

Sex differences in dopamine integrity and brain structure among healthy older adults: Relationships to episodic memory

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ABSTRACT

Normal brain aging is a multidimensional process that includes deterioration in various brain structures and functions, with large heterogeneity in patterns and rates of decline. Sex differences have been reported for various cognitive and brain parameters, but little is known in relation to neuromodulatory aspects of brain aging. We examined sex differences in dopamine D2-receptor (D2DR) availability in relation to episodic memory, but also, grey-matter volumes, white-matter lesions, and cerebral perfusion in healthy older adults ($n = 181$, age: 64–68 years) from the Cognition, Brain, and Aging study. Women had higher D2DR availability in midbrain and left caudate and putamen, as well as superior episodic memory performance. Controlling for left caudate D2DR availability attenuated sex differences in memory performance. In men, lower left caudate D2DR levels were associated with lower cortical perfusion and higher burden of white-matter lesions, as well as with episodic memory performance. However, sex was not a significant moderator of the reported links to D2DR levels. Our findings suggest that sex differences in multiple associations among DA receptor availability, vascular factors, and structural connectivity contribute to sex differences in episodic memory. Future longitudinal studies need to corroborate these patterns by lead-lag associations. This manuscript is part of the Special Issue entitled 'Cognitive Neuroscience of Healthy and Pathological Aging' edited by Drs. M. N. Rajah, S. Belleville, and R. Cabeza. This article is part of the Virtual Special Issue titled COGNITIVE NEUROSCIENCE OF HEALTHY AND PATHOLOGICAL AGING. The full issue can be found on ScienceDirect at <https://www.sciencedirect.com/journal/neurobiology-of-aging/special-issue/105379XPWJP>.

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1. Introduction

Sex differences have been found for several brain parameters (Ritchie et al., 2018; Ruigrok et al., 2014) and researchers have highlighted the importance of understanding those for purposes of personalized medicine, susceptibility to neuropathology, and cognitive deficits in aging (Miller et al., 2015). Dissimilarities may stem from sex differences in gene expression (Trabzuni et al.,

2013), and regulatory effects of the principal sex hormones, estrogen and testosterone (Wilson and Davies, 2007). Multimodal brain imaging studies demonstrate that normal (non-pathological) aging is a multifaceted process with large individual differences (Gorbach et al., 2017; Lindenberger, 2014; Lövdén et al., 2018; Nyberg and Pudas, 2018). However, surprisingly little is known about differences in brain-behavior relations between groups of healthy older women and men.

Sex differences have been found in brain morphology, function, neurochemistry, and synaptic function (Cahill, 2006; Cosgrove et al., 2007; Wilson and Davies, 2007). Mounting evidence demonstrates neurotrophic and neuroprotective effects of estrogen via a broad array of mechanisms, such as promotion

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of cell survival upon nutrient-deprived milieu, protection against glutamate toxicity, oxidative damage, and accumulation of beta-amyloid (Brann et al., 2007; McEwen and Alves, 1999; Zárate et al., 2017). Interestingly, several brain regions, such as hippocampus, amygdala, and the association cortices are sexually dimorphic (Cahill, 2006), likely contributing to sex differences in personality traits (Hoffman, 1977; Mestre et al., 2009; Schmitt et al., 2008) and cognitive functioning (de Frias et al., 2006; Deary et al., 2007; Herlitz et al., 1997). Sex differences have also been found for cerebrovascular health in aging. Compared to women, men are at higher risk of cardiovascular disease (Kivipelto et al., 2006; Klöner et al., 2016; Webb and Collins, 2017), possibly due to reduced levels of testosterone (Oskui et al., 2013). By contrast, estrogen may postpone the incidence of cardiovascular disease, by counteracting atherosclerosis (Baker et al., 2003; Rosano and Panina, 1999; Sullivan and Fowlkes, 1996). Mapping onto the described differences, women demonstrate a younger metabolic brain age than men throughout adulthood (Goyal et al., 2019).

The dopamine (DA) system modulates cognitive processes, including episodic memory (Lisman and Grace, 2005; Nyberg et al., 2016; Shohamy and Adcock, 2010). Notably, women display superior episodic memory function throughout life (for review, see (Asperholm et al., 2019), and are underrepresented in groups exhibiting severe episodic-memory decline in aging (Josefsson et al., 2012). Sex-dependent differences in DA-system integrity may contribute to performance differences in episodic memory, but also to differences in susceptibility to DA pathology (Jurado-Coronel et al., 2018). Reduced incidence and higher age at onset for Parkinson's disease (PD) in women have been related to the protective role of estrogen for the DA system (Haaxma et al., 2007). Experimental research demonstrates that estrogen enhances DA release and DA-mediated behaviors, and protects against DA lesions (Becker, 1999; Bourque et al., 2011; Gillies et al., 2014). In support, positron emission tomography (PET) imaging studies have demonstrated higher levels of DA biomarkers in women than in men, including DA transporters and D2 receptors (D2DRs) (Kaasinen et al., 2015; Kaasinen et al., 2001; Lavalaye et al., 2000; Pohjalainen et al., 1998; Wong et al., 2012).

Given the proposed female advantage in DA integrity, cerebrovascular health, and episodic memory, the purpose of the present work was to examine the relationship among these variables in a sample of healthy older adults ($n=181$, age: 64–68 years, 100 men) from the Cognition, Brain, and Aging (COBRA) study (Nevalainen et al., 2015). Participants had undergone ^{11}C -raclopride/PET to evaluate D2DR status, magnetic resonance imaging (MRI) to assess brain structure, and cognitive testing. In previous descriptive analyses we showed a complex pattern of cognitive sex differences, with a female superiority for episodic memory, a male superiority for working memory, and no sex differences in speed of processing (Nevalainen et al., 2015).

In the present study, we report on markers of the nigrostriatal DA system, brain volumes, vascular status as assessed by cerebral perfusion and white-matter lesions, and episodic memory separately for men and women. This allows us to explore sex differences in mean levels and associations among these sets of variables. Specifically, we investigate whether these variables show: (i) sex differences in means (Goal 1); sex differences in associations (Goal 2); and (iii) whether markers of the nigrostriatal DA system, brain volumes, and vascular status might qualify as potential contributors to sex differences in episodic memory (Goal 3). We focus on episodic memory because it is an important cognitive ability with well-documented sex differences (Asperholm et al., 2019) that starts to show average longitudinal decline around 60 years of age (Nyberg, 2017). Furthermore, assessment of working memory is challenged by the absence of a linear working memory-

Table 1

Sex differences in demographic, lifestyle, and health variables (mean and standard deviation, or frequencies).

	Men	Women	<i>p</i>
N	98	72	
Age (years)	66.3 (1.3)	66.1 (1.1)	0.358
Education (years)	13.4 (3.5)	13.1 (3.5)	0.612
Social activity (h)	29.4 (13.5)	35.9 (18.2)	0.009
Intellectual activity (h)	32.7 (16.6)	37.4 (15.6)	0.055
Physical activity (h)	10.2 (6.9)	11.5 (7.2)	0.193
MMSE	29.2 (0.7)	29.3 (0.9)	0.793
Smoking	10.0%	6.2%	0.353
Hypertension diagnosis	29.0%	38.3%	0.188
Systolic blood pressure (mmHg)	142.7 (17.1)	140.7 (17.8)	0.452
Diastolic blood pressure (mmHg)	84.8 (10.0)	85.4 (9.7)	0.711
BMI	26.1 (3.4)	26.1 (3.7)	0.950
Cardiovascular disease	37.0%	44.4%	0.310
Medicine consumption	55.0%	64.2%	0.211

Note: The significance level was $p=0.004$ after adjustment for the total number of chi-square and t-tests.

D2DR link (Lövdén et al., 2018). Given expected comorbidities and links between DA integrity and cerebrovascular events (Gower and Tiberi, 2018), we expected DA-vascular links to be present, and to possibly differ between men and women. More specifically, higher prevalence of cerebrovascular dysfunction was expected to be found in men, and to be associated with lower D2DR availability. The limited number of subjects in human DA-aging studies (Karrer et al., 2017), and the scarcity of studies with multimodal designs, have hindered previous investigations of sex differences across DA, cerebrovascular, and cognitive domains within the same sample. Consequently, some analyses conducted here are to be considered exploratory.

2. Material and methods

2.1. Sample

This study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained prior to all testing.

The analyses were conducted using data from the COBRA study in which healthy older adults ($n = 181$, age: 64–68 years, 100 men) have undergone ^{11}C -raclopride/PET, MRI, cognitive testing, and lifestyle mapping. Participants were randomly selected from the population registry of Umeå in Sweden. Exclusion criteria were conditions and medications that affect brain and cognitive functions, including brain trauma, neurological disorders (e.g. stroke, dementia, epilepsy), psychiatric disorders, intellectual disability, functional impairments and movement disorders (e.g. Parkinson's disease), diabetes, and ongoing malignancy treatment. Additional exclusion criteria consisted of MRI-inhibiting factors. A Mini-Mental State Examination (required: 27 of 30) and radiological evaluation of MR images served as objective measures in the screening process. Intellectual, social, and physical activity levels (hours per week) were assessed via questionnaires. We refer to a detailed description of the COBRA study for further information (Nevalainen et al., 2015). There were overall no differences between men and women with respect to demographic, lifestyle, and health variables (Table 1).

2.2. Volumetric assessments

MRI was performed with a 3-Tesla Discovery MR 750 scanner (General Electric, WI, US) equipped with a 32-channel phased-array head coil. A 3D fast spoiled gradient-echo sequence was used to obtain high-resolution anatomical T1-weighted images. Imag-

ing parameters were 176 sagittal slices, with slice thickness = 1 mm, TR = 8.2 ms, TE = 3.2 ms, flip angle = 12°, and field of view = 25 × 25 cm.

Subcortical brain structures were delineated with the Freesurfer 5.3. software (<http://surfer.nmr.mgh.harvard.edu>) (Fischl et al., 2002), and cortical parcellation was performed according to the Desikan-Killiany atlas (Desikan et al., 2006). The number of voxels within delineated structures represented grey- and white-matter volumes. Before entered into analyses, raw volumes were corrected for total intracranial volume (ICV): adjusted volume = raw volume - $b(\text{ICV} - \text{mean ICV})$, where b is the slope of regression of volume on ICV (Buckner et al., 2004).

2.3. White-matter lesions

A FLAIR sequence was acquired to assess white-matter hyperintensity (WMH) burden. The total number of slices were 48, slice thickness = 3 mm, TE = 120 ms, TR = 8000 ms, and field of view = 24 × 24 cm.

WMHs were segmented by the lesion-growth algorithm (Schmidt et al., 2012), as implemented in the LST toolbox version 2.0.14 (www.statisticalmodelling.de/lst.html) for the statistical parametric mapping software (SPM12). The T1-images were segmented into the three main tissue classes (cerebrospinal fluid, grey matter, and white matter), and co-registered with FLAIR images. Then, lesion probability maps were calculated from FLAIR intensities within white-matter maps. By thresholding these maps with a pre-chosen initial threshold ($\kappa=0.3$, defined by visual evaluation), a binary lesion map was obtained. This map was grown along hyperintense neighboring voxels in the FLAIR image, resulting in a lesion probability map that, after thresholding (50%), yielded a binary map of lesions from which the total volume (cm³) and number of lesions per individual was obtained.

2.4. Perfusion measurements

Perfusion measurements were performed with 3D pseudo-continuous arterial spin labeling (3D pcASL), 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 × 512 (arms x data points), with the number of averages set to 3. This sequence provided whole-brain perfusion in ml/100g/min.

Quantitative perfusion maps were calculated using a post-processing tool installed on the scanner by the manufacturer. Mean perfusion for the regions of interest (ROIs) were calculated using the Freesurfer segmentation.

2.5. D2DR availability

A 55-min, 18-frame dynamic PET scan was acquired during resting-state conditions with a Discovery PET/CT 690 (General Electric, WI, US), following an intravenous bolus injection of 250 MBq ¹¹C-raclopride. A CT scan (20 mA, 120 kV, 0.8 s/revolution) preceded tracer injection for attenuation-correction purposes. 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 mm³) were reconstructed with the iterative algorithm VUE Point HD-SharpIR (GE Healthcare), using 6 iterations, 24 subsets, 3.0 mm post filtering, yielding full width at half maximum (FWHM) of 3.2 mm. Head movements were minimized with individually fitted thermoplastic masks attached to the bed surface.

PET data were converted from DICOM to NiftI format and corrected for head movement. The PET and T1 images were co-

Table 2

Sex differences in nigrostriatal D2DR availability (mean and standard deviation).

	Men	Women	% diff	η^2	p
D2DR availability					
Caudate L	2.17 (0.24)	2.29 (0.26)	5%	0.052	0.003
Caudate R	2.32 (0.24)	2.33 (0.25)	0.5%	0.001	0.679
Putamen L	3.03 (0.25)	3.12 (0.26)	3%	0.031	0.021
Putamen R	3.24 (0.27)	3.27 (0.25)	1%	0.003	0.457
Midbrain	0.32 (0.06)	0.34 (0.06)	6%	0.027	0.033

Note. L = Left; R = Right; diff = difference. Significant sex differences (assessed with MANOVA) are presented in bold font. Effect size is illustrated with partial eta squared (η^2).

registered with SPM8. ¹¹C-raclopride binding potential (BP_{ND}) was calculated with Logan analysis (Logan et al., 1996), using the median activity value within Freesurfer-segmented ROIs for time frames 10–18 (18–55 min). Cerebellar grey matter served as the reference area.

Furthermore, midbrain ¹¹C-raclopride BP_{ND} values were extracted using a probabilistic atlas (Murty et al., 2014). First, the probabilistic atlas was thresholded at 25% to obtain a midbrain mask. Second, dynamic PET images were transformed into MNI-coordinate space and frame-wise midbrain activity concentrations were extracted using the midbrain mask. The midbrain time-activity curve (TAC) data were modeled using the multi-linear reference tissue model (Ichise et al., 2003), with the FreeSurfer-derived cerebellar grey matter TACs as a reference to estimate BP_{ND}.

2.6. Cognitive assessment

Episodic memory was assessed with tests of word recall, number-word recall, and object-position recall (two blocks for each task; max scores: 32, 16, and 24, respectively). For each of the three tests, scores were summarized across the total number of blocks. The three sum scores were standardized (via z-transformation), and averaged to form one composite episodic-memory score (T score: mean = 50; SD = 10). Missing values (< 1.2% for all variables) were replaced by the average of the available observed scores.

2.7. Statistical evaluation

Statistical analyses were conducted with IBM SPSS Statistics 24 (IBM Corp., Armonk, NY, USA). Descriptive data are presented as frequencies, or mean values and standard deviations (SD). Correlations are reported with the Pearson correlation coefficient (r). Exclusions were handled via pairwise deletions and encompassed values for D2DR availability in caudate: $n = 7$; putamen: $n = 8$; midbrain: $n = 3$, volumes (all regions $n = 1$; subcortical regions $n = 2$). Reasons for exclusions were imperfect quality or segmentation of T1-images, issues with PET/MR co-registration, and statistical outliers according to the outlier labeling rule with 2.2 interquartile ranges. In addition, there were missing cases for WMHs ($n = 4$) and cerebral perfusion ($n = 2$).

Sex differences in demographic, lifestyle, and health variables were tested with independent sample t-tests (Table 1), and alpha level was adjusted for number of tests ($0.05/13 = 0.004$). In accordance with the first aim of the present work, sex differences in mean levels of D2DRs, volumes, perfusion, and white-matter lesions were assessed with multivariate analysis of variance (MANOVA; Tables 2 and 3; Results 3.1 and 3.2). Within men and women, hemispheric differences were evaluated with dependent sample t-tests (Table 2). The second aim was to address sex differences in the interrelation among D2DR availability, and structural and vascular factors. This was explored with multiple linear

Table 3
Sex differences in structural brain measures (mean and standard deviation).

	Men	Women	η^2	p
Volumes (cm ³)				
Caudate L	3.6 (0.5)	3.6 (0.5)	0.002	0.580
Caudate R	3.7 (0.5)	3.8 (0.5)	0.001	0.731
Putamen L	4.6 (0.5)	4.2 (0.5)	0.136	<0.001
Putamen R	4.6 (0.5)	4.2 (0.5)	0.098	<0.001
Hippocampus L	3.8 (0.4)	3.8 (0.5)	0.001	0.675
Hippocampus R	4.0 (0.5)	3.9 (0.4)	0.019	0.072
Frontal cortex	168.4 (15.2)	159.6 (14.8)	0.080	<0.001
White matter	627.7 (60.5)	576.2 (50.2)	0.175	<0.001
Brain per intracranial ratio (%)	71.7 (8.6)	74.7 (7.8)	0.031	0.021
Perfusion (ml/100g/min)				
Caudate L	43.7 (7.4)	44.7 (7.1)	0.004	0.374
Caudate R	43.6 (7.2)	45.1 (7.4)	0.011	0.161
Putamen L	46.2 (7.9)	47.0 (7.6)	0.003	0.478
Putamen R	44.6 (7.4)	46.4 (7.9)	0.013	0.126
Hippocampus L	40.2 (7.8)	42.9 (8.3)	0.027	0.027
Hippocampus R	39.6 (7.5)	42.7 (8.5)	0.035	0.012
Frontal L	41.9 (9.1)	48.0 (9.8)	0.094	<0.001
Frontal R	40.4 (8.9)	46.7 (10.2)	0.100	<0.001
White-matter lesions				
Volume L (cm ³)	1.6 (1.8)	1.2 (1.2)	0.019	0.066
Volume R (cm ³)	1.4 (1.7)	1.1 (1.4)	0.009	0.214
Number of lesions L	18.6 (11.2)	14.6 (7.1)	0.040	0.008
Number of lesions R	19.5 (12.8)	15.1 (7.8)	0.039	0.008

Note. L = Left; R = Right. Significant sex differences from MANOVAs (one per brain domain) are presented in bold. Effect size is illustrated with partial-eta squared (η^2).

regression models in men and women, separately (Results 3.3.) Independent variables were representative of each structural domain (Table 3) and consisted of brain per intracranial ratio (as volume estimates), frontal perfusion, and number of white-matter lesions. To investigate whether the association between frontal perfusion and caudate D2DR availability was moderated by sex, multiple regression analyses were performed with frontal perfusion, sex, and the interaction term sex \times perfusion as independent variables. To address the third aim of this work, the influences of D2DR availability and structural and vascular measures were assessed on sex differences in episodic memory through linear regression models, as described above, and analysis of covariance (ANCOVA; Results 3.4). ANCOVAs were also used to assess the influence of hippocampal D2DR levels and volumes as covariates on sex differences in episodic memory (Results 3.4), and grey matter volumes as covariates on sex differences in D2DR availability (Results 3.1). Effect sizes are indicated by partial-eta squared (η^2).

3. Results

3.1. Higher nigrostriatal D2DR availability in women

Significant sex differences were found for nigrostriatal D2DR availability ($F(5, 163) = 6.73$, Wilks' lambda (Λ) = 0.83, $p < 0.001$). Compared to women, men had lower D2DR availability in left caudate ($F(1, 167) = 9.21$), left putamen ($F(1, 167) = 5.39$), and midbrain ($F(1, 167) = 4.63$; Table 2). Sex differences in left caudate ($F(1,171) = 8.69$, $p = 0.004$, $\eta^2 = 0.048$) and left putamen ($F(1,170) = 4.92$, $p = 0.028$, $\eta^2 = 0.028$) were maintained after adjusting for regional volumes. In both sexes, lower levels were observed in left, compared to right caudate (men: $t(94) = -8.15$, $p < 0.001$; women: $t(77) = -2.80$; $p = 0.007$) and putamen (men: $t(94) = -13.95$; women: $t(77) = -10.06$; $p < 0.001$ for both).

3.2. Sex differences in regional volumes, perfusion, and lesion burden

Sex differences were observed for several structural measures, including volumes ($F(9, 163) = 13.89$, $\Lambda = 0.57$, $p < 0.001$), perfu-

sion ($F(8, 170) = 5.55$, $\Lambda = 0.79$, $p < 0.001$), and at trend level, for white-matter lesion burden ($F(4, 171) = 2.29$, $\Lambda = 0.95$, $p = 0.062$). Men had larger putaminal ($F(1, 171) = 26.99$ and 18.50 for left and right), cortical ($F(1, 171) = 14.89$), and white-matter volumes ($F(1, 171) = 36.16$), but smaller overall brain per intracranial ratios ($F(1, 171) = 5.45$; Table 3). In addition, men had lower perfusion in frontal cortex ($F(1, 177) = 18.43$ and 19.69 for left and right) and hippocampus ($F(1;177) = 4.95$ and 6.49 for left and right), and higher frequency of lesions in the white-matter ($F(1, 174) = 7.30$ and 7.14 for left and right).

3.3. Interrelation between D2DR availability and structural brain measures

Next, we explored whether the observed sex differences in caudate D2DR availability (Table 2) and structural brain measures (one indicator per domain: brain per intracranial ratios, frontal perfusion, number of white-matter lesions; Table 3) showed different associations in men versus women. For this purpose, we conducted multiple regressions, separately in men and women. A linear regression model ($F(3,89) = 7.06$, $p < 0.001$) revealed that left caudate D2DR levels were linked to frontal perfusion ($\beta = 0.209$, $t(89) = 2.02$, $p = 0.046$; Fig. 1A) and number of lesions ($\beta = -0.295$, $t(89) = -2.92$, $p = 0.004$) in men. The corresponding model for left caudate D2DR levels in women was not significant ($F(3,72) = 2.49$, $p = 0.067$), nor were models for right caudate D2DR levels for men ($F(3,90) = 2.27$, $p = 0.085$) or women ($F(3,71) = 2.56$, $p = 0.062$).

To further disentangle the associations among independent variables and D2DR levels, partial correlations were performed for each independent variable (adjusting for the other two independent variables). Correlations between left caudate D2DR levels and lesion burden were similar for men and women (men: $r = -0.30$, $p = 0.004$; women: $r = -0.30$, $p = 0.010$), whereas correlations with perfusion were only found in men (men: $r = 0.21$, $p = 0.046$; women: $r = 0.02$, $p = 0.840$), and no associations were found with brain per intracranial ratios (men: $r = 0.07$, $p = 0.486$; women: $r = 0.08$, $p = 0.487$). With respect to the right caudate, correlations between D2DR levels and lesion burden were similar for men and women (men: $r = -0.24$, $p = 0.019$; women: $r = -0.31$, $p = 0.007$), whereas no correlations were found with perfusion (men: $r = 0.05$, $p = 0.633$; women: $r = 0.01$, $p = 0.958$), or brain per intracranial ratios (men: $r = -0.06$, $p = 0.554$; women: $r = 0.04$, $p = 0.734$). Moreover, linear regression analyses were conducted to test whether the link between frontal perfusion and D2DR availability was moderated by sex. The model for left caudate D2DR levels ($F(3,168) = 6.67$, $p < 0.001$) revealed main effects for frontal perfusion ($\beta = 0.328$, $t(168) = 3.03$, $p = 0.003$) and sex ($\beta = 0.791$, $t(168) = 2.25$, $p = 0.026$). However, the interaction effect between sex and frontal perfusion (Fig. 1A) did not approach conventional significance ($\beta = 0.679$, $t(168) = 1.78$, $p = 0.077$). The corresponding model for right caudate D2DR was non-significant ($F(3, 168) = 0.69$, $p = 0.557$).

3.4. Sex differences in episodic memory

As reported before (Nevalainen et al., 2015), there was a female advantage in episodic memory ($F(1, 179) = 7.02$, $p = 0.009$, $\eta^2 = 0.038$). Given that caudate D2DR availability has been linked to episodic memory in past research (Cervenka et al., 2008; Nyberg et al., 2016), we tested whether some of the sex differences in episodic memory was accounted for by caudate D2DR availability. Multiple linear regressions revealed that D2DR availability in left caudate was associated with episodic memory in men ($F(1,93) = 7.55$, $p = 0.007$), but not in women ($F(1,77) = 0.07$,

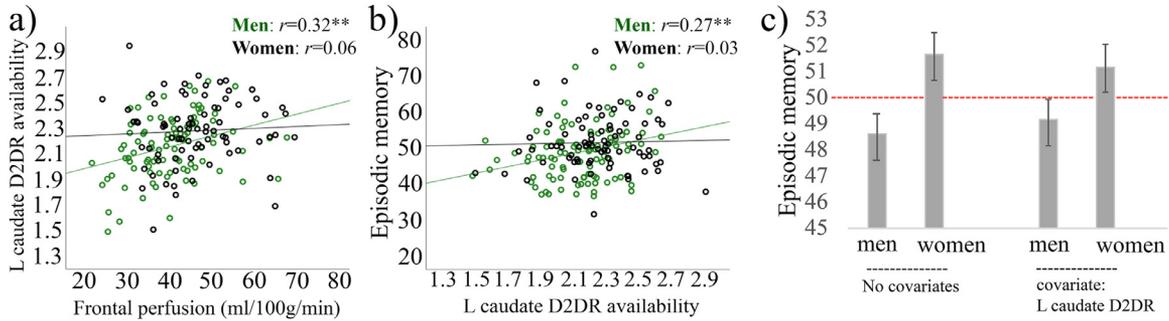


Fig. 1. Sex differences in relationship between left caudate D2DR availability and frontal cortical perfusion and episodic memory. Left caudate D2DR availability was associated with frontal perfusion (A) and episodic memory (B) in men but not in women. Sex differences in episodic memory performance were attenuated following adjustment for left caudate D2DR (C). Red line indicates mean performance for the sample. ** $p < 0.01$. L: left.

$p = 0.796$; Fig. 1B). Similar sex differences in patterns of associations were found for right caudate D2DR availability (*men*: $F(1,94) = 4.56$, $p = 0.035$, $r = 0.22$; *women*: $F(1,76) = 0.08$, $p = 0.779$, $r = 0.03$). In testing whether sex moderated the association between D2DR levels and episodic memory, main effects were found for left caudate D2DR availability ($F(3,170) = 4.27$, $p = 0.006$; $\beta = 0.292$, $t(170) = 2.76$, $p = 0.006$), however, sex ($\beta = 1.279$, $t(170) = 1.92$, $p = 0.057$), and the interaction between sex and left caudate D2DR levels ($\beta = -1.192$, $t(170) = 1.73$, $p = 0.085$) bordered to statistical significance. The corresponding model for right caudate D2DR and episodic memory ($F(3,170) = 3.19$, $p = 0.025$) demonstrated main effects for D2DR availability ($\beta = 0.211$, $t(170) = 2.15$, $p = 0.033$), but no relationships to sex ($t(170) = 1.40$, $p = 0.162$) or sex \times D2DR availability ($t(170) = 1.18$, $p = 0.239$).

Moreover, sex differences in episodic memory remained after adjusting for right caudate D2DR levels ($F(1,171) = 4.33$, $p = 0.039$, $\eta^2 = 0.025$), but were attenuated and non-significant after adjusting for left caudate D2DR availability ($F(1,171) = 2.88$, $p = 0.091$, $\eta^2 = 0.017$; Fig. 1C). In comparison, adjustment for the structural measures assessed in relation to D2DR availability, did not attenuate sex differences in episodic memory (number of lesions: ($F(1,174) = 4.13$, $p = 0.044$, $\eta^2 = 0.023$; frontal perfusion: ($F(1,176) = 4.29$, $p = 0.040$, $\eta^2 = 0.024$; brain per intracranial ratio: ($F(1,177) = 5.44$, $p = 0.021$, $\eta^2 = 0.030$).

Episodic memory performance has been linked to hippocampal volume and D2DR levels (Nyberg et al., 2016). Yet, sex differences in performance remained after adjusting for hippocampal D2DR availability (average left and right; $F(1,170) = 6.61$, $p = 0.011$, $\eta^2 = 0.037$) and volume (average left and right; $F(1,176) = 6.61$, $p = 0.011$, $\eta^2 = 0.036$).

4. Discussion

The present work sought to elucidate sex differences in neurocognitive status at older age, focusing on episodic memory performance, the nigrostriatal DA system, and structural brain measures. Due to previous indications of reduced DA integrity (Kaasinen et al., 2015; Kaasinen et al., 2001; Lavalaye et al., 2000; Pohjalainen et al., 1998; Wong et al., 2012) and more vascular alterations in men (Kivipelto et al., 2006; Klöner et al., 2016; Webb and Collins, 2017), we investigated interrelations between these domains, and specifically whether possible links differed between men and women. We demonstrate lower episodic memory performance and lower levels of nigrostriatal D2DR markers, particularly in the left hemisphere, in men compared to women. Furthermore, left caudate D2DR levels accounted for a small portion of sex differences in memory performance. Higher white-

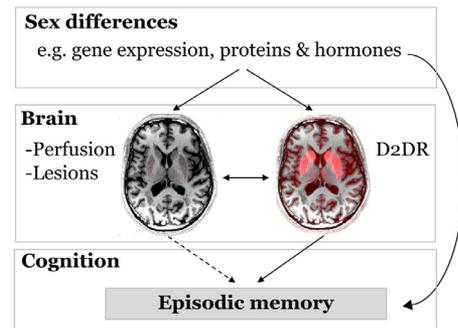


Fig. 2. Overview of findings. Sex differences were observed for mean levels and associations between vascular status and D2DR integrity, and episodic memory performance in older adults. Single-headed arrows indicate direction of links. The hatched arrow indicates expected associations that are not apparent in the COBRA study. Double-headed arrow indicates a reciprocal relationship.

matter lesion burden and lower cortical perfusion in men, with links to caudate D2DR levels, suggest that cerebrovascular status may be one factor that underlies sex differences in DA integrity (Karalija et al., 2019). That said, sex was not a significant moderator of the perfusion-D2DR and D2DR-memory links. These relationships are illustrated in Fig. 2, although causal links are not possible to derive from the current analyses.

Sex differences in the DA system have been reported previously, with evidence for higher levels of DA markers in women (Kaasinen et al., 2015; Kaasinen et al., 2001; Lavalaye et al., 2000; Pohjalainen et al., 1998; Wong et al., 2012). Notably, one age-comparative study showed that striatal receptor availability in older men was half of that in older women (Pohjalainen et al., 1998). Moreover, men are at higher risk of pathological DA decline. The risk of PD is at least 1.5 times greater in men, upon which accelerated DA decline and greater symptom severity is observed (Elbaz et al., 2002; Gillies et al., 2014; Haaxma et al., 2007; Lubomski et al., 2014; Lyons et al., 1998; Wooten et al., 2004). Lower levels of DA decline in women, in healthy as well as pathological aging, have been related to neuroprotective effects of estrogen (Becker, 1999; Bourque et al., 2011; Gillies et al., 2014), which could be exerted via estrogen receptors in nigrostriatal areas (Creutz and Kritzer, 2004). In support of this assertion, animal data demonstrate that toxin-induced DA depletion is aggravated in male animals, and that estrogen replacement in ovariectomized animals leads to less grave DA lesions (Miller et al., 1998).

Asymmetries in the DA system have been observed across studies involving healthy samples, and in groups with pathologies (Larisch et al., 1998; Molochnikov and Cohen, 2014). Studies in animals and humans have demonstrated that hemispheric differences

in D2DR levels are found in younger subjects, yet are reduced in aging (Giardino, 1996; Vernaleken et al., 2007). Inter-hemispheric asymmetries were found in the present work, with lower D2DR levels in left striatum in both sexes, that were more pronounced in men. The physiology behind DA asymmetries remain inconclusive; however, it may have important functional consequences for behavior (Nieoullon, 2002; Tomer et al., 2008; Tomer et al., 2012). Unilateral striatal DA loss is typically found in early stages of PD, and predominantly in the left hemisphere for right-handed PD patients (Kaasinen et al., 2015; Scherfler et al., 2012). Interestingly, left- versus right-sided DA loss in PD gives rise to diverging cognitive deficits, where left-sided DA deficits were associated with memory impairments (Verreyt et al., 2011). The present work indicates that similar patterns may apply to healthy aging as well.

There is consistent evidence for that men are at higher risk for cardiovascular disease (Pilote et al., 2007). Such differences are believed to stem from genetic, epigenetic, and hormonal factors (Regitz-Zagrosek and Kararigas, 2016). The present study shows that even in samples of healthy, older adults, indications of reduced cerebrovascular health were more pronounced in men. Here, cerebrovascular status was assessed via perfusion and white-matter lesion burden, where the latter is considered a manifestation of small-vessel disease (Wardlaw et al., 2013). The higher risk in men may derive from declining levels of testosterone with aging (Kloner et al., 2016), as testosterone regulates cardiac repolarization and interacts with cardiovascular risk factors (Oskui et al., 2013). In men over 70 years of age, cardiovascular risk was associated with serum testosterone levels (Ruige et al., 2011), which has led to suggestions of treatment with testosterone for preventive purposes (Goodale et al., 2017; Kloner et al., 2016). Interestingly, increased midbrain and cortical perfusion was found following testosterone treatment in hypogonadal men (Azad et al., 2003). Protective effects of estrogen may contribute to maintained vascular integrity and a younger metabolic age in women throughout the lifespan (Goyal et al., 2019; Gustafsson, 1997; Iafrazi et al., 1997).

Due to the scarcity of multimodal brain imaging studies, there is a lack of knowledge regarding the relation among age-sensitive brain variables. This is particularly the case for DA, owing to limited sample sizes and lack of multimodal designs of most *in vivo* DA studies (Karrer et al., 2017). Changes in various neural substrates are likely correlated, where some may trigger others. Cross-sectional data suggest DA decline to be a continuous process across the lifespan (Bäckman et al., 2010; Bäckman et al., 2006; Karrer et al., 2017). Vascular risk factors may modulate DA integrity throughout adulthood, even though vascular disease is more prevalent in older populations (Strait and Lakatta, 2012). In healthy aging, reduced DA markers have been associated with increased load of white-matter lesions (Karalija et al., 2019; Rieckmann et al., 2016), and structural and functional brain measures (Lövdén et al., 2018). The present work demonstrates that cortical perfusion was significantly lower in men than in women. Although sex did not moderate the perfusion-D2DR link, the significant correlation between perfusion and caudate D2DR levels in men suggests that reduced vascular health may underlie DA reductions, and, possibly lateralization of these. Relatedly, DA decline in PD is paralleled by cortical atrophy and hypoperfusion (Claassen et al., 2016; Lin et al., 2016). Stroke studies in animals and humans suggest that ischemia is followed by changes in the DA system (Gower and Tiberi, 2018; Momosaki et al., 2017). However, the reverse causal chain is also plausible, due to the vasoactive characteristics of DA. Dopaminergic terminals are located in close proximity to brain microvasculature and administration of DA agonists results in a vasomotor response (Krimmer et al., 1998). Also, animal and human PET work demonstrate effects of DA release on striatal blood flow (Knutson and

Gibbs, 2007; Schott et al., 2008). Conceivably, there is a reciprocal relationship between these two directions of influence, such that DA activity affects vascular parameters inasmuch as the opposite is true (double-headed arrow in Fig. 2; (Bäckman and Nyberg, 2013).

In line with recent meta-analytic evidence (Asperholm et al., 2019), we have earlier reported a female advantage in episodic memory in the same sample (Nevalainen et al., 2015). Our study sample involves only adults in their mid 60s, hence limiting the generalizability of the findings to early and middle adulthood, and to very old age. The relatively young age and high level of health in the COBRA sample (Nevalainen et al., 2015) may underlie the lack of the expected association between cerebrovascular parameters and episodic memory (hatched arrow in Fig. 2). Vascular abnormalities such as hypoperfusion, lesion manifestation, and silent infarcts are recognized as early signs of memory impairment and dementia (Iturria-Medina et al., 2016; Smith et al., 2017; Wählin and Nyberg, 2019). This age range was chosen as it represents the age at which average decline in several cognitive abilities typically starts to manifest. Several studies have shown that caudate DA markers, including D2DRs, predict episodic memory performance (Cervenka et al., 2008; Chen et al., 2005; Erixon-Lindroth et al., 2005; Nyberg et al., 2016). Recent work shows impaired episodic memory following induction of striatal DA-lesions in animals, and modulatory effects of sex hormones (Conner et al., 2020). The present study extends previous work and suggests that sex differences in caudate D2DR levels may be one source of sex differences in episodic memory performance. Conceivably, caudate function is critical for updating of long-term episodic memory representations (Persson et al., 2015), and exerts its role via interactions with other key regions for memory encoding and retrieval, such as hippocampus and prefrontal regions (Brown et al., 2012; Müller et al., 2018). Sex differences have been reported for hippocampal structure and function (Yagi and Galea, 2019), and as shown here, seem to include hippocampal perfusion. However, adjusting for hippocampal volume and D2DR levels did not attenuate sex differences in episodic memory in our sample.

4.1. Conclusions

In summary, the present data demonstrate sex differences in cerebrovascular status, DA integrity, and episodic memory in aging. Still, longitudinal multivariate data and a closer link to animal models are needed to ascertain how physiological differences between women and men contribute to sex differences in cognitive aging.

Disclosure statement

The authors report no conflicts of interest.

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CRediT authorship contribution statement

Nina Karalija: Conceptualization, Formal analysis, Investigation, Writing – original draft. **Goran Papenberg:** Conceptualization, Formal analysis, Investigation, Writing – original draft. **Anders Wählin:** Software, Validation, Formal analysis, Writing – review & editing. **Jarkko Johansson:** Software, Validation, Writing – review & editing. **Micael Andersson:** Software, Validation, Formal analysis, Writing – review & editing. **Jan Axelsson:** Software, Validation, Writing – review & editing. **Katrine Riklund:** Project administration, Funding acquisition, Writing – review & editing. **Ulman Lindenberger:** Project administration, Funding acquisition, Writing – review & editing. **Lars Nyberg:** Project administration, Funding acquisition, Writing – review & editing. **Lars Bäckman:** Project administration, Funding acquisition, Supervision, Conceptualization, Writing – review & editing.

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