

# Aging-related losses in dopamine D2/3 receptor availability are linked to working-memory decline across five years

Goran Papenberg<sup>1,\*</sup>, Nina Karalija<sup>2,3</sup>, Alireza Salami<sup>1,3,4</sup>, Jarkko Johansson<sup>3,4,5</sup>, Anders Wåhlin<sup>3,5,6</sup>, Micael Andersson<sup>3,5</sup>, Jan Axelsson<sup>3,5</sup>, Douglas D. Garrett<sup>1,7,8</sup>, Katrine Riklund<sup>3,5</sup>, Ulman Lindenberger<sup>7,8</sup>, Lars Nyberg<sup>2,3,5</sup>, Lars Bäckman<sup>1</sup>

<sup>1</sup>Aging Research Center, Karolinska Institutet and Stockholm University, Tomtebodavägen 18 A, SE-171 65 Solna, Sweden

<sup>2</sup>Department of Medical and Translational Biology, Umeå University, Johan Bures väg 12, SE-90187 Umeå, Sweden

<sup>3</sup>Umeå Center for Functional Brain Imaging (UfBI), Umeå University, Johan Bures väg 12, SE-90187 Umeå, Sweden

<sup>4</sup>Wallenberg Centre for Molecular Medicine, Johan Bures väg 12, Umeå University, SE-90187 Umeå, Sweden

<sup>5</sup>Department of Diagnostics and Intervention, Radiation Physics, Umeå University, Norrlands universitetssjukhus, SE-90187 Umeå, Sweden

<sup>6</sup>Department of Applied Physics and Electronics, Håken Gullerströms väg 20, Umeå University, SE-90187 Umeå, Sweden

<sup>7</sup>Center for Lifespan Psychology, Max Planck Institute for Human Development, Lentzeallee 94, DE-14195 Berlin, Germany

<sup>8</sup>Max Planck UCL Centre for Computational Psychiatry and Ageing Research, Lentzeallee 94, DE-14195 Berlin, Germany and Max Planck UCL Centre for Computational Psychiatry and Ageing Research, 10-12 Russell Square, London WC1B 5EH, United Kingdom

\*Corresponding author: Aging Research Center, Karolinska Institutet, Tomtebodavägen 18 A, SE-17165 Solna, Sweden. Email: goran.papenberg@ki.se

Although age differences in the dopamine system have been suggested to contribute to age-related cognitive decline based on cross-sectional data, recent large-scale cross-sectional studies reported only weak evidence for a correlation among aging, dopamine receptor availability, and cognition. Regardless, longitudinal data remain essential to make robust statements about dopamine losses as a basis for cognitive aging. We present correlations between changes in D2/3 dopamine receptor availability and changes in working memory measured over 5 yr in healthy, older adults ( $n = 128$ , ages 64 to 68 yr at baseline). Greater decline in D2/3 dopamine receptor availability in working memory-relevant regions (caudate, middle frontal cortex, hippocampus) was related to greater decline in working memory performance in individuals who exhibited working memory reductions across time ( $n = 43$ ; caudate:  $r_s = 0.494$ ; middle frontal cortex:  $r_s = 0.506$ ; hippocampus:  $r_s = 0.423$ ), but not in individuals who maintained performance ( $n = 41$ ; caudate:  $r_s = 0.052$ ; middle frontal cortex:  $r_s = 0.198$ ; hippocampus:  $r_s = 0.076$ ). The dopamine–working memory link in decliners was not observed in the orbitofrontal cortex, which does not belong to the core working memory network. Our longitudinal analyses support the notion that aging-related changes in the dopamine system contribute to working memory decline in aging.

**Key words:** dopamine 2/3-receptor availability; working memory; aging; cognitive decline; longitudinal.

## Introduction

The neurotransmitter dopamine (DA) supports molecular mechanisms central to various cognitive functions (Williams and Goldman-Rakic 1995; Kimberg et al. 1997; Liggins 2009). In particular, working memory (WM) has been associated with dopaminergic modulation in fronto-striatal brain regions. Animal work shows that maintenance of WM representations is related to the prefrontal D1 DA receptor system (Sawaguchi 2001; Wang et al. 2004). However, DA D2/3-like receptors (D2/3DRs) also have a role in phasic WM processes, relevant to updating the contents of WM (D'Esposito and Postle 2015). Accordingly, mice deficient for D2/3DRs exhibit spatial WM deficits (Glickstein et al. 2002) and blocking D2/3DRs in prefrontal cortex impairs both learning of new stimulus–response associations and cognitive flexibility (Puig et al. 2014), relevant for WM processes. In humans, WM impairment is related to lower D2/3DR availability in frontal cortex (Lövdén et al. 2018; Salami et al. 2018) and striatum

(Lövdén et al. 2018; Juarez et al. 2019). Results from an intervention study showed that WM updating affected DA activity before training and that training across 5 wk further increased striatal DA release during updating (Bäckman et al. 2011). Moreover, hippocampal D2/3DRs have also been implicated in executive functions and verbal fluency, which draw on WM processes (Takahashi et al. 2007, 2008).

Findings from cross-sectional studies involving relatively small sample sizes (typically below 30 subjects; Karrer et al. 2017) have suggested age-related DA reductions as a mechanism underlying cognitive aging (Bäckman et al. 2006). For instance, DA measures derived from positron emission tomography (PET) were shown to account for more cognitive variance across the adult lifespan than chronological age (Bäckman et al. 2000; Erixon-Lindroth et al. 2005). Although the aging-DA-cognition link is one of the most cited mechanisms in the cognitive neuroscience of aging, recent large-scale cross-sectional data reported only weak evidence for a

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correlative triad among aging, D2/3DR availability, and cognition (Juarez et al. 2019). Specifically, with respect to WM, digit span was the only measure for which D2/3DR availability partially mediated the age effect on cognition. That said, simulation work (Maxwell and Cole 2007) and formal analyses (Lindenberger and Pötter 1998; Lindenberger et al. 2011) have shown that even though a variable may be identified as a mediator in cross-sectional analyses, the corresponding longitudinal changes may not be in line with the cross-sectional observations (Raz and Lindenberger 2011). Moreover, if there is lack of mediation for a specific variable cross-sectionally, the same variable may still be a longitudinal mediator of the same relationship (Lindenberger et al. 2011). Given these considerations and the fact that cross-sectional data can be heavily influenced by cohort effects (Nyberg et al. 2012), only longitudinal data can resolve the discrepant findings in relation to DA's role in cognitive aging.

Based on cross-sectional data, we reported that impairment in WM, but not episodic memory, was accompanied by lower frontal dopamine D2/3DR availability (Salami et al. 2018). Here, we investigate whether changes in D2/3DR availability across 5 yr are related to WM changes in healthy older adults, aged 64 to 68 yr at baseline ( $n = 128$ ). A priori regions of interest are the prefrontal cortex (caudal and rostral middle frontal gyrus), caudate, and the hippocampus, regions considered central for dopaminergic modulation of WM processes (Takahashi et al. 2008; Eriksson et al. 2015). Recently, we demonstrated longitudinal decline in D2/3DR availability for these regions (Karalija et al. 2022).

Given that cognitive changes across 5 yr are relatively small in magnitude (Rast and Hofer 2014), we reason that D2/3DR-cognition associations may be restricted to older individuals who actually exhibit cognitive decline (e.g. Satz 1993; Korkki et al. 2021). We hypothesized that these individuals would display D2/3DR-WM change associations. Such links were not expected in individuals showing improvements in performance, typically arising from test-retest effects (Daugherty et al. 2015; Rieckmann et al. 2017; Gustavsson et al. 2022).

Using an extreme-groups approach, we categorize individuals based on their changes in WM into 3 groups, which resulted in separation of individuals with relative maintenance of cognitive performance (Nyberg et al. 2012) from decliners and improvers (Rieckmann et al. 2017). Focusing on D2/3DR availability, statistical models were adjusted for shared contributions of brain integrity [gray-matter (GM) volumes and perfusion].

## Materials and methods

### Participants

The initial sample included 181 healthy older individuals (64 to 68 yr of age; mean = 66.2; SD = 1.2; 81 women), who were randomly selected from the population register of Umeå, a city in northern Sweden. The parent sample has been described in detail elsewhere (Nevalainen et al. 2015; Karalija et al. 2022). Exclusion criteria were neurological and psychiatric disorders, epilepsy, previous brain trauma, intellectual disability, a Mini-Mental State Examination score <27, structural brain abnormalities (inspection performed by neuroradiologists), cancer, diabetes, severe auditory and visual impairments, claustrophobia, and metal implants. From the baseline sample, 128 returned for the 5-year follow up (ages: 69 to 73 yr, mean: 71.2 ± 1.2 SD, 60 women). The effective sample for analyses (baseline and follow-up sessions) ranged between 124 and 126 for brain variables (PET:  $n = 126$ ; perfusion:  $n = 124$ ), while the full sample was available for WM ( $n = 128$ ). A detailed description of the follow-up sample, including selectivity

analysis, is described elsewhere (Karalija et al. 2022). In brief, 3 individuals had passed away between test waves. Two individuals refused to undergo PET at follow-up. Five participants, that were included in the analyses, had been diagnosed with diabetes mellitus between waves, which was an exclusion criterion at baseline, but not at follow-up. No cases of neurological disorders (Alzheimer's disease, Parkinson's disease) were reported at follow-up. 67% of the sample were retired at baseline and 91% at follow-up.

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

### Brain imaging: acquisition and analyses

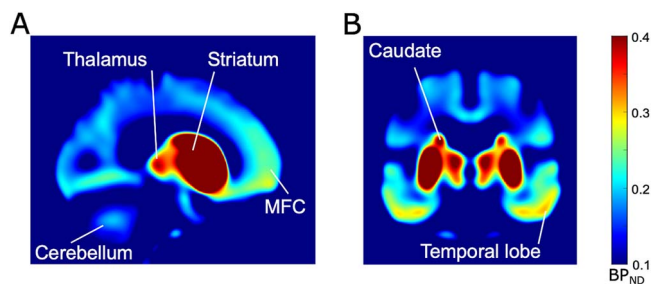
The same scanners and protocols were used at both test sessions. MRI was performed with a 3 T Discovery MR 750 scanner (General Electric, WI, United States), equipped with a 32-channel phased-array head coil. PET was acquired with a Discovery PET/CT 690 (General Electric, WI, United States) and 250 MBq  $^{11}\text{C}$ -raclopride. The spatial resolution of the PET scanner was 3.2 mm full width at half maximum (fwhm) at both time points and all data has been reconstructed with identical reconstruction algorithms.

### Regional volumes

T1-weighted images were obtained with echo time 3.2 ms, flip angle 12°, repetition time 8.19 ms, 176 slices with thickness 1.0 mm, field of view 25.0 x 25.0 cm with resolution 0.98 mm upsampled to 0.49 mm. The longitudinal image processing pipeline in Freesurfer, version 6.0 was used to process T1-weighted images and derive estimates of GM, white matter, and lateral ventricle size. Subcortical GM segmentations and cortical parcellations (Desikan et al. 2006) were used to define regions-of-interest (ROIs) for D2/3DR and perfusion assessment. The following cortical and subcortical parcellations were delineated: middle frontal cortex (MFC; caudal and rostral divisions), orbitofrontal cortex (OFC; lateral and medial divisions), caudate, and hippocampus. For the purpose of discriminant validity, OFC was selected as a control region in the analyses reported below, because it does not belong to the canonical WM network (Rottschy et al. 2012). GM volume was calculated as the sum of the left and right hemispheres.

### D2/3DR availability

A 55-min, 18-frame dynamic PET scan was acquired during rest starting at time of intravenous bolus injection of 250 MBq  $^{11}\text{C}$ -raclopride (baseline: 263.5 ± 19.0 MBq; follow-up: 260.2 ± 15.0 MBq;  $[t(123) = 1.8; P = 0.076]$ ). The range for the injected mass of raclopride was larger at baseline (0.17 to 9.48  $\mu\text{g}$ ) than at follow-up (0.11 and 2.67  $\mu\text{g}$  [ $t(124) = 4.6; P < 0.001$ ]), but none of the doses were considered sufficient for inducing pharmacological effects. The range of specific activity was lower at baseline compared with follow-up (baseline: 1 and 518 GBq/ $\mu\text{mol}$ ; follow-up: 33 and 1480 GBq/ $\mu\text{mol}$  [ $t(125) = -11.4; P < 0.001$ ]). An attenuation CT scan (20 mA, 120 kV, 0.8 s/revolution) preceded ligand injection. 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<sup>3</sup>) were reconstructed with the iterative algorithm VUE Point HD-SharpIR (GE; 6 iterations, 24 subsets, 3.0 mm post filtering; FWHM: 3.2 mm). PET images were motion-corrected and co-registered to the structural T1-weighted images from the corresponding session (baseline and



**Fig. 1.** Mean  $BP_{ND}$  image of 177 subjects assessed at baseline, created by averaging individual  $BP_{ND}$  images that were transformed to MNI space and smoothed with a 6 mm filter. We visualize binding in the rostral MFC, striatum, and cerebellum (A). Binding in the temporal lobe (inferior temporal and middle temporal) and caudate is shown in 1B. To visualize extrastriatal binding, the color range in the figure is set to 0.1 to 0.4.

follow-up), using the Statistical Parametric Mapping software (SPM12). Motion correction was done with SPM's realignment function with default parameters according to the PET-modality. The same method and atlas were used for baseline and follow-up. As source for co-registration, the mean of the first 5 time-frames were used. For 3 participants, PET images from both time points were co-registered with the baseline T1 image (no MRI at follow-up). D2/3DR binding potential ( $BP_{ND}$ ), was estimated using reference-Logan analysis (Logan et al. 1996) from time-activity curves within T1-segmented ROIs (median of ROI voxel values from time frames between 18 and 55 min). Cerebellar GM served as the reference area.

Despite the low signal-to-noise ratio and questions of suitability for measurements in low-density DRD2 regions due to failed displacement studies (Farde et al. 1988; Svensson et al. 2019; Freiburghaus et al. 2021), we and others have reported high long-term test-retest reliability for extrastriatal  $^{11}C$ -raclopride binding (Alakurtti et al. 2015; Karalija et al. 2020) and validity (Johansson et al. 2023; Papenberg et al. 2019).

Previously, we also ruled out several factors that could potentially inflate or bias extrastriatal  $BP_{ND}$ , which include the use of the iterative image reconstruction method, Logan analysis, and partial-volume effects (for details see Papenberg et al. 2019). Another study compared striatal and extrastriatal values of  $BP_{ND}$  across 4 common methods of analysis with no significant differences in estimates (Khodaii et al. 2023). Figure 1 displays the pixel-wise average  $BP_{ND}$  image calculated over all subjects of the baseline sample ( $n = 177$ ), which illustrates significant striatal and extrastriatal binding. While 181 individuals were assessed at baseline, 4 cases were excluded due to imperfect segmentations of MR images and PET/MR image co-registration.

### Perfusion measurements

3D pseudo-continuous arterial spin labeling (3D pcASL) was acquired with background suppression and a spiral readout. Labeling time = 1.5 s, post-labeling delay time = 1.5 s, field of view = 24 cm, slice thickness = 4 mm, and acquisition resolution =  $8 \times 512$  (arms  $\times$  data points), with the number of averages set at 3. This sequence provided whole-brain perfusion in ml/100 g/min units. Total scanning time was approximately 5 min. Quantitative perfusion maps were calculated using a post-processing tool installed on the scanner by the manufacturer. Mean GM perfusion was computed for Freesurfer-segmented ROIs as the average of the individual perfusion estimates weighted by volume.

### Cognitive measures

The main cognitive domains examined offline (i.e. outside the scanner) in COBRA are WM, episodic memory, and perceptual speed (see Nevalainen et al. 2015, for a more detailed description). These domains were tested with 3 separate tasks each (a verbal, a numerical, and a figural task). For each task, summary scores were computed across the total number of blocks or trials. Here, we restrict our description to the measures of WM. Papers relating changes in D2/3DR  $BP_{ND}$  to changes in episodic memory and processing speed have been published elsewhere (Karalija et al. 2024; Papenberg et al. 2024).

### Working memory

This work focuses on WM; hence, we restrict our description to the measures of WM inside and outside the scanner (Nevalainen et al. 2015). WM outside the scanner was tested with 3 separate tasks (a verbal, a numerical, and a figural task, as described below). For each test, summary scores were standardized (Z scores; with mean values and standard deviations for the whole baseline sample). Both baseline and follow-up scores were standardized on performance of the baseline sample. Z scores for the 3 tasks were then averaged to create a composite score for WM at baseline and follow-up, respectively. Finally, the composite score was T scored ( $M = 50$ ;  $SD = 10$ ). In addition, a numerical n-back task was performed inside the scanner.

**Letter-updating task.** A sequence of letters (A to D) appeared one-by-one on the computer screen, and participants were instructed to continuously update and remember the 3 lastly shown letters. Letters were presented during 1 s, with an inter-stimulus interval (ISI) of 0.5 s. Then, at an unknown time point in the sequence, the 3 last letters were to be typed using the keyboard. In case of failure, participants guessed. The test consisted of 16 trials, with 4 trials of 7, 9, 11, or 13 letter sequences presented in random order (maximum score = 16 trials  $\times$  3 responses = 48).

**Columnized numerical 3-back task.** A grid consisting of  $1 \times 3$  boxes was presented on the screen. In each box, one at a time and starting from the left, a number (1 to 9) was presented for 1.5 s, with the next number presented after an ISI of 0.5 s. After a number was presented in the rightmost box, the next number appeared in the leftmost box. In each trial, 30 numbers were presented. The task consisted of deciding whether the number appearing in a specific box was the same as the last number displayed in that particular box. A response was required for all 3 boxes throughout the test, by pressing labeled keys on the keyboard corresponding to "yes" (right index finger) or "no" (left index finger). The first 3 numbers all received a "no", as no numbers had appeared before that (maximum score = 4 trials  $\times$  27 numbers = 108).

**Spatial-updating task.** Participants were presented with 3 separate grids ( $3 \times 3$  squares in each) placed adjacent to each other. Three circular objects, at random positions in each grid, were presented simultaneously for 4 s, after which they disappeared. Following this, an arrow appeared beneath each grid for 2.5 s (one at a time, from left to right, with an ISI of 0.5 s), pointing in the direction where each circle should be mentally moved. This manipulation was done twice for each grid (i.e. 6 updating operations in total). Following updating, participants were asked to mark the correct object position in each grid, using the computer mouse. In case of uncertainty, participants guessed the position of the object. The test consisted of 10 test trials (maximum score = 10 trials  $\times$  3 grids = 30).

**In-scanner numerical n-back task.** The sum of correct responses was obtained from a numerical *n*-back task. In this task, a sequence of single numbers appeared on the screen. Each number was shown for 1.5 s, with an ISI of 0.5 s. During every item presentation, participants reported if the number currently seen on the screen was the same as that shown 1, 2, or 3 digits back. A heading that preceded each subtest indicated the actual condition. Participants responded by pressing one of 2 adjacent buttons with the index or middle finger to reply “yes, it is the same number” or “no, it is not the same number”, respectively. Nine blocks for each condition (1-, 2-, and 3-back) were performed in random order, each block consisting of 10 items. The trial sequence was the same for all participants. In calculating the total score, each correct answer was given 1 credit point, except for the first item in each 1-back condition, and for items 1 to 2 and 1 to 3 in each 2- and 3-back condition. Thus, the maximum score for each condition was 81, 72, and 63, respectively.

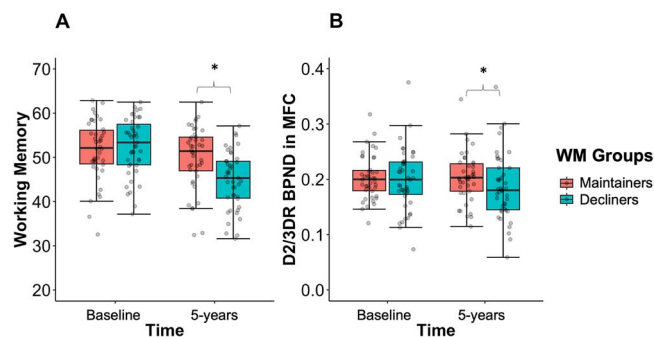
## Statistical analyses

Behavioral and demographic data were analyzed using SPSS for Windows 29 (SPSS, Chicago, IL, United States). Multivariate outliers within and across groups were determined using Cook's Distance (Cook 1979), using the recommended threshold (4/number of subjects; Bollen and Jackman 1990). This measure reflects the extent to which model residuals would change if a particular subject's data were excluded from regression-coefficient estimation, with larger values indicating more influential subjects. For all analyses, the alpha level was set to  $P < 0.05$  (corrected  $p$ -value:  $0.05/4$  ROIs = 0.0125). Effect sizes are indicated by partial  $\eta^2$ .

**Working-memory groups.** Applying an extreme-groups approach, a composite score based on 3 WM measures assessed outside the scanner was used to classify individuals into 3 groups of equal size based on their 5-year WM changes (Preacher et al. 2005), whereas the online (i.e. inside the scanner) WM task served to validate group differences. Change across time was calculated as a simple linear slope (i.e.  $t_2-t_1$ ), with negative values indicating decline. The 3 groups differed in terms of % changes in WM,  $F[1,127] = 271.06$ ,  $P < 0.001$ , partial  $\eta^2 = 0.813$ , with the first group showing improvement across time (improvers: 11.96% improvement,  $n = 43$  of which all had positive change values, indicating improvement), the second remained relatively stable in performance (maintainers:  $-3.16\%$  decline,  $n = 42$ ; over 80% had negative change values, indicating WM decline), and the third showed marked decline across 5 yr (decliners:  $-14.70\%$  decline,  $n = 43$ ). Note that one maintainer did not have any PET data, therefore the effective sample is 41.

Regression to the mean is a common statistical phenomenon in longitudinal studies with 2 time points (Barnett et al. 2005), which may be driven by an unfamiliar testing situation and failure to comprehend the tasks or to follow instructions at baseline. Therefore, we examined whether baseline performance was correlated with % changes in WM as a function of group status. Although WM maintainers and decliners did not differ in baseline performance ( $P = 0.562$ ), WM improvers performed significantly worse at baseline than decliners ( $P = 0.013$ ) and, at trend level, than maintainers ( $P = 0.058$ ). Among individuals with performance improvements over time, there was a negative correlation between baseline and % change in performance ( $r = -.512$ ,  $P = 0.000$ ), indicating that lower baseline performance was related to larger improvement over time. No such correlation was apparent in the other 2 groups (maintainers:  $r = 0.187$ ,  $P = 0.236$ ; decliners:  $r = 0.119$ ,  $P = 0.449$ ).

Furthermore, we validated the performance changes of the groups with respect to changes in the *n*-back task (2- and 3-back)



**Fig. 2.** (A) Working-memory performance and (B) D2/3DR BP<sub>ND</sub> in MFC at baseline and follow-up in maintainers and decliners. \*  $P < 0.05$ .

performed inside the MR scanner. A repeated measures analyses of variance indicated a significant interaction between WM group and time,  $F[1,99] = 4.53$ ,  $P = 0.013$ , partial  $\eta^2 = 0.084$ . Follow-up analyses revealed that the groups did not differ at baseline on 2- or 3-back performance ( $ps > 0.8$ ). At the 5-year follow-up, decliners performed worse than maintainers ( $P = 0.008$ ). Notably, improvers and maintainers did not differ from each other ( $P = 0.626$ ) and none of these groups showed any longitudinal changes ( $Ps > 0.30$ ).

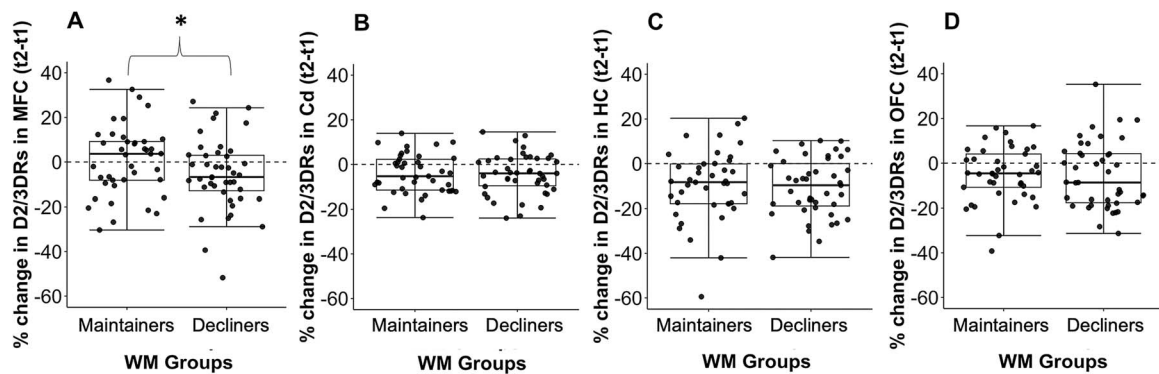
Based on the failure to validate the group of improvers and the strong correlation between baseline and change during offline performance, suggesting that individuals who improved over time may not have understood or failed to execute the tasks at baseline, we excluded this group from further analyses. Thus, we focus on WM maintainers and decliners in our analyses (Fig. 2A). Detailed performance data are presented in Table S1.

**Brain-behavior analyses.** Analyses involving D2/3DR BP<sub>ND</sub> were always adjusted for region-specific changes in GM volumes, to control for changing impact of partial-volume effects. Change in GM volumes were calculated as a simple linear slope (i.e.  $t_2-t_1$ ).

First, we conducted repeated-measures ANCOVAs to test whether WM and D2/3DR availability changed across 5 yr in the regions of interest for the total sample ( $n = 128$  for WM;  $n = 126$  for BP<sub>ND</sub>). To test whether the WM groups differed on D2/3DR BP<sub>ND</sub>, separate univariate ANCOVAs were conducted with 4 dependent variables (% change in D2/3DR BP<sub>ND</sub> in MFC, caudate, hippocampus, and the OFC control region), with WM group (maintainers, decliners) as between-subjects factor. Given potential sex differences in D2/3DR BP<sub>ND</sub> (Karalija et al. 2021) and relationships between perfusion and D2/3DR BP<sub>ND</sub> (Selvaggi et al. 2019; Karalija et al. 2022), we added sex and changes in perfusion as covariates. Previously, we reported that D2/3DR changes across different brain regions are positively correlated (Karalija et al. 2022). In addition to the above-mentioned covariates, the analyses involving different WM groups were adjusted for global changes in D2/3DR BP<sub>ND</sub> (averaged across the whole brain) given our interest in the influence of region-specific changes on WM changes.

Spearman's correlations ( $r_s$ ) were carried out between changes in D2/3DR BP<sub>ND</sub> and WM changes. Change-change correlational analyses were further adjusted for baseline levels of D2/3DR availability and WM to control for potential regression to the mean effects. Given potential impact of education on cognition (Nyberg et al. 2012), analyses were adjusted for education as well as age.

In addition to Bonferroni correction for multiple tests, we conducted bootstrapping analyses to confirm the stability of significant associations. The bootstrapping analyses were based on 5000 samples. Thus, we also report the bias-corrected (95%) confidence



**Fig. 3.** % changes in D2/3DR BP<sub>ND</sub> in (A) MFC, (B) caudate (Cd), (C) hippocampus (Hc), and (D) orbitofrontal cortex (OFC). \*  $P < 0.05$ .

intervals (CIs) of parameter estimates for the correlation coefficients. If 95% confidence intervals for the regression coefficients did not include zero, the effects were considered reliable.

## Results

### Five-year decline in WM performance and D2/3DR BP<sub>ND</sub>

Repeated-measures ANCOVAs on the whole sample showed significant WM decline ( $F[1121]=5.10$ ,  $P=0.026$ , partial  $\eta^2=0.040$ ,  $n=126$ ) and overall significant decline in D2/3DR BP<sub>ND</sub> in all 4 regions of interest: MFC,  $F[1124]=5.51$ ,  $P=0.005$ , partial  $\eta^2=0.062$ , caudate,  $F[1121]=44.36$ ,  $P<0.001$ , partial  $\eta^2=0.263$ , hippocampus,  $F[1121]=25.291$ ,  $P<0.001$ , partial  $\eta^2=0.169$ , and OFC,  $F[1124]=11.79$ ,  $P<0.001$ , partial  $\eta^2=0.087$ .

Next, we investigated whether change–change correlations (i.e. the correlations between changes in BP<sub>ND</sub> and changes in WM) were apparent in individuals who declined in WM. Individuals were classified into 3 groups based on changes in WM: improvers ( $n=43$ ), maintainers ( $n=41$ ), and decliners ( $n=43$ ; Preacher et al. 2005). Notably, the group of individuals with performance improvements could not be validated with another WM task performed inside the scanner (see Methods). Given this pattern and our focus on cognitive decline, this group was excluded from further analyses.

A univariate ANCOVA revealed a significant WM group (maintainers, decliners) effect on % change in MFC D2/3DR BP<sub>ND</sub>,  $F[1,79]=7.42$ ,  $P=0.008$ , partial  $\eta^2=0.091$ , but not for the other ROIs (caudate:  $F[1,80]=0.022$ ,  $P=0.882$ , partial  $\eta^2=0.000$ ; hippocampus:  $F[1,80]=0.046$ ,  $P=0.830$ , partial  $\eta^2=0.001$ ; OFC:  $F[1,79]=0.16$ ,  $P=0.692$ , partial  $\eta^2=0.002$ ; see Figs 2B and 3). The significant group differences for the MFC indicated larger D2/3DR BP<sub>ND</sub> decline (estimated marginal means:  $-4.78\%$ ) in individuals with WM decline as compared with maintainers (estimated marginal means:  $1.20\%$ ). These analyses were adjusted for general decline in D2/3DR BP<sub>ND</sub> across the whole brain, as well as for region-specific changes in GM volume and perfusion.

### D2/3DR-WM change–change correlations

Focusing on individuals who either maintained or declined in WM performance, significant correlations were found between changes in MFC D2/3DR BP<sub>ND</sub> and changes in WM performance ( $r_s=0.310$ , 95% CI [.116, 0.476],  $P=0.005$ ,  $n=80$ ; see Fig. 4 for all ROIs). Such associations were not found for the other ROIs (caudate:  $r_s=0.039$ ,  $P=0.734$ ,  $n=80$ ; hippocampus:  $r_s=0.145$ ,  $P=0.196$ ,  $n=81$ ; OFC:  $r_s=0.009$ ,  $P=0.934$ ,  $n=81$ ). The association between

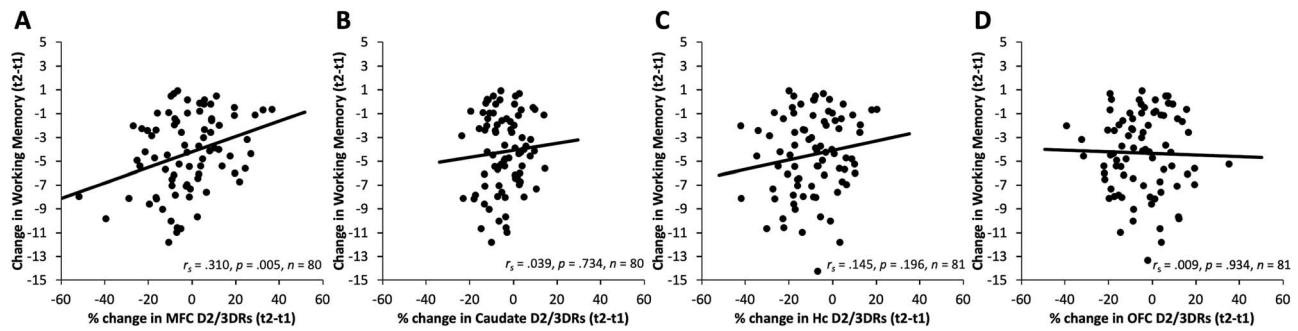
WM and MFC D2/3DR BP<sub>ND</sub> remained after adjusting for potential confounders ( $r_s=0.365$ , 95% CI [.158, 0.540],  $P=0.001$ ,  $n=76$ ), and was significantly different (all  $ps<0.05$ ) from the associations involving the other 3 ROIs (caudate:  $r_s=0.094$ ,  $P=0.418$ ,  $n=76$ ; hippocampus:  $r_s=0.066$ ,  $P=0.566$ ,  $n=77$ ; OFC:  $r_s=-.040$ ,  $P=0.728$ ,  $n=77$ ).

Stratifying analyses by maintainers and decliners, correlational analyses revealed significant change–change correlations for MFC, caudate, and hippocampus in individuals with significant WM decline only (see Table 1 and Fig. 5). The patterns of results did not change after adjusting for covariates.

## Discussion

The main aim of this study was to examine the DA–cognition link in aging, focusing on WM. Decline in D2/3DR availability was observed across brain regions of interest (Karalija et al. 2022), and for WM performance. Most importantly, WM decline across 5 yr was generally related to decline in D2/3DR availability in the prefrontal cortex. The prefrontal DA system, via striatal conjunctions, has been linked to maintenance and updating of WM representations (D'Esposito and Postle 2015). This work is the first to reveal longitudinal D2/3DR–WM correlations in aging. In line with the involvement of the striatum in WM (e.g. Bäckman et al. 2011; Lövdén et al. 2018; Juarez et al. 2019; Papenberg et al. 2020), changes in caudate D2/3DR availability were associated with WM changes, but in WM decliners only. Hence, this work highlights the role of fronto-striatal dopaminergic modulation of WM (Williams and Goldman-Rakic 1995; Kimberg et al. 1997; Liggins 2009), and suggests that changes both in caudate and MFC D2/3DR availability may be driving WM decline in aging. In addition, change–change correlations were identified for the hippocampus, which has also been implicated in dopaminergic modulation of WM (Piekema et al. 2007; Takahashi et al. 2007, 2008).

Notably, losses in the MFC were related to declines in the WM in both WM decliners and maintainers, suggesting that receptor losses in regions with very low D2/3DRs may be particularly relevant for WM changes. By contrast, the ability of the DA-rich striatum to buffer in initial stages of DA decline (e.g. in early stages of Parkinson's disease; Tedroff et al. 1999) likely underlie the absence of group differences in striatal D2/3DR decline between WM decliners and maintainers. Such differences may become evident only at later time points, following extensive aging-related decline in the nigrostriatal pathway. This trajectory may generalize to other brain regions with relatively higher D2/3 receptor availability, such as the hippocampus.

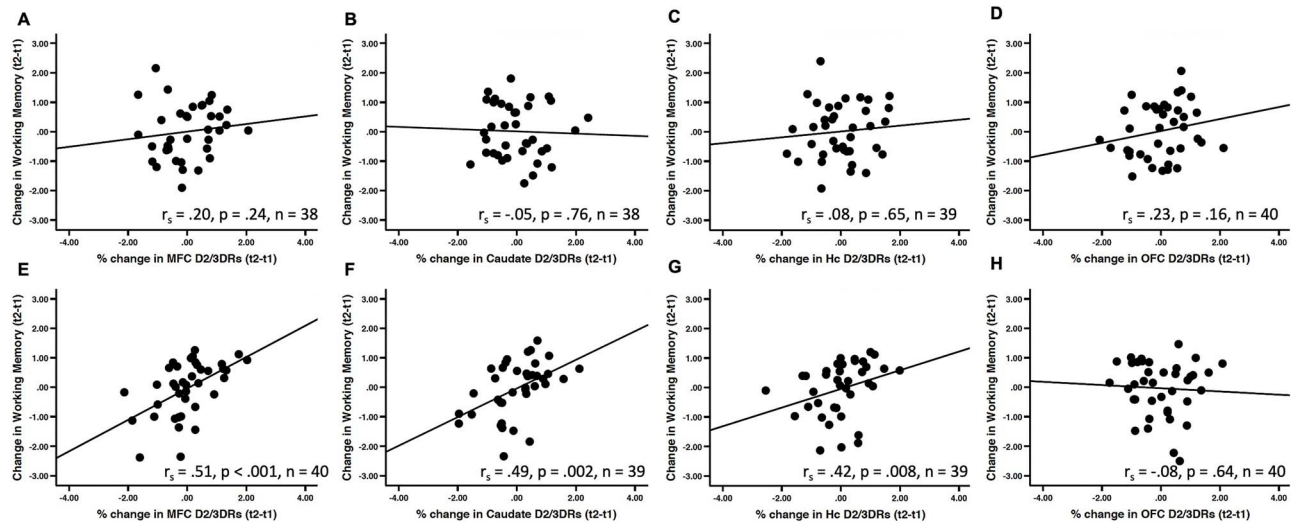


**Fig. 4.** Relationship between changes in WM and changes in D2DR BPND for individuals who declined or maintained WM performance over 5 yr for (A) MFC, (B) caudate, (C) hippocampus (Hc), and (D) orbitofrontal cortex (OFC).

**Table 1.** Spearman correlations (95% CI) between changes in D2/3DR BP<sub>ND</sub> and WM as a function of WM group.

	WM maintainers n = 41		WM decliners n = 43	
	unadjusted	adjusted	unadjusted	adjusted
% change in MFC D2/3DR BP <sub>ND</sub>	0.023 [−0.044, 0.490]	0.198 [−0.126, 0.505]	0.375* [−0.056, 0.633]	0.506** [0.247, 0.702]
% change in caudate D2/3DR BP <sub>ND</sub>	−0.119 [−0.423, 0.195]	−0.052 [−0.395, 0.280]	0.410** [0.139, 0.624]	0.494** [0.256, 0.671]
% change in OFC D2/3DR BP <sub>ND</sub>	0.241 [−0.050, 0.490]	0.229 [−0.040, 0.471]	−0.119 [−0.438, 0.207]	−0.079 [−.390, 0.257]
% change in Hc D2/3DR BP <sub>ND</sub>	0.102 [−0.188, 0.363]	0.076 [−0.279, 0.415]	0.368* [0.072, 0.605]	0.423** [0.155, 0.621]

Note. \*  $P < 0.05$ , \*\*  $P < 0.01$ . <sup>a</sup>Adjusted for age, sex, education, baseline D2/3DR and WM, changes in region-specific GM, and perfusion. Exact sample sizes are reported in Fig. 5. Deviations indicate exclusion of multivariate outliers or missing of perfusion data ( $n = 40$  for WM maintainers;  $n = 41$  for WM decliners).



**Fig. 5.** Relationship between changes in WM and changes in D2/3DR BP<sub>ND</sub> for individuals who maintained WM performance over 5 yr for (A) MFC, (B) caudate, (C) hippocampus (Hc), and (D) orbitofrontal cortex (OFC). The corresponding figures for WM decliners are shown in panels E to H. Data are adjusted for age, sex, education, region-specific baseline D2/3DRs and baseline WM, as well as for changes in region-specific GM volume and perfusion.

Many PET studies have emphasized the role of DA in cognitive aging, based on cross-sectional data (Bäckman et al. 2006). Studies involving lifespan samples showed that DA PET markers account for cognitive variation above and beyond age (Bäckman et al. 2000; Erixon-Lindroth et al. 2005). Recently, however, 2 studies have questioned the strength of the correlative triad among DA, cognition, and aging (Juarez et al. 2019). Juarez et al. reported only a significant association between striatal D2/3DR availability and digit span, but not for measures of executive functioning and episodic memory.

However, cross-sectional designs in combination with mediational analyses hamper the interpretation of findings across studies. As discussed, if a mediating variable is identified at

cross-section, the variables in question may still show divergent trajectories across time. Conversely, if a variable of interest is not found to be a mediator in a cross-sectional analysis, it may still be a significant mediator in a longitudinal analysis (Raz and Lindenberger 2011). Our longitudinal data support the view that DA losses may indeed underlie WM decline in aging. That said, the DA-cognition link was only apparent in individuals with accelerated cognitive and D2/3DR losses in MFC. Juarez et al. investigated the associations between DA, cognition, and aging in a lifespan sample and found limited evidence for the DA-cognition link. In light of our data, this may not be surprising, as the DA-cognition link may only be revealed once a certain threshold of decline is surpassed.

In any case, future studies should examine other cognitive measures, to establish whether DA decline is a general cause of age-related cognitive deficits (Juarez et al. 2019). Toward this end, episodic memory changes were unrelated to WM changes in the COBRA sample (Nyberg et al. 2022). Hereditary predisposition related to plasticity- and D2/3DR-genetic factors may play a role in DA's modulation of episodic memory (Karalija et al. 2019; Papenberg et al. 2019). Thus, D2/3DR changes may not be readily related to general cognitive decline, but change–change associations may differ across cognitive domains.

Until recently, the prevailing notion was that moderate-affinity ligands such as  $^{11}\text{C}$ -raclopride are not suitable to assess extrastriatal D2/3DR  $\text{BP}_{\text{ND}}$ . Our longitudinal data contribute to increasing evidence that D2/3DR availability is measurable outside the striatum with  $^{11}\text{C}$ -raclopride, which provides a reliable signal over time (Alakurtti et al. 2015; Karalija et al. 2020, 2022). The fact that changes in D2/3DR availability in WM-related ROIs were linked to WM changes among WM decliners further support the validity and reliability of the extrastriatal D2/3DR signal when using  $^{11}\text{C}$ -raclopride.

In addition to the longitudinal assessment, the strengths of the COBRA design include the narrow age range of the sample, selected around the age at which cognitive decline typically begins (Nyberg et al. 2012). This way confounding influences of cohort effects, resulting from rectangular age-distribution sampling, are eliminated (Bäckman et al. 2000; Erixon-Lindroth et al. 2005). That said, regression to the mean effects are likely present in our data, which lead to the exclusion of individuals who showed marked improvements over time in our offline WM tasks. We did not observe such performance improvements during the WM task, performed inside the scanner. Hence, it is highly likely that this subgroup failed to understand the current WM tasks at baseline, resulting in performance improvements across time.

Another advantage of the COBRA design is its multimodal imaging nature. Changes in neurochemical and anatomical brain measures may be correlated, and contribute to cognitive decline (Nevalainen et al. 2015). To this end, changes in D2/3DR availability in the prefrontal cortex and caudate were linked to WM changes, independent of region-specific changes in either GM volume or perfusion. However, in a related study focusing on numerical 3-back tasks (of which 1 was an in-scanner task), we found that individuals who maintain n-back performance across 5 yr also maintain general brain integrity (Nyberg et al. 2022). In that study, WM maintenance was related to preserved task-related prefrontal activation, hippocampal volume, lower load of white-matter hyperintensities, as well as to higher caudate D2/3DR  $\text{BP}_{\text{ND}}$ . The classification of WM decliners in this study mapped well onto performance inside the scanner as illustrated above. This underlines the importance of adjusting for other brain parameters to depict DA-specific effects on WM performance. Our analyses extend these findings showing that changes in frontostriatal and hippocampal DA integrity are related to WM decline.

In summary, our results contribute novel information on the neurochemical changes underlying WM decline with aging. Losses of D2/3DR availability in domain-relevant brain regions were uniquely related to WM decline, contributing to lack of maintenance of brain health and cognitive functioning.

## Author contributions

Goran Papenberg (Formal analysis, Visualization, Writing—original draft, Writing—review & editing), Nina Karalija (Data curation, Formal analysis, Writing—review & editing), Alireza

Salami (Data curation, Formal analysis, Writing—review & editing), Jarkko Johansson (Formal analysis, Writing—review & editing), Anders Wählin (Formal analysis, Writing—review & editing), Micael Andersson (Data curation, Formal analysis, Software, Supervision, Visualization, Writing—review & editing), Jan Axelsson (Formal analysis, Visualization, Writing—review & editing), Douglas Garrett (Formal analysis, Writing—review & editing), Katrine Riklund (Conceptualization, Writing—review & editing), Ulman Lindenberger (Conceptualization, Funding acquisition, Writing—review & editing), Lars Nyberg (Conceptualization, Funding acquisition, Writing—review & editing), and Lars Backman (Conceptualization, Funding acquisition, Writing—original draft, Writing—review & editing).

## Supplementary material

Supplementary material is available at *Cerebral Cortex* online.

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*Conflict of interest:* The authors declare no competing financial interests.

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