderly adults and yields several new findings regarding D1 receptors in humans: 1) There was a global age-related loss of D1 receptors generalizing across striatal, limbic, and neocortical areas; 2) Interregional correlations for D1 receptor densities were high within the nigrostriatal, mesocortical, and mesolimbic pathways as well as between the mesocortical and the mesolimbic pathways for younger and elderly adults alike, suggesting that D1 receptor densities are regulated via the midbrain; 3) For younger adults, D1 receptor densities between the nigrostriatal pathway and the mesolimbic and mesocortical pathways were also highly correlated. This finding supports the idea that striato-midbrain-striato pathways connect the VTA to the SN and suggests that D1 receptor densities in separate DA pathways are not regulated independently in early adulthood; 4) In elderly adults, striato-midbrain-striatal connections appear to be altered, as we found weak correlations of the nigrostriatal pathway to the mesolimbic and mesocortical pathways, indicating an age-related segregation between circuitries; and 5) Critically, weak between-pathway correlations between frontal areas and SMS sensorimotor striatum in elderly adults were linked to slower responding during cognitive interference resolution.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/

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Notes

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