# Dedifferentiation of caudate-cortical connectivity is linked to reduced D1 dopamine receptor availability and poorer memory function in aging

Saana M. Korkki[1,2*], Jarkko Johansson[3,4], Kristin Nordin[2], Robin Pedersen[1,4,5], Anna Rieckmann[6], Alireza Salami[1,2,4,5]

[1]Department of Medical and Translational Biology, Umeå University, Umeå, Sweden,

[2]Aging Research Centre, Karolinska Institutet and Stockholm University, Solna, Sweden,

[3]Department of Diagnostics and Intervention, Umeå University, Umeå, Sweden,

[4]Umeå Center for Functional Brain Imaging, Umeå University, Umeå, Sweden,

[5]Wallenberg Centre for Molecular Medicine, Umeå University, Umeå, Sweden,

[6]Department of Human Sciences, University of the Bundeswehr Munich, Germany

*Corresponding author: Saana M. Korkki, saana.korkki@umu.se

**Abstract**

Decreasing integrity of striato-cortical circuits has been highlighted as an important determinant of declines in flexible, higher-order cognition in older age. Here, leveraging multi-modal (fMRI, PET) neuroimaging data from a large adult lifespan sample, we demonstrate older age to be associated with less specific functional coupling between the caudate and cortical association networks. This age-related dedifferentiation of caudate-cortical connectivity was present during both rest and an active working memory task, and predicted poorer short and long-term memory performance with older age. Notably, reduced striatal and prefrontal dopamine D1-like receptor (D1DR) availability was associated with less specific caudate-cortical coupling across the lifespan and accounted for age-related variation in this measure. These findings highlight decreased dopaminergic neuromodulation as one factor contributing to differences in striato-cortical function, and memory performance, with older age.

## Introduction

Aging is associated with various changes in functional, structural, and neurochemical properties of the brain, contributing to cognitive deficits observed in older age (Grady, 2012; Jagust, 2013; Nyberg et al., 2012). On the functional level, a frequent finding in past neuroimaging studies has been age-related loss of selectivity and specificity of neural processing, known as age-related *neural dedifferentiation* (reviewed in Koen et al., 2020; Koen & Rugg, 2019). During behavioural task performance, older adults display reduced stimulus- and process-specificity of regional brain activity (Dennis & Cabeza, 2011; Park et al., 2004; Srokova et al., 2024; Trelle et al., 2019). Similarly, the organization of brain large-scale functional networks has been shown to become less segregated in older age during both rest and task performance (Chan et al., 2014; Geerligs et al., 2014, 2015; Pedersen et al., 2021), reflecting age-related decreases in functional coherence between regions belonging to the same functional network, and increases in connectivity between regions belonging to different functional networks (Chan et al., 2014; Damoiseaux, 2017; Geerligs et al., 2015).

These age-related reductions in the specificity of neural processing have been linked to poorer cognitive performance in older age (Koen et al., 2020), yet the underlying neurobiological mechanisms remain unclear. Aging is associated with reduced efficiency of ascending neuromodulatory systems that act to tune the function of widespread cortical and subcortical circuits (Cools, 2019; Shine et al., 2021). In particular, the dopaminergic neurotransmitter system exhibits age-related deterioration (Johansson et al., 2023; Karalija et al., 2022; Karrer et al., 2017) that has been linked to decreases in higher-order cognition, including short- and long-term memory, in older age (Bäckman et al., 2000; Landau et al., 2009; Nyberg et al., 2016). Long-standing computational accounts suggest dopaminergic decreases in older age to attenuate neural gain, leading to less distinctive neural representations and non-selective recruitment of functional networks (Li et al., 2000, 2001; Li & Sikström, 2002). While these accounts correspond to observations from functional neuroimaging studies of the aging brain, direct in vivo evidence linking markers of the dopaminergic system to functional measures of neural dedifferentiation in aging remains scarce.

In the human brain, dopaminergic modulation of striatal and prefrontal regions plays a crucial role in flexible, goal-oriented behaviour (Cools, 2019; Cools & D'Esposito, 2011; Gerfen & Surmeier, 2011; Westbrook et al., 2021). The striatum communicates with cortical regions via multiple topographically-organized cortico-striato-thalamic-cortical loops, with the caudate and anterior parts of the putamen coupling with heteromodal cortical regions

implicated in higher-order cognitive function, and the posterior putamen and ventral striatum with cortical regions implicated in motor and reward-related processes, respectively (Alexander et al., 1991; Haber & Knutson, 2010; Parent & Hazrati, 1995). Within the caudate, functional neuroimaging studies suggest a further medial-to-lateral gradient of cortical connectivity, with centrolateral parts of the caudate coupling with the cortical fronto-parietal control network (FPN) and a more medial wall zone with the cortical default-mode network (DMN) (Choi et al., 2012; Rieckmann et al., 2018). Prior evidence indicates age-related dedifferentiation of centrolateral caudate connectivity with the cortical FPN to contribute to memory decline in older age (Rieckmann et al., 2018). However, it remains unclear whether such dedifferentiation may in part be attributed to age-related alterations in dopaminergic neuromodulation. No evidence for an association between striatal dopamine transporter (DAT) availability, which mediates the reuptake of dopamine from the synaptic cleft (Elsworth & Roth, 1997), and caudate-cortical connectivity was observed in a previous study (Rieckmann et al., 2018). It is possible that functional coupling within the striato-cortical circuit may be more closely related to post-synaptic markers of the dopaminergic system. In particular, activation of dopamine D1-like receptors (D1DR) promotes stability of network patterns of activity (Durstewitz et al., 2000), and has previously been linked to functional connectivity within cortico-cortical (Rieckmann et al., 2011; Roffman et al., 2016) and striato-cortical (Johansson et al., 2023) networks.

Here, we leveraged data from the largest human positron emission tomography (PET) study (*N* = 180) on D1DRs to date to investigate the role of dopaminergic decreases in age-related dedifferentiation of striato-cortical function. Healthy adult volunteers (20-79 years old) underwent fMRI scans during rest and while performing an n-back working memory task that taxes coordinated activity of striatal and fronto-parietal circuits (D'Esposito & Postle, 2015; Murty et al., 2011; Nyberg & Eriksson, 2016). PET assessment of D1DR availability in the striatum and the prefrontal cortex was conducted with the radioligand [$^{11}$C]SCH2339. Consistent with previous work (Rieckmann et al., 2018), we expected older age to be associated with dedifferentiation of centrolateral caudate connectivity with the cortical FPN. Motivated by dopaminergic accounts of age-related neural dedifferentiation (Li et al., 2001), we further predicted reduced D1DR availability to be associated with less specific caudate-cortical connectivity across the lifespan, and that less differentiated caudate-cortical connectivity predicts poorer performance on memory measures reliant on executive control operations supported by striato-cortical circuits (Cools, 2019; Cools & D'Esposito, 2011).

## Methods

The current study used baseline fata from the DopamiNe, Age, connectoMe, and Cognition (DyNAMiC) cohort, described in detail in Nordin et al. (2022). Here, we report only methodological details relevant for the current work. Data collection for the DyNAMiC study was approved by the Regional Ethical board and the local Radiation Safety Committee of Umeå, Sweden.

### *Participants*

The baseline sample consisted of 180 healthy adult volunteers, evenly distributed across the age range of 20 – 79 years old (mean age = 49.8, SD: 17.4; 90 female). Participants were invited to participate via random selection from the population registry at Umeå, Sweden. Study exclusion criteria included impaired cognitive function (Mini Mental State Examination score < 26), medical conditions or treatment that could affect brain or cognitive function (e.g., neurological, psychiatric, or developmental disorder, use of psychoactive medications, substance abuse, brain injury) or preclude participation in the neuroimaging assessments (e.g., metal implants). Individuals with other chronic or serious medical conditions (e.g., cancer, diabetes) were also excluded. All participants were right-handed native Swedish speakers and provided informed written consent prior to participation.

PET data on D1DR availability were missing from four participants due to drop out, technical issues, or indications of subcutaneous tracer injection. Behavioural data for one or more of the memory tasks performed outside of the scanner was missing for 17 participants due to technical issues or misunderstanding of task instructions. Outliers > 3.29 SDs from the mean were excluded from analyses of cognitive and neuroimaging measures. Moreover, individuals with excessive movement in the scanner (mean framewise displacement; FD, > 0.30mm, Jenkinson et al., 2002) were excluded from analyses of the fMRI data ($N$ = 1 for rest, $N$ = 3 for n-back). We restricted analyses of the in-scanner n-back data to individuals who performed the task above chance-level accuracy (> 50%) for all load conditions ($N$ = 165).

### *Image acquisition*

MRI and PET scanning were performed at the Umeå Center for Functional Brain Imaging (UFBI) and the Umeå University Hospital in Umeå, Sweden.

*MRI*

MRI scanning was performed using a 3T Discovery MR 750 scanner (General Electric) with a 32-channel phased-array head coil. High-resolution anatomical T1-weighted images were acquired with a 3D fast spoiled gradient-echo sequence (176 sagittal slices, slice thickness = 1mm, repetition time (TR) = 8.2 ms, echo-time (TE) = 3.2 ms, flip angle = 12º, field of view (FOV) = 250 × 250 mm, voxel size = 0.49 x 0.49 x 1mm). Functional MRI data were acquired during rest and an n-back working memory task using a T2*-weighted single-shot echo-planar imaging (EPI) sequence. The resting-state scan consisted of 350 volumes and the n-back scan of 330 volumes, acquired as 37 transaxial slices (slice thickness = 3.4 mm, interslice gap = 0.5 mm, TR = 2 000 ms, TE = 30 ms, flip angle = 80°, FOV = 250 × 250 mm, voxel size = 1.95 x 1.95 x 3.9mm). During the resting-state scan, participants were instructed to stay awake and focus on a white fixation cross presented on a black background in the centre of the screen. The n-back task consisted of three load conditions (1-back, 2-back, 3-back) that were performed in a blocked fashion, described in detail below.

*PET*

PET scanning was performed during rest with a Discovery PET/CT 690 scanner (General Electric) and the radioligand [$^{11}$C]SCH23390. Head movements were minimized with individually fitted thermoplastic masks attached to the bed surface. Prior to tracer injection, a low-dose CT scan (10 mA, 120 kV, 0.8s rotation time) was acquired for PET attenuation correction. An intravenous bolus injection of [$^{11}$C]SCH23390 with target radioactivity of 350 MBq was administered at the start of a 60min dynamic PET scan (6 x 10 s, 6 x 20 s, 6 x 40 s, 9 x 60 s, 22 x 120 s frames). The average radioactivity dose administered to participants was 337 ± 27 MBq (range 205–391 MBq). Time-framed, attenuation-, scatter-, and decay-corrected PET images (47 slices, 25 cm field of view, 256×256-pixel transaxial images, voxel size = 0.977×0.977×3.27mm) were reconstructed using the manufacturer-supplied iterative VUE Point HD-SharpIR algorithm (6 iterations, 24 subsets, resolution-recovery).

*Image preprocessing and analyses*

*FMRI*

Functional data were preprocessed using Statistical Parametric Mapping 12 (SPM12, www.fil.ion.ucl.ac.uk/spm) and the Data Processing & Analysis of Brain Imaging toolbox (DPABI, version 6.1; Yan et al., 2016, http://rfmri.org/DPABI). Functional images were

corrected for differences in slice acquisition time, movement, and distortion using subject-specific field maps. Distortion correction was not applied to data from three participants due to technical issues with field map acquisition. The functional data were coregistered with corresponding anatomical images and underwent nuisance regression to attenuate the influence of non-neural sources of noise. Nuisance regressors included mean cebrospinal fluid (CSF) and white matter (WM) signals, Friston's 24-parameter motion model (Friston et al., 1996), and a binary scrubbing regressor indicating volumes contaminated by movement (i.e., FD > 0.2mm, Jenkinson et al., 2002). Data were bandpass filtered (0.009 – 0.09 Hz), normalized into MNI space using a sample-specific structural template created with Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) toolbox (Ashburner, 2007), and spatially smoothed using an isotropic 6mm full width at half maximum Gaussian kernel.

Regions of interest (ROIs) for the functional connectivity analyses included two caudate seeds, created as bilateral 6mm spheres centred at high-confidence regions of the caudate shown to preferentially couple with the cortical FPN (x, y, z = ± 12, 10, 8) and DMN (x, y, z = ± 8, 10, 1) networks (Choi et al., 2012). However, in initial analysis of the resting-state data, we did not observe evidence for preferential connectivity of the caudate DMN seed to the cortical DMN over the cortical FPN in younger adults ($p$ = .500). Using the entire caudate parcel preferentially coupled with the DMN from Choi et al. (2012), we replicated the pattern of preferential caudate-DMN over caudate-FPN connectivity in the younger adults $t(58)$ = 2.73, $p$ = .008, but did not observe evidence for age-related dedifferentiation of cortical connectivity in this caudate subregion ($p$ = .473, see Supplementary material). Therefore, we focus our analyses of the caudate subregion preferentially coupling with the cortical FPN, previously implicated in age-related memory decline (Rieckmann et al., 2018).

ROIs for cortical FPN and DMN regions were created as 6mm bilateral spheres centred at peak coordinates of three key nodes of the FPN (lateral prefrontal cortex, x, y, z = ± 41, 55, 4; medial prefrontal cortex, x, y, z = ± 5, 22, 47; anterior parietal cortex, x, y, z = ± 52, -50, 49) and DMN (medial prefrontal cortex, x, y, z = ± 7, 46, -2; posterior parietal cortex, x, y, z = ± 42, -61, 31; precuneus, x, y, z = ± 3, -49, 25), following Choi et al. (2012) and Rieckmann et al. (2018).

Functional connectivity of the caudate seed to each of the two cortical networks was computed as the average pairwise correlation between the caudate seed and the cortical targets. For the n-back scan, connectivity was calculated separately for timepoints corresponding to each load condition (1-back, 2-back, 3-back), accounting for the hemodynamic lag (i.e., shifting timepoints by 4s, see Salami et al., 2018).

*PET*

PET data were corrected for head movement using frame-to-frame image coregistration, coregistered with T1-weighted structural images and resliced to dimensions of the structural images (1mm$^3$ isotropic, 256 x 256 x 256) using SPM 12 (www.fil.ion.ucl.ac.uk/spm). The T1-weighted structural images were segmented with FreeSurfer 6.0 (Fischl et al., 2002, https://surfer.nmr.mgh.harvard.edu) to obtain ROIs for the PET analyses. D1DR availability in target regions was estimated as the binding potential relative to non-displaceable binding in a reference region ($BP_{ND}$, Innis et al., 2007), using cerebellum as the reference. The simplified reference-tissue model (SRTM) was used to model regional time-activity course (TAC) data (Lammertsma & Hume, 1996). Regional TAC data were adjusted for partial volume effects (PVE) by using the symmetric geometric transfer matrix (SGTM) method implemented in FreeSurfer (Greve et al., 2016), and an estimated point-spread-function of 2.5 mm full-width-at-half-maximum (FWHM). ROIs for the PET analyses included the caudate as well as the prefrontal cortex (comprising the caudal and rostral middle frontal gyrus, inferior frontal gyrus pars orbitalis and pars triangularis, and the frontal pole, see Johansson et al., 2023).

*In-scanner n-back task*

The working memory task performed in the MRI scanner was a numerical n-back task consisting of three load conditions (1-back, 2-back, 3-back) that were completed in a blocked manner (c.f., Nevalainen et al., 2015; Nordin et al., 2022). In each task block, a sequence of 10 single numbers was presented on the screen (stimulus duration: 1.5s, inter-stimulus interval, ISI: 0.5s) and participants were instructed to indicate whether each item presented matched the one *n*-back (i.e., 1-, 2-, or 3-back) in the sequence by pressing one of two adjacent buttons on a scanner-compatible button box using their index and middle finger. Load condition for each task block was indicated by a cue presented on the screen before the start of the block. Nine task blocks were completed for each task load, with the order of blocks randomized but kept constant across participants.

*Memory tasks outside of the scanner*

In addition to the in-scanner working memory task, participants completed a battery of episodic and working memory tasks outside of the scanner (Nordin et al., 2022). Episodic memory was assessed with a word recall, a number-word recall, and an object-location recall task. In the word recall task, participants were presented with 16 concrete nouns that

appeared one by one on the computer screen (stimulus duration: 1s, ISI: 1s). After presentation of the entire list, participants used the keyboard to type in as many words as they could remember from the preceding list in any order. Two blocks of the word recall task were completed (maximum score = 32). In the number-word recall task, participants were presented with pairs of two-digit numbers and concrete plural nouns (e.g., 46 dogs). Ten number-digit pairs were first sequentially presented (stimulus duration: 6s, ISI: 1s), after which each word reappeared on the screen in a randomized order and participants were instructed to recall the associated number by typing their responses with the keyboard. Two blocks of the number-word recall task were completed (maximum score = 20). In the object-location recall task, 12 objects were sequentially presented in different locations of a 6 x 6 square grid on the computer screen (stimulus duration: 8s, ISI: 1s). Following the encoding phase, all objects appeared next the grid and participants' task was to place them to their correct location in the grid using the computer mouse. Participants could place the objects in any order. Two blocks of the object location recall task were completed (maximum score = 24).

Working memory was assessed with a letter updating, a number updating, and a spatial updating task. In the letter updating task, a sequence of capital letters (A-D, stimulus duration: 1s, ISI: 0.5s) appeared on the screen and participants were instructed to try and keep in mind the three most recently presented letters. When prompted, participants were asked to type the last three letters with the computer keyboard. The task consisted of 16 trials of 7, 9, 11, or 13 letter sequences (4 trials per sequence length), presented in a random order (maximum score = 48). The number updating task was a columnized numerical 3-back task, where a single digit number (stimulus duration: 1s, ISI: 0.5s) appeared in one of three boxes present on the screen, in a sequence from left to right. Participants' task was to judge whether the current number matched the one previously presented in the same box (i.e., three numbers before) by pressing one of two assigned keys on the keyboard. Four task blocks each consisting of presentation of 30 numbers were completed (maximum score = 108). In the spatial updating task, three 3 x 3 square grids were presented next to each other on the computer screen. At the beginning of each trial, a blue dot appeared in a random location in each grid for 4s. After this, an arrow appeared below each grid to indicate the direction to which participants should mentally move the object to by one step. The arrows appeared sequentially from left to right (stimulus duration: 2.5s, ISI: 0.5s), and twice below each grid (i.e., each object should be moved by two steps). Participants were then asked to indicate using the computer mouse where in each grid the object had moved to. Ten blocks of the spatial updating task were completed (maximum score = 30).

Performance in all tasks was measured as the number of correct answers. To generate a composite score of memory performance, we performed a principal component analysis across all three episodic and all three working memory measures (z-scored). The first principal component from this analysis accounted for 54.96% variance in the data with high loadings across all tasks (*r*s .64 - .80, see Supplementary material), and was used as a measure of general memory function.

*Statistical analyses*

Statistical analyses were conducted with R (version 4.3.2, R Core Team 2023) and JASP (version 0.18.1, JASP Team 2023). Age group (i.e., young, 20-39 years; middle-aged, 40-59 years; older, 60-79 years) differences in caudate functional connectivity during rest and working memory were analysed with mixed ANOVAs. Linear regression and linear mixed effects models were used to assess the relationship between functional connectivity and D1DR availability and memory during rest and working memory, respectively. Linear mixed effects models were implemented with the R package lme4 (version 1.1-35) including random effect of participant, and *p*-values estimated via the Satterthwaite's degrees of freedom method implemented in the R package lmerTest (version 3.1-3). Age, sex, education, and mean FD were included as covariates in all connectivity-D1DR and connectivity-memory analyses, unless otherwise specified in text. We further investigated whether D1DR availability mediated the effects of age on functional connectivity. Mediation analyses were implemented with the R package mediation (version 4.5.0), controlling for age, sex, education, and mean FD.

## Results

*Age-related differences in caudate-cortical connectivity during rest*

We first examined age-related differences in caudate-cortical functional connectivity during rest. A mixed ANOVA indicated a significant interaction between age group and cortical target, $F(2, 175) = 8.63$, $p < .001$, $\eta_p^2 = .09$ (Figure 1A). Consistent with the pattern expected from prior work (Choi et al., 2012; Rieckmann et al., 2018), younger adults demonstrated significantly stronger functional connectivity between the centrolateral caudate and the cortical FPN than the cortical DMN, $t(58) = 4.85$, $p < .001$, $d = .63$, whereas no such preferential connectivity was detected in the middle-aged ($p = .131$) or older adults ($p = .255$). This age-related loss of specificity of caudate-cortical coupling was driven both by age-related reductions in caudate-FPN connectivity (i.e., the preferred network in younger

adults), $F(2,175) = 6.00$, $p = .003$, $\eta_p^2 = .06$, and age-related increases in caudate-DMN connectivity (i.e., the non-preferred network in younger adults), $F(2,175) = 5.61$, $p = .004$, $\eta_p^2 = .06$. Specifically, we observed caudate-FPN connectivity to be decreased in older in comparison to young, $t(119) = 2.68$, $p = .009$, $d = .49$, and middle-aged adults, $t(117) = 3.00$, $p = .003$, $d = .55$, whereas elevated caudate-DMN connectivity was observed in both older, $t(119) = 2.37$, $p = .020$, $d = .43$, and middle-aged adults, $t(114) = 3.39$, $p < .001$, $d = .63$, when compared to the young adults.

*Age-related differences in caudate-cortical connectivity during working memory*

We further examined whether this pattern of age-related dedifferentiation of caudate-cortical connectivity extended to a working memory task that places greater demands on coordinated activity of striatal and frontoparietal regions (D'Esposito & Postle, 2015; Nyberg & Eriksson, 2016). During the n-back working memory task that participants performed in the scanner, we similarly observed a significant interaction between age and cortical network, $F(2, 160) = 10.13$, $p < .001$, $\eta_p^2 = .11$ (Figure 1A). During n-back, both young, $F(1, 58) = 48.49$, $p < .001$, $\eta_p^2 = .46$, and middle-aged adults, $F(1, 56) = 21.42$, $p < .001$, $\eta_p^2 = .28$, exhibited significantly stronger caudate-FPN over caudate-DMN connectivity across memory loads, whereas no significant differences between caudate-FPN and caudate-DMN connectivity were observed in the older adults ($p = .511$). The degree of preferential caudate-FPN connectivity was further modulated by memory load in the young, $F(2,116) = 3.60$, $p = .030$, $\eta_p^2 = .06$, and middle-aged, $F(2,112) = 4.66$, $p = .011$, $\eta_p^2 = .08$, but not older adults ($p = .837$), however, the 3-way interaction between age, target, and load did not reach significance ($p = .225$). During working memory, age-related differences in caudate-cortical were driven by reduced caudate-FPN connectivity in older adults across memory loads (effect of age, $F(2, 160) = 18.06$, $p < .001$, $\eta_p^2 = .18$; old vs. young, $t$s > 3.36, $p$s < .002, old vs. middle-aged, $t$s > 2.78, $p$s < .007), whereas no significant age-related differences were detected for caudate-DMN connectivity during working memory ($p = .127$). Thus, older age was associated with decreased specificity of caudate-cortical connectivity during both rest and working memory, with the age-related differences driven by both decreased caudate-FPN and increased caudate-DMN connectivity during rest and primarily by decreased caudate-FPN connectivity during working memory.

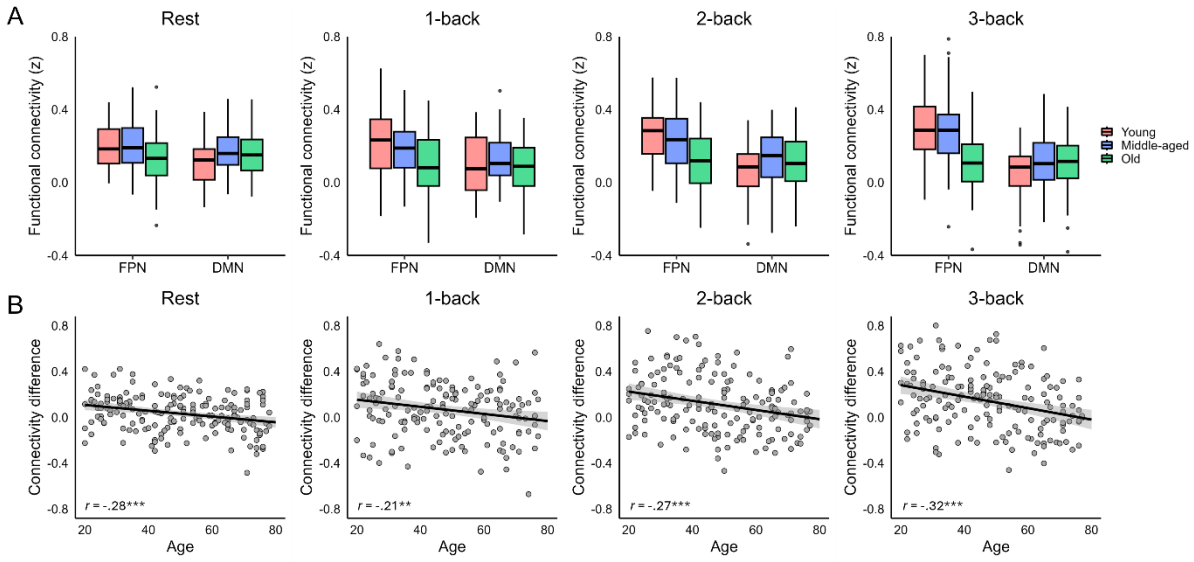


*Figure 1.* A) Functional connectivity (Fisher's z) between the centrolateral caudate and the fronto-parietal (FPN) and default-mode (DMN) networks in each age group (young, 20-39 years, middle-aged, 40-59 years, old, 60-79 years old) and condition. B) Associations between age and the specificity of caudate-cortical connectivity (i.e., the difference in caudate-FPN vs. caudate-DMN connectivity) in each condition.

*D1DR integrity contributes to maintaining the specificity of caudate-cortical connectivity across the adult lifespan*

Given the proposed role of dopamine in age-related dedifferentiation of brain function (Li et al., 2000, 2001; Li & Sikström, 2002) and in regulation of striato-cortical connections (Cools, 2019; Gerfen & Surmeier, 2011), we next assessed whether integrity of the D1DR system may contribute to maintaining the specificity of caudate-cortical connectivity across the lifespan. For this purpose, we first quantified the degree of preferential caudate-FPN connectivity for each individual and task condition as the difference between caudate connectivity with the FPN and the DMN. The degree of preferential caudate-FPN connectivity was negatively associated with age for each condition (*r*s -.21 to -.32, Figure 1B). Across the sample, caudate D1DR availability positively predicted the specificity of caudate-cortical connectivity during rest, $\beta$ = .22, *SE* = .10, *t* = 2.19, *p* = .030, controlling for age, sex, education, and mean FD (Figure 2A). This association did not significantly vary with age (*p* = .289). Prefrontal D1DR availability, on the other hand, was not significantly associated with the specificity of caudate-cortical connectivity during rest (D1DR, *p* = .181, D1DR x age, *p* = .129), but predicted the specificity of caudate-cortical connectivity during working memory, $\beta$ = .14, *SE* = .07, *t* = 2.05, *p* = .042 (Figure 2B). The association between

prefrontal D1DR availability and caudate-cortical connectivity did not significantly vary with memory load ($p$ = .544), age ($p$ = .394), or as an interaction between memory load and age ($p$ = .457). Caudate D1DR was not associated with the specificity of caudate-cortical coupling during working memory ($p$s > .298). Given the different pattern of D1DR-connectivity relationships observed during rest and working memory, we further included both caudate and prefrontal D1DR in the same model to assess the specificity of these associations. The association between prefrontal D1DR and the caudate-cortical connectivity during working memory persisted after inclusion of caudate D1DR availability as an additional covariate, $\beta$ = .23, $SE$ = .10, $t$ = 2.42, $p$ = .017, whereas the association of caudate D1DR and resting-state connectivity became marginal after inclusion of prefrontal D1DR availability, $\beta$ = .22, $SE$ = .13, $t$ = 1.69, $p$ = .092.

To assess whether reduced D1DR availability accounted for age-related dedifferentiation of caudate-cortical connectivity, we performed further mediation analyses (Figure 2C and 2D). For functional connectivity during rest, we observed a significant indirect effect of age on the specificity of caudate-cortical connectivity via caudate D1DR availability, $\beta$ = -.14, 95% CI [-.25, -.04], $p$ = .011, accounting for 48% of the age effect. The direct effect of age was non-significant, $\beta$ = -.16, 95% CI [-.37, .05], $p$ = .123. Similarly, for the mean specificity of caudate-cortical connectivity during working memory, we observed a significant indirect effect of age via prefrontal D1DR availability, $\beta$ = -.10, 95% CI [-.21, .00], $p$ = .040, accounting for 30% of the age effect. The direct effect of age was also significant, $\beta$ = -.23, 95% CI [-.40, -.04], $p$ = .013.

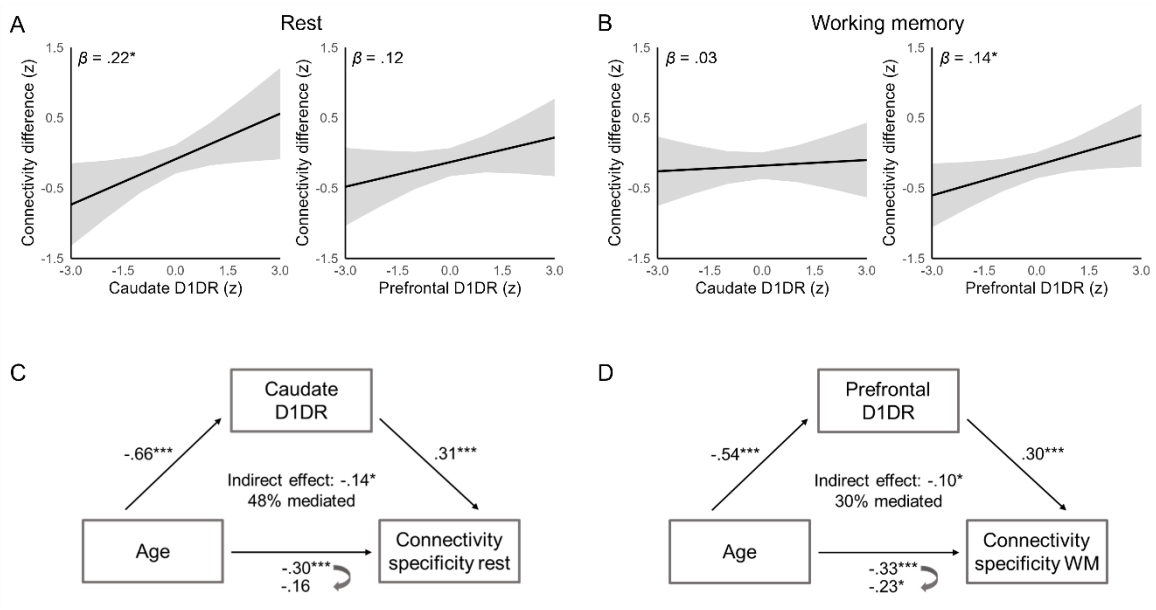


*Figure 2.* Associations between D1DR availability and the specificity of caudate-cortical connectivity (difference in caudate-FPN and caudate-DMN connectivity) during A) rest and B) working memory. Plots illustrate predicted effects of D1DR availability on connectivity specificity from A) linear regression and B) linear mixed effects analyses, controlling for A) age, sex, education, mean framewise displacement (FD), and B) age, sex, education, mean FD, and working memory load. Mediation analyses indicated D1DR availability in the C) caudate and D) the prefrontal cortex to mediate the effect of age on the specificity of caudate-cortical coupling during C) rest and D) working memory, respectively.

*Dedifferentiation of caudate-cortical connectivity predicts poorer memory performance with older age*

Lastly, we examined the behavioural relevance of differences in caudate-cortical coupling across the lifespan. We expected integrity of caudate-cortical circuits supporting flexible cognitive control to be associated with more efficient memory performance across short and long-term memory tasks. General memory function was indexed as the first principal component from an analysis involving all three episodic (i.e., word recall, number-word recall, object-location memory) and working memory (letter updating, number updating, spatial updating) tasks included in a cognitive task battery that participants performed outside of the scanner (all task loadings *r*s > .64, see Supplementary material). Greater specificity of caudate-cortical connectivity during rest was associated with better memory function across the lifespan, $\beta$ = .14, *SE* = .06, *t* = 2.39, *p* = .018. Controlling for age, sex, and mean FD, we further observed the association between resting-state connectivity and memory to vary with age, $\beta$ = .11, *SE* = .05, *t* = 2.06, *p* = .041, with the association between

connectivity and memory becoming stronger with older age (Figure 3A). However, we note that this interaction did not survive inclusion of education as an additional covariate, $\beta$ = .08, *SE* = .05, $t$ = 1.46, $p$ = .146. Indeed, when examining associations between resting-state connectivity and memory within the three age groups separately, the specificity of caudate-cortical coupling was positively associated with memory in the middle-aged, $\beta$ = .30, SE = .13, $t$ = 2.39, $p$ = .021, and older individuals, $\beta$ = .34, SE = .14, $t$ = 2.45, $p$ = .018, but not in the younger adults ($p$ = .803). A similar interaction between age and resting-state connectivity was observed for the mean in-scanner n-back performance, $\beta$ = .12, SE = .06, $t$ = 2.02, $p$ = .045, controlling for age, sex and mean FD, which become marginal after inclusion of education as an additional covariate, $\beta$ = .11, SE = .06, $t$ = 1.83, $p$ = .069.

Assessing associations between functional connectivity during the n-back working memory task and in-scanner memory accuracy, we observed a significant 3-way interaction between age, memory load, and connectivity specificity, $F(2, 339.97) = 3.52$, $p$ = .031. This was driven by a significant interaction between age and connectivity for the 3-back condition, $\beta$ = .23, SE = .07, $t$ = 3.35, $p$ = .001, where greater specificity of caudate-cortical connectivity was associated with better working memory performance with older age (see Figure 3B). When examining associations between 3-back functional connectivity and accuracy within the age groups separately, we observed positive associations between the specificity of caudate-cortical connectivity and memory in the middle-aged and older adults, controlling for age, sex, and mean FD (middle-aged, $\beta$ = .27, SE = .13, $t$ = 2.01, $p$ = .049; old, $\beta$ = .29, SE = .14, $t$ = 2.04, $p$ = .048), although these associations became non-significant after controlling for education (middle aged, $\beta$ = .21, SE = .13, $t$ = 1.63, $p$ = .110; old, $\beta$ = .27, SE = .15, $t$ = 1.84, $p$ = .074). The specificity of caudate-cortical connectivity during 3-back was not associated with in-scanner working memory performance in the young ($p$ = .547), nor did it predict performance on the memory tasks outside of the scanner ($p$s > .274).

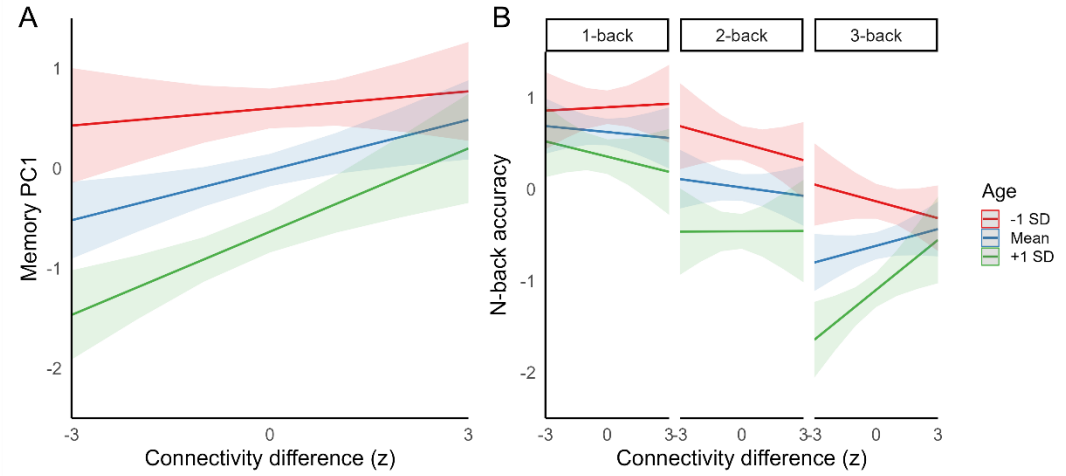


*Figure 3.* A) Association between the specificity of caudate-cortical connectivity (difference between caudate-FPN and caudate-DMN connectivity) during rest and out-of-scanner memory performance (1st principal component from analysis including three episodic and three working memory tasks performed outside of the scanner). B) Associations between the specificity of caudate-cortical connectivity during working memory and in-scanner memory performance. Plots illustrate predicted the effects of connectivity on memory at mean ± 1 SD of age from A) linear regression and B) linear mixed effects analyses, controlling for A) age, sex, and mean framewise displacement (FD), and B) age, sex, mean FD, and education.

## Discussion

Using data from the largest human PET cohort on D1DRs to date, we examined the role of the dopaminergic neurotransmitter system in age-related alterations in striato-cortical function. Consistent with previous findings (Rieckmann et al., 2018), older age was associated with reduced specificity of functional coupling between the centrolateral caudate and the fronto-parietal control network. Such age-related differences were present during both rest and a working memory task that places greater demands on coordinated activity of striatal and fronto-parietal regions (D'Esposito & Postle, 2015; Nyberg & Eriksson, 2016). Across the lifespan sample, lower D1DR availability in the striatum and the prefrontal cortex was associated with less specific caudate-cortical coupling during rest and working memory, respectively, and accounted for age-related variation in this measure. Lower specificity of caudate-cortical connectivity further predicted poorer memory function with older age. Together, these findings align with accounts proposing neural dedifferentiation as one mechanism underpinning cognitive decline in aging and highlight a critical contribution of the dopaminergic neurotransmitter system to maintaining the functional organization of striato-cortical circuits across the lifespan.

The current findings add to increasing evidence indicating reduced integrity of striato-cortical networks to play an important role in age-related deficits in flexible higher-order cognition (e.g., Bonifazi et al., 2018; Fjell et al., 2016; Huang et al., 2017; Klostermann et al., 2012; Podell et al., 2012; Webb et al., 2020). Extending previous findings of particular sensitivity of the centrolateral caudate to age-related deterioration in a sample of young and older individuals (Rieckmann et al., 2018), we here demonstrate gradual age-related decline of the specificity centrolateral caudate coupling with the cortical FPN across the adult lifespan. Age-related differences in functional connectivity of the caudate during rest were driven by both decreases in caudate-FPN coupling (i.e., the preferred network in younger adults) and increases in caudate-DMN coupling (i.e., the non-preferred network in younger adults) in older age, with the increased DMN connectivity already evident in middle-aged adults. In contrast, during working memory, age-related differences in connectivity were primarily driven by decreased caudate-FPN connectivity in older age. While evidence for preferential caudate coupling with the cortical FPN was limited to the younger adults during rest, both young and middle-aged adults exhibited this pattern during working memory, suggesting that the specificity of caudate-cortical coupling could be upregulated to support task performance in middle age. Indeed, the n-back working memory task that participants performed in the scanner places greater demands on coordinated activity of striatal and fronto-parietal regions (D'Esposito & Postle, 2015; Murty et al., 2011; Nyberg & Eriksson, 2016), with the striatum being critical for gating the updating of cortical memory representations in a goal-appropriate manner (Cools & D'Esposito, 2011; Frank et al., 2001).

We further provide novel evidence for a role of decreased dopamine D1DR availability in age-related dedifferentiation of striato-cortical function. Our findings are consistent with prior evidence linking PET markers of D1DR availability to functional coupling within cortico-cortical (Rieckmann et al., 2011; Roffman et al., 2016) and striato-cortical circuits (Johansson et al., 2023). At the single-neuron level, dopaminergic neuromodulation alters neuron's input sensitivity, enhancing the signal-to-noise properties of brain function (Cools, 2019; Servan-Schreiber et al., 1990; Shine et al., 2021). In aging, dopaminergic decreases, modelled as attenuated neural gain, have been proposed to result in less distinctive neural representations and non-selective recruitment of neural networks, impairing cognitive performance (Li et al., 2001). Aligning with these accounts, we here demonstrate reduced D1DR availability in the striatum and the prefrontal cortex to be associated with less specific functional coupling between the caudate and cortical association networks across the lifespan. While striatal D1DR availability predicted the specificity of caudate-cortical connectivity during rest, a similar relationship was observed for prefrontal D1DR availability during working memory. The prefrontal D1DR-connectivity relationship during working

memory further persisted after controlling for individual differences in striatal D1DR availability, suggesting a particular role for prefrontal dopamine in top-down modulation of striato-cortical function during task performance (Ott & Nieder, 2019), and aligning with animal work indicating crucial involvement of prefrontal D1DRs in working memory (Sawaguchi & Goldman-Rakic, 1991). Mediation analyses further indicated D1DR availability to account for age-related differences in the specificity of caudate-cortical coupling during rest and working memory, although we note that these results should be interpreted with caution due to cross-sectional nature of the current data. While the current study focused on examining dopaminergic regulation of specific striato-cortical circuits, recent evidence also links striatal D1DR availability to functional organization of brain large-scale networks (Pedersen et al., 2023), suggesting potential brain-wide influences of striatal dopaminergic signalling beyond the more local striatal circuits (McCutcheon et al., 2021).

Examining the behavioural consequences of individual differences in caudate-cortical connectivity, we observed reduced specificity of caudate-cortical coupling to predict poorer memory function with older age. Resting-state connectivity predicted performance on a battery of working and episodic memory tasks performed outside of the scanner, whereas connectivity during working memory was associated with in-scanner memory performance during the most challenging 3-back condition. We interpret the connectivity-behaviour associations observed across working and episodic memory to reflect shared demands of these tasks on executive control processes supported by striatal and fronto-parietal regions (Cools, 2019; Cools & D'Esposito, 2011; Zanto & Gazzaley, 2013). Interestingly, in contrast to the pattern of stronger connectivity-memory associations with older age observed here, previous studies have largely reported age-invariant associations between measures of neural (de)differentiation and cognition (reviewed Koen & Rugg, 2019). It is possible that the lack of age moderation detected in previous studies may reflect modest sample sizes and low power for detection of such effects, or differences between the types of measures of neural specificity examined (i.e., regional activity vs. inter-regional functional connectivity).

While the current results highlight decreased dopaminergic integrity as one factor contributing to loss of specificity of neural function in older age, we acknowledge that other factors likely also play an important role. For instance, animal (Leventhal et al., 2003) and human work (Chamberlain et al., 2021; Lalwani et al., 2019) implicate age-related decreases in inhibitory GABAergic neurotransmission in reduced distinctiveness of neural processing in aging, including decreased segregation of functional networks (Cassady et al., 2019). Similarly, declining integrity of white matter tracts has been shown to partly account for age-related changes brain functional network organization (Pedersen et al., 2021). Fronto-striatal white matter connections are sensitive to age-related degradation (Webb et al., 2020),

potentially contributing to the pattern of functional differences observed here. Moreover, while age-related decreases in the specificity of brain function have been reported across levels (e.g., univariate and multivariate patterns of regional activity, inter-regional functional connectivity), it remains to be elucidated whether shared or distinct mechanisms might underpin age-related differences across levels. Emerging evidence indicates correlation across representational and network levels of neural specificity (Cassady et al., 2020; Pauley et al., 2024), suggesting at least partly overlapping mechanisms, as proposed by neuromodulatory accounts (Li et al., 2001; Li & Sikström, 2002).

To summarize, we demonstrate advancing adult age to be associated with reduced specificity of functional coupling between the centrolateral caudate and the cortical fronto-parietal control network. Consistent with computational accounts of dopaminergic contributions to age-related neural dedifferentiation (Li et al., 2001), decreased D1DR availability in the striatum and the prefrontal cortex predicted less specific caudate-cortical connectivity across the adult lifespan, and accounted for age-related variation in this measure. Decreased specificity of caudate-cortical connectivity was further associated with poorer memory function with older age, highlighting functional integrity of striato-cortical circuits as an important determinant of the maintenance of memory abilities in older age.

## References


Alexander, G. E., Crutcher, M. D., & DeLong, M. R. (1991). Basal ganglia-thalamocortical circuits: Parallel substrates for motor, oculomotor, “prefrontal” and “limbic” functions. In *Progress in Brain Research, 85*, 119–146. https://doi.org/10.1016/S0079-6123(08)62678-3

Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *NeuroImage*, *38*(1), 95–113. https://doi.org/10.1016/j.neuroimage.2007.07.007

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. *The American Journal of Psychiatry*, *157*(4), 635–637. https://doi.org/10.1176/ajp.157.4.635

Bonifazi, P., Erramuzpe, A., Diez, I., Gabilondo, I., Boisgontier, M. P., Pauwels, L., Stramaglia, S., Swinnen, S. P., & Cortes, J. M. (2018). Structure–function multi-scale connectomics reveals a major role of the fronto-striato-thalamic circuit in brain aging. *Human Brain Mapping*, *39*(12), 4663–4677. https://doi.org/10.1002/hbm.24312

Cassady, K., Gagnon, H., Freiburger, E., Lalwani, P., Simmonite, M., Park, D. C., Peltier, S. J., Taylor, S. F., Weissman, D. H., Seidler, R. D., & Polk, T. A. (2020). Network

segregation varies with neural distinctiveness in sensorimotor cortex. *NeuroImage*, *212*, 116663. https://doi.org/10.1016/j.neuroimage.2020.116663

Cassady, K., Gagnon, H., Lalwani, P., Simmonite, M., Foerster, B., Park, D., Peltier, S. J., Petrou, M., Taylor, S. F., Weissman, D. H., Seidler, R. D., & Polk, T. A. (2019). Sensorimotor network segregation declines with age and is linked to GABA and to sensorimotor performance. *NeuroImage*, *186*, 234–244. https://doi.org/10.1016/j.neuroimage.2018.11.008

Chamberlain, J. D., Gagnon, H., Lalwani, P., Cassady, K. E., Simmonite, M., Seidler, R. D., Taylor, S. F., Weissman, D. H., Park, D. C., & Polk, T. A. (2021). GABA levels in ventral visual cortex decline with age and are associated with neural distinctiveness. *Neurobiology of Aging*, *102*, 170–177. https://doi.org/10.1016/j.neurobiolaging.2021.02.013

Chan, M. Y., Park, D. C., Savalia, N. K., Petersen, S. E., & Wig, G. S. (2014). Decreased segregation of brain systems across the healthy adult lifespan. *Proceedings of the National Academy of Sciences*, *111*(46). https://doi.org/10.1073/pnas.1415122111

Choi, E. Y., Yeo, B. T. T., & Buckner, R. L. (2012). The organization of the human striatum estimated by intrinsic functional connectivity. *Journal of Neurophysiology*, *108*(8), 2242–2263. https://doi.org/10.1152/jn.00270.2012

Cools, R. (2019). Chemistry of the adaptive mind: Lessons from dopamine. *Neuron*, *104*(1), 113–131. https://doi.org/10.1016/j.neuron.2019.09.035

Cools, R., & D'Esposito, M. (2011). Inverted-u–shaped dopamine actions on human working memory and cognitive control. *Biological Psychiatry*, *69*(12), e113–e125. https://doi.org/10.1016/j.biopsych.2011.03.028

Damoiseaux, J. S. (2017). Effects of aging on functional and structural brain connectivity. *NeuroImage*, *160*, 32–40. https://doi.org/10.1016/j.neuroimage.2017.01.077

Dennis, N. A., & Cabeza, R. (2011). Age-related dedifferentiation of learning systems: An fMRI study of implicit and explicit learning. *Neurobiology of Aging, 32*(12), 2318.e17-2318.e30. https://doi.org/10.1016/j.neurobiolaging.2010.04.004

D'Esposito, M., & Postle, B. R. (2015). The cognitive neuroscience of working memory. *Annual Review of Psychology*, *66*(1), 115–142. https://doi.org/10.1146/annurev-psych-010814-015031

Durstewitz, D., Seamans, J. K., & Sejnowski, T. J. (2000). Dopamine-mediated stabilization of delay-period activity in a network model of prefrontal cortex. *Journal of Neurophysiology*, *83*(3), 1733–1750. https://doi.org/10.1152/jn.2000.83.3.1733

Elsworth, J. D., & Roth, R. H. (1997). Dopamine synthesis, uptake, metabolism, and receptors: Relevance to gene therapy of Parkinson's disease. *Experimental Neurology*, *144*(1), 4–9. https://doi.org/10.1006/exnr.1996.6379

Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., van der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., & Dale, A. M. (2002). Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. *Neuron*, *33*(3), 341–355. https://doi.org/10.1016/s0896-6273(02)00569-x

Fjell, A. M., Sneve, M. H., Storsve, A. B., Grydeland, H., Yendiki, A., & Walhovd, K. B. (2016). Brain events underlying episodic memory changes in aging: A longitudinal investigation of structural and functional connectivity. *Cerebral Cortex*, *26*(3), 1272–1286. https://doi.org/10.1093/cercor/bhv102

Frank, M. J., Loughry, B., & O'Reilly, R. C. (2001). Interactions between frontal cortex and basal ganglia in working memory: A computational model. *Cognitive, Affective, & Behavioral Neuroscience*, *1*(2), 137–160. https://doi.org/10.3758/CABN.1.2.137

Friston, K. J., Williams, S., Howard, R., Frackowiak, R. S. J., & Turner, R. (1996). Movement-Related effects in fMRI time-series: Movement Artifacts in fMRI. *Magnetic Resonance in Medicine*, *35*(3), 346–355. https://doi.org/10.1002/mrm.1910350312

Geerligs, L., Maurits, N. M., Renken, R. J., & Lorist, M. M. (2014). Reduced specificity of functional connectivity in the aging brain during task performance: Functional Connectivity in the Aging Brain. *Human Brain Mapping*, *35*(1), 319–330. https://doi.org/10.1002/hbm.22175

Geerligs, L., Renken, R. J., Saliasi, E., Maurits, N. M., & Lorist, M. M. (2015). A brain-wide study of age-related changes in functional connectivity. *Cerebral Cortex*, *25*(7), 1987–1999. https://doi.org/10.1093/cercor/bhu012

Gerfen, C. R., & Surmeier, D. J. (2011). Modulation of striatal projection systems by dopamine. *Annual Review of Neuroscience*, *34*(1), 441–466. https://doi.org/10.1146/annurev-neuro-061010-113641

Grady, C. (2012). The cognitive neuroscience of ageing. *Nature Reviews Neuroscience*, *13*(7), 491–505. https://doi.org/10.1038/nrn3256

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 18F-FDG-PET study of aging. *NeuroImage*, *132*, 334–343. https://doi.org/10.1016/j.neuroimage.2016.02.042

Haber, S. N., & Knutson, B. (2010). The reward circuit: Linking primate anatomy and human imaging. *Neuropsychopharmacology*, *35*(1), 4–26. https://doi.org/10.1038/npp.2009.129

Huang, H., Nguyen, P. T., Schwab, N. A., Tanner, J. J., Price, C. C., & Ding, M. (2017). Mapping dorsal and ventral caudate in older adults: Method and validation. *Frontiers in Aging Neuroscience*, *9*. https://doi.org/10.3389/fnagi.2017.00091

Innis, R. B., Cunningham, V. J., Delforge, J., Fujita, M., Gjedde, A., Gunn, R. N., Holden, J., Houle, S., Huang, S.-C., Ichise, M., Iida, H., Ito, H., Kimura, Y., Koeppe, R. A., Knudsen, G. M., Knuuti, J., Lammertsma, A. A., Laruelle, M., Logan, J., … Carson, R. E. (2007). Consensus Nomenclature for *in vivo* Imaging of Reversibly Binding Radioligands. *Journal of Cerebral Blood Flow & Metabolism*, *27*(9), 1533–1539. https://doi.org/10.1038/sj.jcbfm.9600493

Jagust, W. (2013). Vulnerable Neural Systems and the Borderland of Brain Aging and Neurodegeneration. *Neuron*, *77*(2), 219–234. https://doi.org/10.1016/j.neuron.2013.01.002

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved Optimization for the Robust and Accurate Linear Registration and Motion Correction of Brain Images. *NeuroImage*, *17*(2), 825–841. https://doi.org/10.1006/nimg.2002.1132

Johansson, J., Nordin, K., Pedersen, R., Karalija, N., Papenberg, G., Andersson, M., Korkki, S. M., Riklund, K., Guitart-Masip, M., Rieckmann, A., Bäckman, L., Nyberg, L., & Salami, A. (2023). Biphasic patterns of age-related differences in dopamine D1 receptors across the adult lifespan. *Cell Reports*, *42*(9), 113107. https://doi.org/10.1016/j.celrep.2023.113107

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. *Neurobiology of Aging*, *57*, 36–46. https://doi.org/10.1016/j.neurobiolaging.2017.05.006

Klostermann, E. C., Braskie, M. N., Landau, S. M., O'Neil, J. P., & Jagust, W. J. (2012). Dopamine and frontostriatal networks in cognitive aging. *Neurobiology of Aging*, *33*(3), 623.e15-623.e24. https://doi.org/10.1016/j.neurobiolaging.2011.03.002

Koen, J. D., & Rugg, M. D. (2019). Neural dedifferentiation in the aging brain. *Trends in Cognitive Sciences*, *23*(7), 547–559. https://doi.org/10.1016/j.tics.2019.04.012

Koen, J. D., Srokova, S., & Rugg, M. D. (2020). Age-related neural dedifferentiation and cognition. *Current Opinion in Behavioral Sciences*, *32*, 7–14. https://doi.org/10.1016/j.cobeha.2020.01.006

Lalwani, P., Gagnon, H., Cassady, K., Simmonite, M., Peltier, S., Seidler, R. D., Taylor, S. F., Weissman, D. H., & Polk, T. A. (2019). Neural distinctiveness declines with age in auditory cortex and is associated with auditory GABA levels. *NeuroImage, 201,* 116033. https://doi.org/10.1016/j.neuroimage.2019.116033

Lammertsma, A. A., & Hume, S. P. (1996). Simplified Reference Tissue Model for PET Receptor Studies. *NeuroImage*, *4*(3), 153–158. https://doi.org/10.1006/nimg.1996.0066

Landau, S. M., Lal, R., O'Neil, J. P., Baker, S., & Jagust, W. J. (2009). Striatal dopamine and working memory. *Cerebral Cortex*, *19*(2), 445–454. https://doi.org/10.1093/cercor/bhn095

Leventhal, A. G., Wang, Y., Pu, M., Zhou, Y., & Ma, Y. (2003). GABA and its agonists improved visual cortical function in senescent monkeys. *Science, 300*(5620), 812-815. https://doi.org/10.1126/science.1082874

Li, S.-C., Lindenberger, U., & Frensch, P. A. (2000). Unifying cognitive aging: From neuromodulation to representation to cognition. *Neurocomputing*, *32–33*, 879–890. https://doi.org/10.1016/S0925-2312(00)00256-3

Li, S.-C., Lindenberger, U., & Sikström, S. (2001). Aging cognition: From neuromodulation to representation. *Trends in Cognitive Sciences*, *5*(11), 479–486. https://doi.org/10.1016/S1364-6613(00)01769-1

Li, S.-C., & Sikström, S. (2002). Integrative neurocomputational perspectives on cognitive aging, neuromodulation, and representation. *Neuroscience & Biobehavioral Reviews*, *26*(7), 795–808. https://doi.org/10.1016/S0149-7634(02)00066-0

McCutcheon, R. A., Brown, K., Nour, M. M., Smith, S. M., Veronese, M., Zelaya, F., Osugo, M., Jauhar, S., Hallett, W., Mehta, M. M., & Howes, O. D. (2021). Dopaminergic organization of striatum is linked to cortical activity and brain expression of genes associated with psychiatric illness. *Science Advances*, *7*(24), eabg1512. https://doi.org/10.1126/sciadv.abg1512

Murty, V. P., Sambataro, F., Radulescu, E., Altamura, M., Iudicello, J., Zoltick, B., Weinberger, D. R., Goldberg, T. E., & Mattay, V. S. (2011). Selective updating of working memory content modulates meso-cortico-striatal activity. *NeuroImage*, *57*(3). https://doi.org/10.1016/j.neuroimage.2011.05.006

Nevalainen, N., Riklund, K., Andersson, M., Axelsson, J., Ögren, M., Lövdén, M., Lindenberger, U., Bäckman, L., & Nyberg, L. (2015). COBRA: A prospective multimodal imaging study of dopamine, brain structure and function, and cognition. *Brain Research*, *1612*, 83–103. https://doi.org/10.1016/j.brainres.2014.09.010

Nordin, K., Gorbach, T., Pedersen, R., Panes Lundmark, V., Johansson, J., Andersson, M., McNulty, C., Riklund, K., Wåhlin, A., Papenberg, G., Kalpouzos, G., Bäckman, L., &

Salami, A. (2022). DyNAMiC: A prospective longitudinal study of dopamine and brain connectomes: A new window into cognitive aging. *Journal of Neuroscience Research*, *100*(6), 1296–1320. https://doi.org/10.1002/jnr.25039

Nyberg, L., & Eriksson, J. (2016). Working memory: Maintenance, updating, and the realization of intentions. *Cold Spring Harbor Perspectives in Biology*, *8*(2), a021816. https://doi.org/10.1101/cshperspect.a021816

Nyberg, L., Karalija, N., Salami, A., Andersson, M., Wåhlin, A., Kaboovand, N., Köhncke, Y., Axelsson, J., Rieckmann, A., Papenberg, G., Garrett, D. D., Riklund, K., Lövdén, M., Lindenberger, U., & Bäckman, L. (2016). Dopamine D2 receptor availability is linked to hippocampal–caudate functional connectivity and episodic memory. *Proceedings of the National Academy of Sciences*, *113*(28), 7918–7923. https://doi.org/10.1073/pnas.1606309113

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

Ott, T., & Nieder, A. (2019). Dopamine and cognitive control in prefrontal cortex. *Trends in Cognitive Sciences*, *23*(3), 213–234. https://doi.org/10.1016/j.tics.2018.12.006

Parent, A., & Hazrati, L.-N. (1995). Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. *Brain Research Reviews*, *20*(1), 91–127. https://doi.org/10.1016/0165-0173(94)00007-C

Park, D. C., Polk, T. A., Park, R., Minear, M., Savage, A., & Smith, M. R. (2004). Aging reduces neural specialization in ventral visual cortex. *Proceedings of the National Academy of Sciences*, *101*(35), 13091–13095. https://doi.org/10.1073/pnas.0405148101

Pauley, C., Zeithamova, D., & Sander, M. C. (2024). Age differences in functional connectivity track dedifferentiation of category representations. *bioRxiv*. https://doi.org/10.1101/2024.01.04.574135

Pedersen, R., Geerligs, L., Andersson, M., Gorbach, T., Avelar-Pereira, B., Wåhlin, A., Rieckmann, A., Nyberg, L., & Salami, A. (2021). When functional blurring becomes deleterious: Reduced system segregation is associated with less white matter integrity and cognitive decline in aging. *NeuroImage*, *242*, 118449. https://doi.org/10.1016/j.neuroimage.2021.118449

Pedersen, R., Johansson, J., & Salami, A. (2023). Dopamine D1-signaling modulates maintenance of functional network segregation in aging. *Aging Brain*, *3*, 100079. https://doi.org/10.1016/j.nbas.2023.100079

Podell, J. E., Sambataro, F., Murty, V. P., Emery, M. R., Tong, Y., Das, S., Goldberg, T. E., Weinberger, D. R., & Mattay, V. S. (2012). Neurophysiological correlates of age-

related changes in working memory updating. *NeuroImage*, *62*(3), 2151–2160. https://doi.org/10.1016/j.neuroimage.2012.05.066

Rieckmann, A., Johnson, K. A., Sperling, R. A., Buckner, R. L., & Hedden, T. (2018). Dedifferentiation of caudate functional connectivity and striatal dopamine transporter density predict memory change in normal aging. *Proceedings of the National Academy of Sciences*, *115*(40), 10160–10165. https://doi.org/10.1073/pnas.1804641115

Rieckmann, A., Karlsson, S., Fischer, H., & Backman, L. (2011). Caudate dopamine D1 receptor density is associated with individual differences in frontoparietal connectivity during working memory. *Journal of Neuroscience*, *31*(40), 14284–14290. https://doi.org/10.1523/JNEUROSCI.3114-11.2011

Roffman, J. L., Tanner, A. S., Eryilmaz, H., Rodriguez-Thompson, A., Silverstein, N. J., Ho, N. F., Nitenson, A. Z., Chonde, D. B., Greve, D. N., Abi-Dargham, A., Buckner, R. L., Manoach, D. S., Rosen, B. R., Hooker, J. M., & Catana, C. (2016). Dopamine D1 signaling organizes network dynamics underlying working memory. *Science Advances*, *2*(6). https://doi.org/10.1126/sciadv.1501672

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

Sawaguchi, T., & Goldman-Rakic, P. S. (1991). D1 dopamine receptors in prefrontal cortex: Involvement in working memory. *Science*, *251*(4996), 947–950. https://doi.org/10.1126/science.1825731

Servan-Schreiber, D., Printz, H., & Cohen, J. D. (1990). A network model of catecholamiine effects: Gain, signal-to-noise ratio, and behavior. *Science*, *249*(4971). https://doi.org/10.1126/science.2392679

Shine, J. M., Müller, E. J., Munn, B., Cabral, J., Moran, R. J., & Breakspear, M. (2021). Computational models link cellular mechanisms of neuromodulation to large-scale neural dynamics. *Nature Neuroscience*, *24*(6), 765–776. https://doi.org/10.1038/s41593-021-00824-6

Srokova, S., Aktas, A. N. Z., Koen, J. D., & Rugg, M. D. (2024). Dissociative effects of age on neural differentiation at the category and item levels. *The Journal of Neuroscience*, *44*(4), e0959232023. https://doi.org/10.1523/JNEUROSCI.0959-23.2023

Trelle, A. N., Henson, R. N., & Simons, J. S. (2019). Neural evidence for age-related differences in representational quality and strategic retrieval processes. *Neurobiology of Aging*, *84*, 50–60. https://doi.org/10.1016/j.neurobiolaging.2019.07.012

Webb, C. E., Hoagey, D. A., Rodrigue, K. M., & Kennedy, K. M. (2020). Frontostriatal white matter connectivity: Age differences and associations with cognition and BOLD modulation. *Neurobiology of Aging*, *94*, 154–163. https://doi.org/10.1016/j.neurobiolaging.2020.05.014

Westbrook, A., Frank, M. J., & Cools, R. (2021). A mosaic of cost–benefit control over cortico-striatal circuitry. *Trends in Cognitive Sciences*, *25*(8), 710–721. https://doi.org/10.1016/j.tics.2021.04.007

Yan, C.-G., Wang, X.-D., Zuo, X.-N., & Zang, Y.-F. (2016). DPABI: Data Processing & Analysis for (Resting-State) Brain Imaging. *Neuroinformatics*, *14*(3), 339–351. https://doi.org/10.1007/s12021-016-9299-4

Zanto, T. P., & Gazzaley, A. (2013). Fronto-parietal network: Flexible hub of cognitive control. *Trends in Cognitive Sciences*, *17*(12), 602–603. https://doi.org/10.1016/j.tics.2013.10.001