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Longitudinal support for the correlative triad among aging, dopamine D2-like receptor loss, and memory decline

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ABSTRACT

Dopamine decline is suggested to underlie aging-related cognitive decline, but longitudinal examinations of this link are currently missing. We analyzed 5-year longitudinal data for a sample of healthy, older adults (baseline: n = 181, age: 64–68 years; 5-year follow-up: n = 129) who underwent positron emission tomography with ^{11}C-raclopride to assess dopamine D2-like receptor (DRD2) availability, magnetic resonance imaging to evaluate structural brain measures, and cognitive tests. Health, lifestyle, and genetic data were also collected. A data-driven approach (k-means cluster analysis) identified groups that differed maximally in DRD2 decline rates in age-sensitive brain regions. One group (n = 47) had DRD2 decline exclusively in the caudate and no cognitive decline. A second group (n = 72) had more wide-ranged DRD2 decline in putamen and nucleus accumbens and also in extrastriatal regions. The latter group showed significant 5-year working memory decline that correlated with putamen DRD2 decline, along with higher dementia and cardiovascular risk and a faster biological pace of aging. Taken together, for individuals with more extensive DRD2 decline, dopamine decline is associated with memory decline in aging.

1. Introduction

Among the multitude of changes taking place in the aging brain, dopamine (DA) decline is suggested to be a major determinant of aging-related cognitive decline (Bäckman et al., 2006). Cross-sectional studies have shown that (i) normal aging is associated with reductions in various DAmarkers, including DA receptors (Karrer et al., 2017), and (ii) higher DA system integrity is associated with better cognitive performance (Bäckman et al., 2006). Virtually all current knowledge on the role of DA in cognitive processes emanates from cross-sectional work, which may yield both over- and underestimations of within-person decline in brain and cognitive parameters, and their relationships in aging (Raz and Lindenberger, 2011). In fact, Raz and Lindenberger argued that even perfect cross-sectional studies cannot illuminate the causal structure of longitudinal change. Hence, in the absence of longitudinal evidence, the link between DA decline and cognitive disturbances remains tentative and needs to be validated in a longitudinal setting. The Cognition, Brain, and Aging (COBRA) study recently

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provided 5-year longitudinal evidence for DA D2-like receptor (DRD2) losses in several associative brain regions (Karalija et al., 2022), including the striatum, hippocampus, orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC). Here, we assess the cognitive implications of individual differences in regional DRD2 decline rates in aging.

The concept of *brain maintenance* is defined as the relative absence of detrimental brain changes that allow some individuals to go through the later decades of life with relatively spared cognitive functions (Nyberg et al., 2012). The preservation of DA system integrity has been suggested to constitute an integral part of brain maintenance, and preserved youth-like integrity across dopaminergic pathways was found to characterize high-performing older individuals (Rieckmann et al., 2011). Furthermore, pharmacological augmentation of DA tone and DA receptor stimulation improve memory performance (Luciana and Collins, 1997; Sawaguchi and Goldman-Rakic, 1994). DRD2 availability has been positively associated with performance in several age-sensitive functions, including episodic memory, working memory, executive functions, and processing speed (Bäckman et al., 2000; Lövden et al., 2018; Nyberg et al., 2016; Takahashi et al., 2008). Several mechanisms by which DRD2s may modulate cognitive processes have been suggested, including gating of striato-cortical circuits (O'Reilly, 2006) and modulation of ventral tegmental-hippocampal interactions (Lisman and Grace, 2005) or hippocampal-cortical interactions (Takahashi et al., 2008).

The shortage of longitudinal studies has hindered assessments of whether DA decline in specific brain regions is associated with deficits in specific cognitive functions. Longitudinal findings from the COBRA study have demonstrated that individuals declining in working memory performance over 5 years have reductions in prefrontal functional activation patterns and caudate DRD2 levels (Nyberg et al., 2022), but cognitive implications of the extent of DRD2 losses, i.e. when decline is limited versus spanning over several brain regions, have thus far not been investigated. Conceivably, striatal and extrastriatal DRD2 decline may impair fronto-striatal functions, e.g., working memory (Salami et al., 2018), as well as hippocampus-based functions, e.g. episodic memory (Nyberg et al., 2016). Yet another important gap in our knowledge is the *specific* contribution of DA decline to aging-related cognitive reductions (i.e., does DA decline account for variance in cognitive decline above and beyond other co-occurring aging-related brain changes?). Lack of multimodal DA studies has hampered such investigations. To exemplify, vascular insult is associated with accelerated DA decline in normal aging (Karalija et al., 2022), and with exacerbated memory decline and dementia incidence (Farnsworth von Cederwald et al., 2022).

The present work used data from the longitudinal COBRA study to assess whether more marked 5-year DRD2 reductions are associated with cognitive decline, and vice versa whether preservation of DRD2 levels is associated with cognitive stability. Heterogeneity in DA integrity has been found to impact the DA-cognition link (Lövden et al., 2018). Moreover, exacerbated DA decline was observed in multiple brain regions, including dorsal and ventral striatum, hippocampus and cingulate cortex, in unsuccessful cognitive agers (i.e. those with mild cognitive impairment and dementia (Sala et al., 2021). To capture heterogeneity, we employed a data-driven approach to identify groups that differed maximally in the regional patterns of DRD2 decline. Thereafter, we assessed cognitive performance and DRD2-cognition links within these groups. In addition, we explored potential risk factors for DRD2 decline, and examine whether these differed between the identified groups. Based on the original hypothesis that "age-related DA losses are associated with age-related cognitive deficits" (Bäckman et al., 2006), we predicted that individuals with more pronounced DRD2 decline (e.g., across several DA pathways) would display reductions in cognitive functions (episodic memory, working memory, and/or perceptual speed), such that more DRD2 loss related to greater cognitive decline.

2. Material and methods

This study was approved by the Swedish Ethical Review Authority (Umeå, Sweden; registration number: 2012–57-31 M), and carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from participants prior to any testing.

2.1. Sample

The original sample consisted of 181 healthy, older adults (100 men, 81 women; ages: 64–68 years) from Umeå in northern Sweden. Exclusion criteria were dementia and other neurological or psychiatric disorders, previous stroke or head trauma, and ongoing treatment for diabetes and cancer. Approximately 70 % of the baseline sample returned for the 5-year follow up (69 men, 60 women; ages: 69–73 years, mean: 71.2 ± 1.2). At both data collection waves, participants underwent positron emission tomography (PET) with ^{11}C-raclopride, magnetic resonance imaging (MRI), cognitive assessments, and collection of health and lifestyle factors. Blood sampling, allowing genetic assessment, was performed at baseline only. The test battery, exclusion criteria, a priori statistical power analyses, and attrition have been described in detail elsewhere (Karalija et al., 2022; Nevalainen et al., 2015). The exact duration between test waves was 60.1 ± 0.6 months for PET and 60.0 ± 0.4 months for MRI. These minor deviations from the planned 5-year interval in between test waves were not considered in the statistical analyses.

2.2. Brain imaging – acquisition and analyses

The same scanners and protocols were used at both data-collection waves. MRI was performed with a 3 tesla Discovery MR 750 scanner (General Electric, WI, US), equipped with a 32-channel phased-array head coil. PET data were acquired with a Discovery PET/CT 690 (General Electric, WI, US) and ^{11}C-raclopride.

2.2.1. Regional volumes

T1-weighted images (176 slices with thickness 1.0 mm) were obtained with an FSPGR sequence with echo time: 3.2 ms, flip angle: 12°, repetition time: 8.19 ms, inversion time: 450 ms, field of view: 25 cm with resolution 0.98 mm (isotropic) upsampled to 0.49 mm. Estimates of grey matter (GM), white matter (WM), and lateral ventricle size were derived from T1-weighted images with the longitudinal image processing pipeline in Freesurfer (version 6.0). Cortical parcellation was obtained with the Desikan-Killany atlas (Desikan et al., 2006). MRI-incompatible factors hindered three participants to undergo MRI at follow-up.

2.2.2. DRD2 availability

A 55-min, 18-frame dynamic PET scan was acquired during rest following intravenous bolus injection of approximately 250 MBq ^{11}C-raclopride (baseline: 263.5 ± 19.0 MBq; follow-up: 260.2 ± 15.0 MBq). Attenuation- and decay-corrected images (47 slices, field of view = 25 cm, 256 × 256-pixel transaxial images, voxel size = 0.977 × 0.977 × 3.27 mm^3) were reconstructed with the iterative VUE Point HD-SharpIR algorithm (GE; 6 iterations, 24 subsets, 3.0 mm post filtering; FWHM: 3.2 mm). PET images were motion-corrected and co-registered with the structural T1-weighted images from the corresponding session (baseline or follow-up) using the Statistical Parametric Mapping software (SPM12). For those who did not undergo MRI at follow-up (n = 3), PET images from both time points were co-registered with the baseline T1 image. The mean of the first five frames was used as source for co-registration. DRD2 availability (binding potential; BP_{ND}) was estimated with correction for partial-volume effects (PVE) using the symmetric geometric-transfer matrix implemented in Freesurfer (Greve et al., 2016). The size of the secondary correction kernel (point-spread function (PSF) of 2.5 mm; isotropic) was guided by earlier work (Smith

et al., 2019). In brief, Freesurfer segmentations and PET data were used to estimate PVE-corrected regional radioactivity concentrations in each ROI and time frame. PVE-corrected BP_{ND} estimates were calculated with the multilinear reference-tissue model (MRTM) on dynamic PVE-corrected data, with cerebellar GM as the reference region. BP_{ND}–values at both waves were standardized to Z-scores, using the mean value and standard deviation for the whole baseline sample. By so doing, we gain information on how DRD2 levels changes in relation to the original distribution.

2.2.3. Perfusion

3D pseudo-continuous arterial spin labeling (3D pcASL) was acquired with a five-pulse background suppression scheme and spiral readout (type: 3D fast spin-echo interleaved stack-of-spirals). Details for the GE pcASL pulse sequence, including the arterial labeling strategy, have been described previously (Mutsaerts et al., 2014). TR: 4.68 s and TE: 10.53, Labeling time: 1.5 s, post-labeling delay time: 1.5 s, field of view: 24 cm, slice thickness: 4 mm, acquisition resolution: 8 × 512 (arms x data points), with the number of averages set at 3. Total scanning time was 5 min, providing whole-brain perfusion in ml/100 g/min. Reconstructed voxel size was 1.875 × 1.875 × 4 mm^3. Quantitative perfusion maps were calculated using a post-processing tool installed in the scanner host environment (software version: DV26.0_R01_1725.a). Mean perfusion in total GM (via Freesurfer segmentation) was computed as the average of the individual perfusion estimates weighted by volume.

2.2.4. White-matter lesions

WM hyperintensities were segmented from FLAIR images (48 slices, slice thickness: 3 mm, TE: 120 ms, TR: 8000 ms, and field of view: 24 x 24 cm). In-plane resolution was 0.94 x 0.94 mm, upsampled to 0.469 x 0.469 mm. Segmentation was performed with the lesion-growth algorithm in the LST toolbox version 2.0.14 for SPM12 (Schmidt et al., 2012). The algorithm segmented the T1-weighted images into three main tissue classes (cerebrospinal fluid, GM, and WM). This information was combined with the co-registered FLAIR intensities to calculate lesion-belief maps. Maps were thresholded ($\kappa = 0.3$, defined by visual inspection) to obtain an initial binary lesion map. Lesion maps were then grown along hyperintense neighboring voxels in the FLAIR image, and thresholded at 50 % to yield a binary lesion map. From this, the total volume (ml) was obtained. Lesion maps were visually inspected and graded according to the Fazekas scale (Fazekas et al., 1987). We found that increasing lesions severity grade corresponded well with segmented lesion volumes (*wave 1:* 1.2 ± 1.0 ml for Fazekas grade 1, 3.0 ± 1.7 ml for grade 2, 5.3 ± 1.8 ml for grade 3; *wave 2:* 1.8 ± 1.4 ml for Fazekas grade 1, 4.2 ± 2.9 ml for grade 2, 10.1 ± 4.1 ml for grade 3, *p*-values <0.001 for between-group comparisons) and we thus concluded that the algorithm delineated lesions accurately.

2.3. Cognition

Participants performed the Mini-Mental State Examination (MMSE), in which a minimum of 27 points (out of max: 30 points) was required for study inclusion at baseline (but not at follow-up). The main cognitive domains in COBRA are episodic memory, working memory, and perceptual speed (Nevalainen et al., 2015). Episodic memory was assessed with tests of word recall, number-word recall, and object-position recall. Working memory was tested with a letter-updating task, a columnized numerical 3-back task, and a spatial-updating task. Perceptual speed was assessed with letter-, number-, and figure-comparison tasks. Tests were repeated for reliability. Outcome measures were number of correct answers for episodic memory and working memory, and total number of correct responses per minute for perceptual speed tasks. For each of the nine tests, scores were summarized across the total number of blocks or trials, and then standardized (Z-score; with mean value and standard deviation for the whole baseline sample). Z-scores for the three tasks per ability were then averaged to create composite scores for episodic memory, working memory, and speed at baseline and follow-up, respectively. Previous modelling examined the factor structure reflected by the 9 cognitive measures (3 each for episodic memory, working memory, and speed), and found a good fit along with moderate-to-high and reliable factor loadings (Nevalainen et al., 2015).

2.4. Lifestyle, health, and genetic assessments

History of known disorders, medicine consumption, smoking, and physical activity were documented (Nevalainen et al., 2015). Blood pressure was measured in a sitting position. ApoE ε4 status was analyzed from blood samples (Lövden et al., 2018). DNA methylation was analyzed with Infinium MethylationEPIC BeadChip (at Bioinformatic and Expression Analysis core facility, Karolinska Institutet, Stockholm, Sweden). DNA methylation data were used to calculate DunedinPACE (see supplementary material) - a biomarker of biological aging (Belsky et al., 2022). A score of 1 indicates that biological age corresponds to chronological age, a score >1 indicates accelerated aging, and a score <1 reflects slowed biological aging. Two composite risk scores were calculated. One estimated the probability of 10-year cardiovascular disease event using an algorithm from the Framingham Heart Study (D'Agostino et al., 2008). The other assessed risk for dementia, using an algorithm developed in the Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) study (Kivipelto et al., 2006). Both risk scores have been associated with cognitive decline and dementia risk previously (Farnsworth von Cederwald et al., 2022; Kivipelto et al., 2006). Variables that are part of both scores include systolic blood pressure, BMI, age, and sex. The dementia score further considers ApoE ε4 status, education, and physical activity (where active is defined as a minimum of 2 h of physical activity per week).

2.5. Statistical analyses

For all brain, behavioral and health variables, univariate outliers were defined as > 3.29 SD from the mean at each timepoint (Tabachnick and Fidell, 2013), and multivariate outliers were defined according to Mahalanobis Distance ($p < 0.001$). To achieve normal distributions, univariate outliers were excluded as pairwise deletions and multivariate outliers as listwise deletions, respectively. Exclusions for WM lesions and GM perfusion were performed twice, due to remaining outliers after the first round of exclusions. The effective sample for analyses (baseline and follow-up sessions) ranged between 120 and 128 for brain variables, 126–129 for cognitive variables, and 126–129 for lifestyle and health variables. Descriptive data are presented as mean or sum (over the left and right hemispheres for brain data), standard deviations (SDs), and frequencies. Regional DRD2 availability is presented as mean values over the left and right hemispheres. Change for DRD2 and cognition was defined as the difference between follow-up and baseline ($Z_{follow\text{-}up} - Z_{baseline}$). Analyses were performed with SPSS (version 27), the graphical modelling software Ωnyx (http://onyx.brandmaier.de/) (von Oertzen et al., 2015), and MATLAB. Alpha level for all tests was $p < 0.05$, and we provide information on significance after Bonferroni correction.

The primary regions-of-interest (ROIs) encompassed regions where 5-year DRD2 losses were observed (Karalija et al., 2022), i.e., putamen, caudate, nucelus accumbens, hippocampus, OFC, and ACC. The cortical ROIs included lateral and medial divisions for OFC, and rostral and caudal anterior divisions of ACC. Despite the low signal-to-noise ratio and questions of suitability for measurements in low-density DRD2 regions (Farde et al., 1988; Svensson et al., 2019), an increasing amount of evidence speak for the reliability and validity for extrastriatal ^{11}C-raclopride measurements (Alakurtti et al., 2015; Karalija et al., 2019a; Papenberg et al., 2019). K-means cluster analysis was chosen as the method for group delineation according to DRD2 change which does not require neither normal distribution assumptions nor selection of

linkage type, and K-means clustering readily lends itself to evaluation using the silhouette method. Thus, a comparison of clustering solutions, with k varying between 2 and 6, was performed via silhouette evaluation, which supported a solution with two groups (see Supplementary Fig. 1). Group comparisons were assessed by means of analysis of variance (ANOVA) or independent samples t-tests. Change over time was assessed with paired-sample t-tests.

In analyses of the DRD2-cognition link, we first focused on striatal DRD2 decline and cognitive functions showing aging-related decline, i.e., working memory (see Table 2). Striatum-focused analyses were complemented with models considering mean DRD2 decline over the six regions. In addition, outcomes for extrastriatal ROIs are presented in Supplementary Fig. 2. Associations between changes in DRD2 and cognition were assessed with multivariate regression and bivariate difference-score models. The latter allow for assessment of baseline-baseline, baseline-change, and change-change correlations. In the difference-score model (see Fig. 2B) rectangles represent measured variables and the circle represents change. The obtained parameters include variances and standardized covariances (i.e., correlations). Z-values of >1.96 or <–1.96 indicate statistical significance at $p < 0.05$. Covariates in the multivariate regression models were age, sex, and education. Linear associations are reported with Pearson's correlation coefficient (r). The values in the scatter plot in Figure 2B are standardized residuals for age, sex, and education. To test for the influence of other significant brain changes on the DRD2-cognition association, multivariate regression models were repeated with GM perfusion and caudate atrophy as additional covariates (as these were the only measures for which a between-group difference was observed; see Table 1).

3. Results

3.1. Individual differences in patterns of aging-related DRD2 losses

The k-means analysis suggested two separate groups, where the first group (n = 47) consisted of individuals with significant DRD2 decline in the caudate (t(46) = 4.9, $p < 0.001$; "*caudate-specific decliners*"; Fig. 1). These individuals were spared from extrastriatal DRD2 losses, and showed positive DRD2 change for OFC (t(46) = 6.6, $p < 0.001$). Mean DRD2 change across the six regions was negligible for this group (Z = 0.01 ± 0.32, $p = 0.882$; Fig. 2A). The second group (n = 72) is referred to as "*broad-ranged DRD2 decliners*", as these individuals were characterized by DRD2 decline in putamen, nucleus accumbens, and in the extrastriatal regions (Fig. 1), which translated into significant mean DRD2 decline across the ROIs (Z = –0.44 ± 0.38, $p < 0.001$; Fig. 2A). Notably, caudate DRD2 change was significantly lower at baseline for the broad-ranged DRD2 decliners, as compared to the caudate-specific decliners (F(1,117)= 7.3; $p = 0.008$). Caudate DRD2 change was, however, negligible for the broad-ranged DRD2 decliners (Fig. 1). The Bonferroni-adjusted p-threshold for 14 t-tests is $p = 0.004$ (12 comparisons for 6 ROIs for two groups in Fig. 1B; and 2 comparisons for average DRD2 for two groups in Fig. 2A). All the reported DRD2 changes had p-values < 0.002 and thus survived Bonferroni correction. Between-group comparisons (analyzed within one model) revealed significant differences for DRD2 change across most regions (F(6, 112)= 35.2, $p < 0.001$), except for putamen and ACC ($p > 0.20$; Fig. 1B).

Next, we investigated whether the groups differed in other brain measures (Table 1). Overall, no significant group differences were found for brain volumes, grey-matter perfusion, or white-matter lesion burden at baseline. The 5-year declines in caudate volumes and GM perfusion were significantly greater for the broad-ranged DRD2 decliners. It should however be noted that these group-differences did not survive Bonferroni correction, and thus, DRD2 decline groups were deemed comparable in terms of atrophy and cerebrovascular measures.

Table 1
Structural and vascular brain integrity for caudate-specific and broad-ranged dopamine D2-receptor (DRD2) decliners.

	Caudate-specific DRD2 decliners	Broad-ranged DRD2 decliners	p
Baseline			
Putamen volume (ml)	4.73 (0.61)	4.65 (0.50)	0.418
Caudate volume (ml)	3.62 (0.52)	3.58 (0.49)	0.689
Accumbens volume (ml)	0.58 (0.10)	0.56 (0.09)	0.343
Hippocampus volume (ml)	3.96 (0.33)	3.89 (0.42)	0.274
ACC volume (ml)	4.27 (0.66)	4.17 (0.64)	0.393
OFC volume (ml)	13.31 (1.54)	13.05 (1.33)	0.339
Lateral ventricle volume (ml)	29.05 (13.27)	31.53 (13.88)	0.335
Total grey matter volume (ml)	629.57 (52.53)	629.73 (53.50)	0.988
Total white matter volume (ml)	436.70 (54.12)	442.97 (57.25)	0.550
Grey matter perfusion (ml/100 g/min)	41.34 (10.06)	39.00 (8.30)	0.168
Total white-matter lesion volume (ml)	1.69 (1.36)	2.05 (1.86)	0.134
5-year change			
Putamen volume (%)	–1.80 (3.08)	–2.81 (3.70)	0.127
Caudate volume (%)	0.05 (3.91)	–1.52 (3.90)	**0.035***
Accumbens volume (%)	–0.80 (2.09)	–1.24 (1.76)	0.213
Hippocampus volume (%)	–2.17 (3.53)	–3.09 (3.44)	0.165
ACC volume (%)	–0.77 (2.07)	–0.77 (2.07)	0.565
OFC volume (%)	–0.65 (2.84)	–1.00 (2.13)	0.079
Lateral ventricle volume (ml)	18.12 (9.91)	18.87 (10.01)	0.693
Total grey matter volume (%)	–1.38 (1.69)	–1.86 (1.62)	0.125
Total white matter volume (%)	–2.93 (1.32)	–3.23 (1.42)	0.243
Grey matter perfusion (%)	–4.71 (14.89)	–11.52 (17.52)	**0.033***
White-matter lesion expansion (ml)	1.15 (1.22)	1.53 (1.45)	0.144

Note: Regional volumes are presented as mean values over left and right hemisphere. Total grey- and white matter, lateral ventricles, and white-matter lesion volumes are presented as sums over hemispheres.
* $p < 0.05$ for two-tailed tests (but non-significant after Bonferroni correction, $p = 0.05/22$ comparisons).

3.2. Memory decline in individuals with broad-ranged DRD2 decline

For the whole sample, significant decline in MMSE performance was observed (mean:-0.51 ± 1.27, t(127) = 4.5, $p < 0.001$), whereas 5-year cognitive changes were modest (Table 2) with significant mean change for working memory (t(127) = 2.4, $p = 0.018$; but $p > 0.05$ after Bonferroni correction for 9 comparisons, i.e. 3 groups and 3 main cognitive domains). Group-specific analyses revealed that both DRD2 groups declined in MMSE performance (*caudate-specific decliners*: –0.38 ± 1.21, t(46) = 2.2, $p = 0.035$; *broad-ranged decliners*: –0.44 ± 1.13, t(70) = 3.3, $p = 0.002$), whereas working-memory decline was restricted to the broad-ranged DRD2 decliners (t(71) = 2.8, $p = 0.006$; $p = 0.05$ after Bonferroni correction), and not observed in caudate-specific DRD2 decliners (Table 2; Fig. 2A). Between-group differences were non-significant (*working memory*: t(116) = 1.7, $p = 0.089$; *episodic memory*: t(114) = 0.5, $p = 0.309$; *perceptual speed*: t(114) = 0.4, $p = 0.342$; *MMSE*: t(116) = 0.2, $p = 0.403$). Decline was not correlated across the cognitive domains (*whole sample*: rs = –0.09 to –0.05; *caudate-specific DRD2 decliners*: rs = –0.01 to 0.08; *broad-ranged DRD2 decliners:* rs = –0.18 to –0.09; all p-values>0.05).

3.3. DRD2-memory relations for broad-ranged DRD2 decliners

We assessed DRD2-cognition associations via multivariate regression

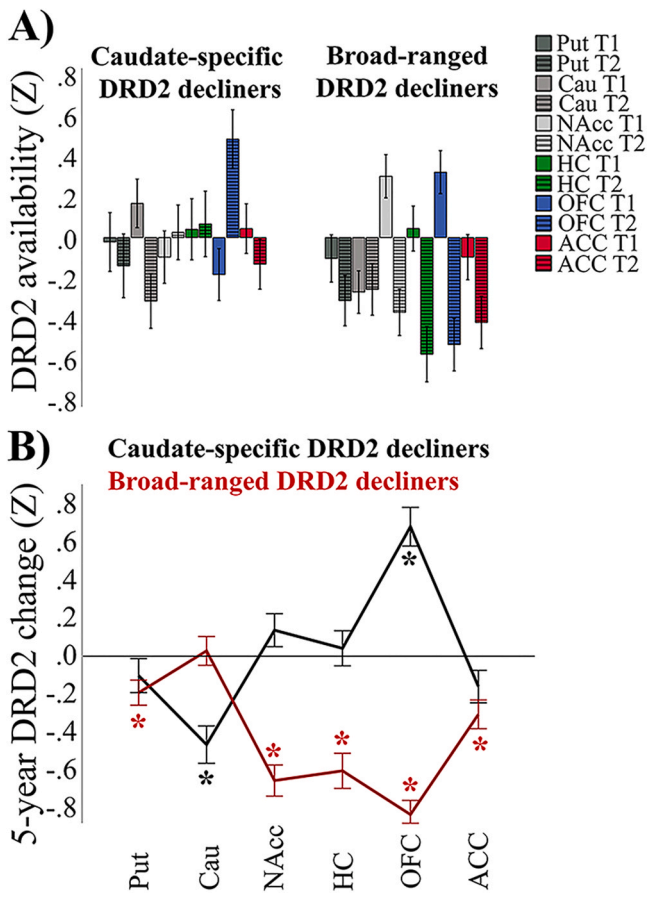

Fig. 1. Differences in 5-year dopamine D2-receptor (DRD2) decline rates in aging. "Broad-ranged DRD2 decliners" (n = 72) showed more widespread DRD2 decline, contrary to "caudate-specific DRD2 decliners" (n = 47). Standardized DRD2 levels (z-scores) are shown for baseline and follow-up (A), and for change for standardized DRD2 levels (B). *$p < 0.002$ for DRD2 change over time per region. These effects survived Bonferroni adjustment for multiple comparisons. Abbreviations include DRD2: dopamine D2 receptors; Put: putamen; Cau: caudate; NAcc: nucleus accumbens; HC: hippocampus; OFC: orbitofrontal cortex (OFC); ACC: anterior cingulate cortex; T1: timepoint 1 (baseline); T2: timepoint 2 (5-year follow-up).

models. Analyses in the whole sample revealed no linear associations between striatal DRD2 and memory changes (*putamen:* F(2,112)=2.4, $p = 0.091$; *caudate:* F= 1.1, $p = 0.333$; *nucleus accumbens:* F= 0.1, $p = 0.948$), nor between mean DRD2 and memory changes (F(2, 109)= 2.0, $p = 0.146$). As minimal cognitive changes were observed for the caudate-specific DRD2 decliners, DRD2-cognition change analyses are not meaningful for this group.

In the broad-ranged DRD2 decliners - showing pronounced DRD2 as well as memory decline - significant associations were found between putamen DRD2 decline and memory performance (F(2, 66)= 4.3, $p = 0.017$), and particularly for working memory (F(1,67)=5.3, $p = 0.024$; Fig. 2B). Associations in broad-ranged DRD2 decliners were positive, indicating that accelerated DRD2 loss was associated with greater decline in working memory performance. No significant associations were found for DRD2 change across all six regions (F(2,66)= 2.7, $p = 0.072$), for nucleus accumbens (F(2,66)= 0.9, $p = 0.420$), or the three extrastriatal ROIs (F(2,66)= 0.5 to1.9, *p*-values >0.05 for hippocampal, OFC, and ACC models; see Supplementary Fig. 2) in relation to memory changes. Finally, the influence of other significant between-group brain differences (Table 1) was tested on the DRD2-memory associations. Inclusion of changes in caudate volume and GM perfusion as additional covariates in the multivariate regression model did not alter the main finding for broad-ranged DRD2 decliners (Fig. 2B; *putamen DRD2–working memory*: F(1,59)= 10.3, $p = 0.002$, $r = 0.39$).

3.4. Risk factors for DRD2 and cognitive decline

We compared the DRD2 decline groups for health, lifestyle, and genetic factors at study entrance (Table 3). Groups were similar in terms of chronological age and education; however, the broad-ranged DRD2 decliners were characterized by faster biological pace of aging (DunedinPACE; t(117) = 2.5; $p = 0.015$), and higher composite risk scores of imminent cardiovascular disease (t(117) = 2.3; $p = 0.022$) and dementia (t(114) = 2.0; $p = 0.049$).

Significant associations were found between cardiovascular disease and dementia risk scores (*whole sample*: $r = 0.36$; *broad-ranged DRD2 decliners*: $r = 0.48$; *p-values*<0.001), but not between biological pace of aging and cardiovascular disease risk (*whole sample*: $r = 0.11$; *broad-ranged DRD2 decliners*: $r = 0.05$ *p-values*>0.05), or between biological pace of aging and dementia risk (*whole sample*: $r = 0.08$; *broad-ranged DRD2 decliners*: $r = 0.01$ *p-values*>0.05).

4. Discussion

The present longitudinal study tested the hypothesized correlative triad among aging, DA, and cognition. Based on previous evidence for heterogeneity in DRD2-cognition associations (Lövden et al., 2018), a data-driven analysis of rate of DRD2 decline identified two sub-groups. First, individuals with broad-ranged DRD2 decline that spanned across nigrostriatal, mesolimbic, and mesocortical DA pathways were found to exhibit modest yet significant decline in working-memory performance, and a significant change-change association was found between DRD2 decline in the putamen and working memory decline. Second, cognitive stability was found to characterize older individuals for whom DRD2 decline was restricted to the caudate.

The DA-cognition hypothesis is one of the most influential theories in the cognitive neuroscience of aging (Bäckman et al., 2006; Karrer et al., 2017). So far, testing of this hypothesis has been done in cross-sectional studies with limited sample sizes. The present longitudinal work shows that DRD2 reduction is associated with aging-related memory changes, even when memory changes are subtle. The COBRA study had strict exclusion criteria at baseline, which led to recruitment of a sample that is healthier than the average population of this age segment (Nevalainen et al., 2015). Moreover, individuals with poorer health and lower cognitive performance dropped out from the follow-up data collection (Karalija et al., 2022), as is typical for longitudinal studies (Lindenberger et al., 2002). The small magnitude of cognitive changes may be a result from factors such as good health, selective attrition, relatively short follow-up times, test-retest effects, and influence of measurement error on true variance in change.

The identified groups with caudate-specific versus broad-ranged DRD2 decline were comparable on age and education, baseline and longitudinal measures of structural and vascular brain integrity (Table 1) and on several measures of health (Table 3). However, the broad-ranged DRD2 decliners had higher burden of vascular and dementia-related risk factors at study entry. Support that vascular health modulates DA integrity comes from demonstrations of cerebrovascular insult being associated with more rapid DRD2 decline in healthy older adults (Karalija et al., 2019; Karalija et al., 2022), and with faster progression of parkinsonism (Oveisgharan et al., 2021). Also, dementia has been associated with exacerbated DA disturbances in ventral striatum, hippocampus, and ACC (Adolfsson et al., 1979; Sala et al., 2021), with links to memory impairment (Kemppainen et al., 2003).

The absence of mean caudate DRD2 change in the broad-ranged DRD2 decliners was unexpected. However, their low caudate DRD2 levels already at the first time-point (Fig. 1A) suggest that caudate DA integrity may have been compromised already at study entrance for this group. If viewing DA decline as a continuous process, as is suggested by cross-sectional patterns across the lifespan (Karrer et al., 2017), decline

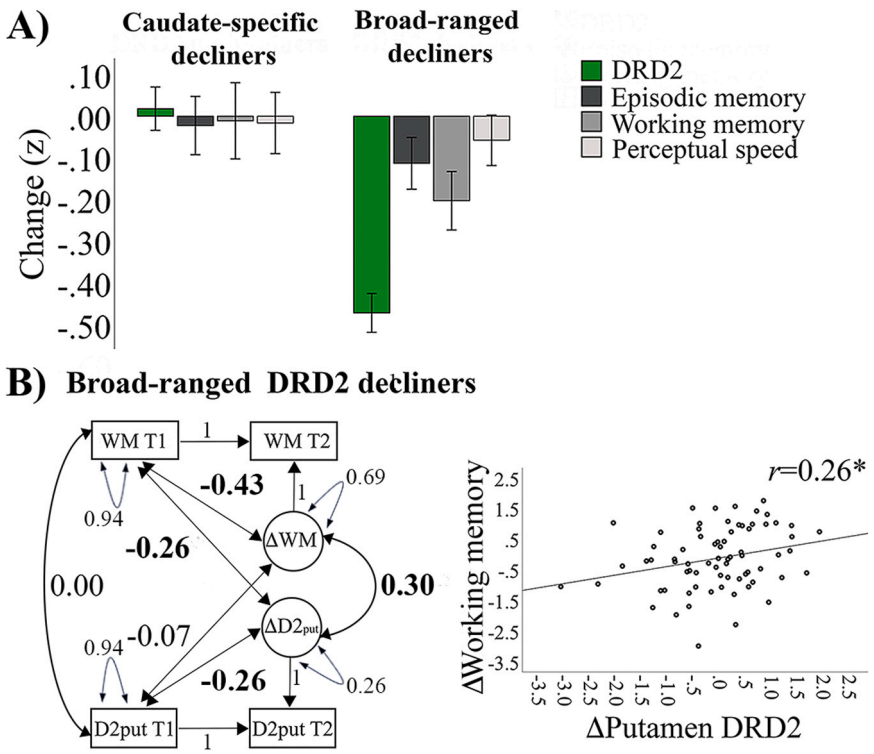

Fig. 2. Associations between dopamine D2-receptor (DRD2) and memory decline in aging. Older adults with broad-ranged DRD2 decline are characterized by memory decline, and particularly working memory reductions (A). In broad-ranged DRD2 decliners, a bivariate difference-score model (left) revealed associated changes between putamen DRD2 loss and reduced working memory performance, as further illustrated in the scatter plot of correlated changes (right; B). Note that mean values have been omitted from the graphical representation of the model for visual clarity. Bold font and * indicates $p < 0.05$. Abbreviations include r: Pearson's correlation coefficient; Put: putamen; WM: working memory; Δ: change; T1: timepoint 1 (baseline); T2: timepoint 2 (5-year follow-up).

Table 2
Cognitive performance for the whole sample, caudate-specific dopamine D2-receptor (DRD2) decliners, and broad-ranged DRD2 decliners.

	Baseline mean (SD)	Follow-up mean (SD)	Change mean (SD)
Whole sample			
Episodic memory	0.09 (0.77)	0.00 (0.75)	–0.08 (0.52)
Working memory	0.09 (0.71)	–0.04 (0.79)	**–0.13 (0.60)** *
Perceptual speed	0.02 (0.85)	–0.02 (0.88)	–0.04 (0.51)
Caudate-specific decliners			
Episodic memory	0.26 (0.77)	0.18 (0.72)	–0.05 (0.50)
Working memory	0.10 (0.78)	0.09 (0.82)	–0.01 (0.59)
Perceptual speed	0.06 (0.88)	0.07 (0.96)	–0.01 (0.48)
Broad-ranged decliners			
Episodic memory	0.05 (0.76)	–0.05 (0.74)	–0.10 (0.54)
Working memory	0.09 (0.65)	–0.12 (0.76)	**–0.20 (0.61)** #
Perceptual speed	–0.09 (0.78)	–0.14 (0.82)	–0.05 (0.53)

Note: Episodic memory, working memory, and perceptual speed are expressed as Z-scores.
*$p < 0.05$ for significant mean change (non-significant after Bonferroni correction).
$p \leq 0.05$ after Bonferroni correction

Table 3
Comparisons of health and genetic factors for caudate-specific and broad-ranged dopamine D2-receptor (DRD2) decliners at study entrance.

	Caudate-specific DRD2 decliners	Broad-ranged DRD2 decliners	*p*
Chronological age	66.2 (1.3)	66.2 (1.2)	0.987
Biological Aging	1.03 (0.10)	1.07 (0.10)	**0.015***
Sex (% men)	45 %	63 %	0.056
Education	13.3 (3.2)	13.5 (3.7)	0.712
Systolic blood pressure	138.0 (15.0)	142.5 (16.9)	0.139
Diastolic blood pressure	83.7 (8.6)	85.8 (10.2)	0.237
BMI	25.5 (2.9)	26.7 (3.7)	0.057
Hyperlipidemia	13 %	15 %	0.702
Hypertension	34 %	28 %	0.467
Smoking	4 %	7 %	0.542
ApoE ε4 carriers	21 %	28 %	0.400
Cardiovascular disease risk (%)	20.6 (9.5)	24.8 (9.9)	**0.022***
Dementia risk	7.7 (1.6)	8.3 (1.8)	**0.049***

Note: Biological Aging: DunedinPACE; Cardiovascular disease risk: score developed in the Framingham Heart study; Dementia risk: score developed in the CAIDE study.
* $p < 0.05$ for two-tailed tests

may start in specific regions (e.g., dorsal striatum) and then propagate across several DA pathways at later stages of aging. Such propagation may in turn result in increasingly severe cognitive disturbances. Hence, the broad-ranged decliners may be further along on their DA decline route, at which stage the predominance of DRD2 decline may have shifted from focal dorsal striatal decline to a more global pattern. In support of this interpretation, the broad-ranged DRD2 decliners were characterized by a faster biological pace of aging (Belsky et al., 2022).

4.1. Limitations

We employed an exploratory approach to delineate groups that differed maximally in regional DRD2 decline patterns. Group separation based on difference scores comes with some challenges, such as influences from regression to the mean effects (Barnett et al., 2005), which may explain the positive change for OFC in the caudate-specific DRD2 decliners. Low baseline DRD2 levels were, however, not predictive of more extensive DRD2 change over time (Karalija et al., 2022), hence

group delineation from baseline DRD2 values is not preferable. We have previously shown that aging related DRD2 decline extend beyond the striatum to select extrastriatal regions (hippocampus, OFC and ACC), with comparable, or even faster, decline rates in the extrastriatal regions (Karalija et al., 2022). Relatedly, assessments with high-affinity DRD2 ligands revealed age-related DRD2 differences in both striatal and extrastriatal regions (Seaman et al., 2019). Still, the validity of using ^{11}C-raclopride for extrastriatal measurement of DRD2 has been questioned (Svensson et al., 2019), but see (Papenberg et al., 2019). Moreover, ^{11}C-raclopride levels correspond well with presynaptic DA markers (Berry et al., 2018; Volkow et al., 1998), however not in direct proportion. Therefore, firm conclusions on the role of DA in cognitive aging require validations with other dopaminergic markers across a variety of cognitive tasks and domains (Juarez et al., 2019). Future work could also consider additional genetic variables beyond the current focus on ApoE ε4 and DNA methylation, such as the DRD2 single nucleotide polymorphism C957T which has been shown to influence DA-cognition associations (Karalija et al., 2019b). Finally, in view of the many statistical between-group comparisons in the present study and the use of Bonferroni correction when appropriate, future replication studies are critical (e.g., of the observed difference in risk factors and biological pace of aging).

4.2. Conclusions

By showing that 5-year striatal DRD2 decline is associated with modest changes in working memory decline, we provide tentative longitudinal support for the correlative triad among aging, DA, and cognition (Bäckman et al., 2006). Given the relatively short follow-up time and subtle working memory decline for the broad-ranged DRD2 decliners, the findings need to be replicated, preferably over longer time periods. The finding that more limited (caudate-specific) DA decliners had no significant cognitive decline is consistent with the brain-maintenance account of well-preserved cognition in older age (Nyberg et al., 2012). An interesting question for future analyses is whether more broad-ranged DA decline will emerge for the individuals in the caudate-specific DRD2 decline group.

Conflict of interest

None.

Verification

The material is original research that has not been published previously nor is under consideration for publication elsewhere. The publication of this work is approved by all co-authors and by the responsible authorities where the work was carried out. If accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright holder.

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CRediT authorship contribution statement

Lövdén Martin: Writing – review & editing, Funding acquisition, Conceptualization. **Lindenberger Ulman:** Writing – review & editing, Funding acquisition, Conceptualization. **Kuznetsov Dmitry:** Writing – review & editing, Formal analysis, Data curation. **Riklund Katrine:** Writing – review & editing, Funding acquisition, Conceptualization. **Andersson Micael:** Writing – review & editing, Validation, Methodology, Data curation. **Axelsson Jan:** Writing – review & editing, Validation, Methodology, Data curation. **Wåhlin Anders:** Writing – review & editing, Validation, Methodology, Data curation. **Salami Alireza:** Writing – review & editing, Validation, Methodology. **Johansson Jarkko:** Writing – review & editing, Validation, Methodology, Data curation. **Bäckman Lars:** Writing – review & editing, Funding acquisition, Conceptualization. **Karalija Nina:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis, Data curation, Conceptualization. **Nyberg Lars:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization. **Papenberg Goran:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization.

Data Availability

The anonymized data sets generated and analyzed during the current study are available from the corresponding author upon reasonable request from a qualified investigator. Prerequisites encompass approval of a formal project outline and data-sharing agreement, and ethical permission for the outlined research questions.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neurobiolaging.2024.02.001.

References

Adolfsson, R., Gottfries, C.G., Roos, B.E., Winblad, B., 1979. Post-mortem distribution of dopamine and homovanillic acid in human brain, variations related to age, and a review of the literature. J. Neural Transm. 45 (2), 81–105. https://doi.org/10.1007/bf01250085.

Alakurtti, K., Johansson, J.J., Joutsa, J., Laine, M., Backman, L., Nyberg, L., Rinne, J.O., 2015. Long-term test-retest reliability of striatal and extrastriatal dopamine D2/3 receptor binding: study with [(11)C]raclopride and high-resolution PET. J. Cereb. Blood Flow. Metab. 35 (7), 1199–1205. https://doi.org/10.1038/jcbfm.2015.53.

Bäckman, L., Ginovart, N., Dixon, R.A., Wahlin, T.B., Wahlin, A., Halldin, C., Farde, L., 2000. Age-related cognitive deficits mediated by changes in the striatal dopamine system. Am. J. Psychiatry 157 (4), 635–637. https://doi.org/10.1176/ajp.157.4.635.

Bäckman, L., Nyberg, L., Lindenberger, U., Li, S.C., Farde, L., 2006. The correlative triad among aging, dopamine, and cognition: current status and future prospects. Neurosci. Biobehav Rev. 30 (6), 791–807. https://doi.org/10.1016/j.neubiorev.2006.06.005.

Barnett, A.G., van der Pols, J.C., Dobson, A.J., 2005. Regression to the mean: what it is and how to deal with it. Int. J. Epidemiol. 34 (1), 215–220. https://doi.org/10.1093/ije/dyh299.

Belsky, D.W., Caspi, A., Corcoran, D.L., Sugden, K., Poulton, R., Arseneault, L., Baccarelli, A., Chamarti, K., Gao, X., Hannon, E., Harrington, H.L., Houts, R., Kothari, M., Kwon, D., Mill, J., Schwartz, J., Vokonas, P., Wang, C., Williams, B.S., Moffitt, T.E., 2022. DunedinPACE, a DNA methylation biomarker of the pace of aging. eLife 11, e73420. https://doi.org/10.7554/eLife.73420.

Berry, A.S., Shah, V.D., Furman, D.J., White 3rd, R.L., Baker, S.L., O'Neil, J.P., Janabi, M., D'Esposito, M., Jagust, W.J., 2018. Dopamine synthesis capacity is associated with D2/3 receptor binding but not dopamine release. Neuropsychopharmacology 43 (6), 1201–1211. https://doi.org/10.1038/npp.2017.180.

D'Agostino, R.B., Sr., Vasan, R.S., Pencina, M.J., Wolf, P.A., Cobain, M., Massaro, J.M., Kannel, W.B., 2008. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 117 (6), 743–753. https://doi.org/10.1161/circulationaha.107.699579.

Desikan, R.S., Segonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Buckner, R.L., Dale, A.M., Maguire, R.P., Hyman, B.T., Albert, M.S., Killiany, R.J.,

2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31 (3), 968–980. https://doi.org/10.1016/j.neuroimage.2006.01.021.

Farde, L., Pauli, S., Hall, H., Eriksson, L., Halldin, C., Hogberg, T., Nilsson, L., Sjogren, I., Stone-Elander, S., 1988. Stereoselective binding of 11C-raclopride in living human brain–a search for extrastriatal central D2-dopamine receptors by PET. Psychopharmacol. (Berl.) 94 (4), 471–478.

Farnsworth von Cederwald, B., Josefsson, M., Wåhlin, A., Nyberg, L., Karalija, N., 2022. Association of cardiovascular risk trajectory with cognitive decline and incident dementia. Neurology 98 (20), e2013. https://doi.org/10.1212/WNL.0000000000200255.

Fazekas, F., Chawluk, J.B., Alavi, A., Hurtig, H.I., Zimmerman, R.A., 1987. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. AJR Am. J. Roentgenol. 149 (2), 351–356. https://doi.org/10.2214/ajr.149.2.351.

Greve, D.N., Salat, D.H., Bowen, S.L., Izquierdo-Garcia, D., Schultz, A.P., Catana, C., Becker, J.A., Svarer, C., Knudsen, G.M., Sperling, R.A., Johnson, K.A., 2016. Different partial volume correction methods lead to different conclusions: an (18)F-FDG-PET study of aging. NeuroImage 132, 334–343. https://doi.org/10.1016/j.neuroimage.2016.02.042.

Juarez, E.J., Castrellon, J.J., Green, M.A., Crawford, J.L., Seaman, K.L., Smith, C.T., Dang, L.C., Matuskey, D., Morris, E.D., Cowan, R.L., Zald, D.H., Samanez-Larkin, G. R., 2019. Reproducibility of the correlative triad among aging, dopamine receptor availability, and cognition. Psychol. Aging 34 (7), 921–932. https://doi.org/10.1037/pag0000403.

Karalija, Wåhlin, A., Ek, J., Rieckmann, A., Papenberg, G., Salami, A., Brandmaier, A.M., Köhncke, Y., Johansson, J., Andersson, M., Axelsson, J., Orädd, G., Riklund, K., Lövdén, M., Lindenberger, U., Bäckman, L., Nyberg, L., 2019. Cardiovascular factors are related to dopamine integrity and cognition in aging. Ann. Clin. Transl. Neurol. 6 (11), 2291–2303. https://doi.org/10.1002/acn3.50927.

Karalija, N., Jonassson, L., Johansson, J., Papenberg, G., Salami, A., Andersson, M., Riklund, K., Nyberg, L., Boraxbekk, C.-J., 2019a. High long-term test–retest reliability for extrastriatal 11C-raclopride binding in healthy older adults. J. Cereb. Blood Flow. Metab. 40 (9), 1859–1868. https://doi.org/10.1177/0271678X19874770.

Karalija, N., Papenberg, G., Wåhlin, A., Johansson, J., Andersson, M., Axelsson, J., Riklund, K., Lövden, M., Lindenberger, U., Bäckman, L., Nyberg, L., 2019b. C957T-mediated variation in ligand affinity affects the association between (11)C-raclopride binding potential and cognition. J. Cogn. Neurosci. 31 (2), 314–325. https://doi.org/10.1162/jocn_a_01354.

Karalija, N., Johansson, J., Papenberg, G., Wåhlin, A., Salami, A., Köhncke, Y., Brandmaier, A.M., Andersson, M., Axelsson, J., Riklund, K., Lövdén, M., Lindenberger, U., Bäckman, L., Nyberg, L., 2022. Longitudinal dopamine D2 receptor changes and cerebrovascular health in aging. Neurology 99 (12), e1278–e1289. https://doi.org/10.1212/wnl.0000000000200891.

Karrer, T.M., Josef, A.K., Mata, R., Morris, E.D., Samanez-Larkin, G.R., 2017. Reduced dopamine receptors and transporters but not synthesis capacity in normal aging adults: a meta-analysis. Neurobiol. Aging 57, 36–46. https://doi.org/10.1016/j.neurobiolaging.2017.05.006.

Kemppainen, N., Laine, M., Laakso, M.P., Kaasinen, V., Nagren, K., Vahlberg, T., Kurki, T., Rinne, J.O., 2003. Hippocampal dopamine D2 receptors correlate with memory functions in Alzheimer's disease. Eur. J. Neurosci. 18 (1), 149–154.

Kivipelto, M., Ngandu, T., Laatikainen, T., Winblad, B., Soininen, H., Tuomilehto, J., 2006. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. Lancet Neurol. 5 (9), 735–741. https://doi.org/10.1016/s1474-4422(06)70537-3.

Lindenberger, U., Singer, T., Baltes, P.B., 2002. Longitudinal selectivity in aging populations: separating mortality-associated versus experimental components in the Berlin Aging Study (BASE). J. Gerontol. B Psychol. Sci. Soc. Sci. 57 (6), P474–P482. https://doi.org/10.1093/geronb/57.6.p474.

Lisman, J.E., Grace, A.A., 2005. The hippocampal-VTA loop: controlling the entry of information into long-term memory. Neuron 46 (5), 703–713. https://doi.org/10.1016/j.neuron.2005.05.002.

Lövden, M., Karalija, N., Andersson, M., Wåhlin, A., Axelsson, J., Köhncke, Y., Jonasson, L.S., Rieckman, A., Papenberg, G., Garrett, D.D., Guitart-Masip, M., Salami, A., Riklund, K., Bäckman, L., Nyberg, L., Lindenberger, U., 2018. Latent-profile analysis reveals behavioral and brain correlates of dopamine-cognition associations. Cereb. Cortex 28 (11), 3894–3907. https://doi.org/10.1093/cercor/bhx253.

Luciana, M., Collins, P.F., 1997. Dopaminergic modulation of working memory for spatial but not object cues in normal humans. J. Cogn. Neurosci. 9 (3), 330–347. https://doi.org/10.1162/jocn.1997.9.3.330.

Mutsaerts, H.J., Steketee, R.M., Heijtel, D.F., Kuijer, J.P., van Osch, M.J., Majoie, C.B., Smits, M., Nederveen, A.J., 2014. Inter-vendor reproducibility of pseudo-continuous arterial spin labeling at 3 Tesla. PLoS One 9 (8), e104108. https://doi.org/10.1371/journal.pone.0104108.

Nevalainen, N., Riklund, K., Andersson, M., Axelsson, J., Ogren, M., Lovden, M., Lindenberger, U., Backman, L., Nyberg, L., 2015. COBRA: a prospective multimodal imaging study of dopamine, brain structure and function, and cognition. Brain Res. 1612, 83–103. https://doi.org/10.1016/j.brainres.2014.09.010.

Nyberg, L., Lövdén, M., Riklund, K., Lindenberger, U., Bäckman, L., 2012. Memory aging and brain maintenance. Trends Cogn. Sci. 16 (5), 292–305. https://doi.org/10.1016/j.tics.2012.04.005.

Nyberg, L., Karalija, N., Salami, A., Andersson, M., Wåhlin, A., Kaboovand, N., Kohncke, Y., Axelsson, J., Rieckmann, A., Papenberg, G., Garrett, D.D., Riklund, K., Lovden, M., Lindenberger, U., Bäckman, L., 2016. Dopamine D2 receptor availability is linked to hippocampal-caudate functional connectivity and episodic memory. Proc. Natl. Acad. Sci. U. S. A. 113 (28), 7918–7923. https://doi.org/10.1073/pnas.1606309113.

Nyberg, L., Karalija, N., Papenberg, G., Salami, A., Andersson, M., Pedersen, R., Vikner, T., Garrett, D.D., Riklund, K., Wåhlin, A., Lövdén, M., Lindenberger, U., Bäckman, L., 2022. Longitudinal stability in working memory and frontal activity in relation to general brain maintenance. Sci. Rep. 12 (1), 20957 https://doi.org/10.1038/s41598-022-25503-9.

O'Reilly, R.C., 2006. Biologically based computational models of high-level cognition. Science 314 (5796), 91–94. https://doi.org/10.1126/science.1127242.

Oveisgharan, S., Yu, L., Poole, V.N., Evia, A.M., Barnes, L.L., Schneider, J.A., Arfanakis, K., Bennett, D.A., Buchman, A.S., 2021. Association of white matter hyperintensities with pathology and progression of parkinsonism in aging. JAMA Neurol. 78 (12), 1494–1502. https://doi.org/10.1001/jamaneurol.2021.3996.

Papenberg, G., Jonasson, L., Karalija, N., Johansson, J., Köhncke, Y., Salami, A., Andersson, M., Axelsson, J., Wåhlin, A., Riklund, K., Lindenberger, U., Lövdén, M., Nyberg, L., Bäckman, L., 2019. Mapping the landscape of human dopamine D2/3 receptors with [11C]raclopride. Brain Struct. Funct. 224 (8), 2871–2882. https://doi.org/10.1007/s00429-019-01938-1.

Raz, N., Lindenberger, U., 2011. Only time will tell: cross-sectional studies offer no solution to the age-brain-cognition triangle: comment on Salthouse (2011). Psychol. Bull. 137 (5), 790–795. https://doi.org/10.1037/a0024503.

Rieckmann, A., Karlsson, S., Karlsson, P., Brehmer, Y., Fischer, H., Farde, L., Nyberg, L., Bäckman, L., 2011. Dopamine D1 receptor associations within and between dopaminergic pathways in younger and elderly adults: links to cognitive performance. Cereb. Cortex 21 (9), 2023–2032. https://doi.org/10.1093/cercor/bhq266.

Sala, A., Caminiti, S.P., Presotto, L., Pilotto, A., Liguori, C., Chiaravalloti, A., Garibotto, V., Frisoni, G.B., D'Amelio, M., Paghera, B., Schillaci, O., Mercuri, N., Padovani, A., Perani, D., 2021. In vivo human molecular neuroimaging of dopaminergic vulnerability along the Alzheimer's disease phases. Alzheimer'S. Res. Ther. 13 (1), 187. https://doi.org/10.1186/s13195-021-00925-1.

Salami, A., Rieckmann, A., Karalija, N., Avelar-Pereira, B., Andersson, M., Wahlin, A., Papenberg, G., Garrett, D.D., Riklund, K., Lovden, M., Lindenberger, U., Backman, L., Nyberg, L., 2018. Neurocognitive profiles of older adults with working-memory dysfunction. Cereb. Cortex 28 (7), 2525–2539. https://doi.org/10.1093/cercor/bhy062.

Sawaguchi, T., Goldman-Rakic, P.S., 1994. The role of D1-dopamine receptor in working memory: local injections of dopamine antagonists into the prefrontal cortex of rhesus monkeys performing an oculomotor delayed-response task. J. Neurophysiol. 71 (2), 515–528.

Schmidt, P., Gaser, C., Arsic, M., Buck, D., Forschler, A., Berthele, A., Hoshi, M., Ilg, R., Schmid, V.J., Zimmer, C., Hemmer, B., Muhlau, M., 2012. An automated tool for detection of FLAIR-hyperintense white-matter lesions in multiple sclerosis. Neuroimage 59 (4), 3774–3783. https://doi.org/10.1016/j.neuroimage.2011.11.032.

Seaman, K.L., Smith, C.T., Juarez, E.J., Dang, L.C., Castrellon, J.J., Burgess, L.L., San Juan, M.D., Kundzicz, P.M., Cowan, R.L., Zald, D.H., Samanez-Larkin, G.R., 2019. Differential regional decline in dopamine receptor availability across adulthood: linear and nonlinear effects of age. Hum. Brain Mapp. 40 (10), 3125–3138. https://doi.org/10.1002/hbm.24585.

Smith, C.T., Crawford, J.L., Dang, L.C., Seaman, K.L., San Juan, D.M., Vijay, A., Katz, D. T., Matuskey, D., Cowan, R.L., Morris, E.D., Zald, D.H., Samanez-Larkin, G.R., 2019. Partial-volume correction increases estimated dopamine D2-like receptor binding potential and reduces adult age differences. J. Cereb. Blood Flow. Metab. 39 (5), 822–833.

Svensson, J.E., Schain, M., Plavén-Sigray, P., Cervenka, S., Tiger, M., Nord, M., Halldin, C., Farde, L., Lundberg, J., 2019. Validity and reliability of extrastriatal [11C]raclopride binding quantification in the living human brain. NeuroImage 202, 116143. https://doi.org/10.1016/j.neuroimage.2019.116143.

Tabachnick, B.G., Fidell, L.S., 2013. Using Multivariate Statistics, 6th Edition.

Takahashi, H., Kato, M., Takano, H., Arakawa, R., Okumura, M., Otsuka, T., Kodaka, F., Hayashi, M., Okubo, Y., Ito, H., Suhara, T., 2008. Differential contributions of prefrontal and hippocampal dopamine D(1) and D(2) receptors in human cognitive functions. J. Neurosci. 28 (46), 12032–12038. https://doi.org/10.1523/jneurosci.3446-08.2008.

Volkow, N.D., Wang, G.J., Fowler, J.S., Ding, Y.S., Gur, R.C., Gatley, J., Logan, J., Moberg, P.J., Hitzemann, R., Smith, G., Pappas, N., 1998. Parallel loss of presynaptic and postsynaptic dopamine markers in normal aging. Ann. Neurol. 44 (1), 143–147. https://doi.org/10.1002/ana.410440125.

von Oertzen, T., Brandmaier, A.M., Tsang, S., 2015. Structural equation modeling with Ωnyx. Struct. Equ. Model.: A Multidiscip. J. 22 (1), 148–161. https://doi.org/10.1080/10705511.2014.935842.