NeuroImage 245 (2021) 118707

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

A common polymorphism in the dopamine transporter gene predicts working memory performance and *in vivo* dopamine integrity in aging

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ARTICLE INFO

Keywords:
Working memory
Dopamine transporter
Dopamine D2 receptor
^{11}C-raclopride
Single-nucleotide polymorphisms

ABSTRACT

Dopamine (DA) integrity is suggested as a potential cause of individual differences in working memory (WM) performance among older adults. Still, the principal dopaminergic mechanisms giving rise to WM differences remain unspecified. Here, 61 single-nucleotide polymorphisms, located in or adjacent to various dopamine-related genes, were assessed for their links to WM performance in a sample of 1313 adults aged 61–80 years from the Berlin Aging Study II. Least Absolute Shrinkage and Selection Operator (LASSO) regression was conducted to estimate associations between polymorphisms and WM. Rs40184 in the DA transporter gene, *SLC6A3*, showed allelic group differences in WM, with T-carriers performing better than C homozygotes ($p<0.01$). This finding was replicated in an independent sample from the Cognition, Brain, and Aging study (COBRA; baseline: $n = 181$, ages: 64–68 years; 5-year follow up: $n = 129$). In COBRA, *in vivo* DA integrity was measured with ^{11}C-raclopride and positron emission tomography. Notably, WM as well as *in vivo* DA integrity was higher for rs40184 T-carriers at baseline ($p<0.05$ for WM and caudate and hippocampal D2-receptor availability) and at the 5-year follow-up ($p<0.05$ for WM and hippocampal D2 availability). Our findings indicate that individual differences in DA transporter function contribute to differences in WM performance in old age, presumably by regulating DA availability.

1. Introduction

Working memory (WM) function, the ability to maintain and manipulate information for effective executive processing, deteriorates in normal aging (Nyberg et al., 2012; Park et al., 1996; Sander et al., 2012). Findings from animal and human studies demonstrate that the neurotransmitter dopamine (DA) is particularly age sensitive, and modulates WM processes (Bäckman and Nyberg, 2013; Karrer et al., 2017). Hence, DA status at older age may underlie individual differences in WM performance (Bäckman et al., 2006). Plausible mechanisms include noisy information processing and less distinctive cortical representations (Li et al., 2000), and disrupted balance between regional DA functions (Cools, 2019; Cools and D'Esposito, 2011; Durstewitz and Seamans, 2008; Frank et al., 2001). Still, we lack conclusive evidence for whether some specific dopaminergic mechanisms may be more strongly linked with individual differences in WM performance. Such knowledge would point at dopaminergic functions particularly critical to preserve in aging.

Imaging studies and pharmacological interventions have demonstrated associations between various DA markers and WM performance

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https://doi.org/10.1016/j.neuroimage.2021.118707.
Received 8 July 2021; Received in revised form 4 October 2021; Accepted 1 November 2021
Available online 3 November 2021.

(Arnsten, 1998; Braver et al., 2001; Bäckman et al., 2011; Landau et al., 2009; Wilkerson and Levin, 1999). Early experimental work showed that DA lesions and surgical ablations of the frontal cortex in monkeys yielded comparable WM impairments, and that administration of DA D1-receptor (DRD1) agonists to DA-depleted animals alleviated WM deficits (Brozoski et al., 1979). In naïve animals, pharmacological DRD1 and DA D2-receptor (DRD2) blockade impaired WM performance, whereas non-excessive DRD1 stimulation improved WM (Arnsten et al., 1994; Sawaguchi and Goldman-Rakic, 1991, 1994). In humans, administration of DRD1 and DRD2 agonists have been found to activate prefrontal cortex and improve WM performance (Gibbs and D'Esposito, 2005; Kimberg and D'Esposito, 2003; Kimberg et al., 1997; Luciana et al., 1992; Muller et al., 1998; Tarantino et al., 2011). Moreover, positron emission tomography (PET) studies performed during resting conditions have collectively shown that high *in vivo* availability of the DA transporter (DAT), DRD1s, and DRD2s generally characterizes individuals with higher WM performance (Erixon-Lindroth et al., 2005; Lövden et al., 2018; Nour et al., 2019; Sambataro et al., 2015; Takahashi et al., 2007, 2012).

The interpretation of the substantial DA literature could be that general maintenance of dopaminergic constituents contribute to proficient WM performance in aging. Alternatively, high integrity of some DA functions may be of particular importance, as such could modulate the rest of the DA system, and possibly, buffer for aging-effects. The DA system has a robust compensatory capacity, which is demonstrated by upregulated DA synthesis, and normalized dopamine levels, in the early stages of DA degeneration in Parkinson's disease (Tedroff et al., 1999). Proteins involved in DA production and metabolism could, via adjustment of dopaminergic tone, regulate postsynaptic DA receptor density in aging (Berry et al., 2018; Volkow et al., 1998). Currently, there is shortage of comparative analyses, and hence, lack of evidence for whether some DA constituents hold a more central role for individual differences in WM in aging. *In vivo* DA studies are conducted with radioactive ligands, for which ethical considerations complicates the use of several ligands, and high costs reduced the sample sizes (Karrer et al., 2017). The general low statistical power of most *in vivo* DA studies compromises replicability and generalizability of findings (Juarez et al., 2018).

To shed light on the question of which DA functions that predict WM performance at older ages, the present work evaluated single-nucleotide polymorphisms (SNPs) in genes encoding for various DA proteins. Previous work show that normal genetic variation gives rise to individual differences in dopaminergic functions (Bilder et al., 2004; Borg et al., 2015; Hirvonen et al., 2009), that may be further magnified in aging (Lindenberger et al., 2008; Papenberg et al., 2015). The selected SNPs were located in, or in the proximity of, genes encoding the DA receptors; proteins involved in synthesis, synaptic storage, reuptake and degradation of DA; and striatal signal transduction. To increase reliability and generalizability of findings, assessments were conducted in two independent samples of healthy older adults (ages: 61–80 years). We used a large sample from the Berlin Aging Study II (BASE-II; $n = 1313$) to explore links among 61 single-nucleotide polymorphisms (SNPs) and WM, and an independent sample from the Cognition, Brain, and Aging Study (COBRA; $n = 181$ and 129 at baseline and at a 5-year follow up, respectively) for confirmation. WM tasks were similar across the two studies. Being one of the largest DA PET studies (Nevalainen et al., 2015), COBRA enabled robust tests of the functional implications of SNPs on *in vivo* DA integrity (via DRD2-like assessment with ^{11}C-raclopride, which binds to DA D2 and D3 receptors).

2. Materials and methods

2.1. Ethics statement

This work was conducted in accordance to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Written informed consent was collected prior to any testing. All experiments were approved by ethical review committees in the respective countries (Germany and Sweden).

2.2. Samples

Data from two independent samples of older adults were analyzed in the present work. These included the BASE-II study ($n = 1313$, ages: 61–80 years (Bertram et al., 2014; Gerstorf et al., 2016)) and the COBRA study ($n = 181$ at baseline, ages: 64–68 years; $n = 129$ at 5-year follow-up, ages: 69–73 years (Nevalainen et al., 2015)). The mean age and sex distributions, and status for select health and cognitive variables are shown in Table 1. Both samples had undergone a Mini Mental State Examination (MMSE, max score: 30), and the digit-symbol coding task from the Wechsler Adult Intelligence Scale (1 point per correct item coding during 90 s). Individuals with MMSE performance below 27 at baseline were excluded ($n = 76$ from BASE-II, $n = 0$ for COBRA at baseline).

2.3. Genetic analyses

The selected SNPs were located in, or in the proximity of, genes encoding DA receptors D1–D5, proteins involved in DA synthesis (tyrosine hydroxylase, *TH*; dopa decarboxylase *DDC*), synaptic DA storage (vesicular monoamine transporter, VMAT2 (*SLC18A2)*), DA reuptake and degradation (catechol-O-methyltransferase, *COMT*; and the DA transporter (*SLC6A3)*), and striatal signal transduction (dopamine and cAMP-regulated phosphoprotein 32 kDa; *PPP1R1B*; Table 2). Additionally, SNPs located in genes encoding *APOE*, KIBRA (*WWC1*), and *BDNF* were selected, due to their established relevance to cognition (Papenberg et al., 2015). By including these, we are able to determine whether dopamine-encoding genes predict the outcome above and beyond these well-established genetic variants. Search terms "single-nucleotide polymorphism" and the gene names were entered in the PubMed database (www.ncbi.nlm.nih.gov), from which SNPs previously assessed in relation to cognition and behavior, DA status, or neurological and psychological disorders were selected. Via this approach, we were able to test the replicability of previous findings, and gain further insights into currently known dopamine-encoding genes that are central to WM performance.

From this initial selection, eight SNPs were excluded because they were each perfectly associated with a different SNP in the same gene within our selection (indicated in gray font color in Table 2).

Following exclusions, 61 SNPs were entered into analyses. Each SNP was binarized, so that homozygotes of the less frequent variants were merged with heterozygotes, and compared with homozygotes of the more common allelic variant. The dichotomization was performed to increase group sizes, as some allelic variants are uncommon and only found in a minority of the population. Frequencies of allelic variants per SNP were similar in BASE-II and COBRA (see distributions for the significant predictors of WM in Supplementary Table 1).

2.3.1. Genotyping in BASE-II

Genotypes for the analyses of this manuscript were derived from SNP genotyping generated using the Genome-Wide Human SNP Array 6.0 (Affymetrix, Inc.). Data processing, quality control and imputation have been described previously (Lill et al., 2016). For the purpose of this manuscript, imputed genotypes dosages were converted into "hard-coded" genotypes using the following arithmetic: a minor allele dose scale<0.2 was assigned to the minor allele homozygous genotype, dose scales 0.8–1.2 to heterozygous genotypes, and dose scales>1.8 to major allele homozygous genotype; dosages falling outside these values were set to missing.

2.3.2. Genotyping in COBRA

DNA analyses were performed by the SNP&SEQ Technology Platform (Department of Medical Sciences, Uppsala university, Sweden). In

Table 1
Descriptives for the BASE-II and COBRA samples.

	BASE-II Baseline	COBRA Baseline	5-year follow-up
n	1313	181	129
Age	61–80 y (71.3 ± 3.6)	64–68 y (66.2 ± 1.2)	69–73 y (71.2 ± 1.2)
Sex	48% men	55% men	54% men
Educational attainment	14.9 ± 2.8	13.3 ± 3.5	13.4 ± 3.4
BMI	26.8 ± 4.2	26.1 ± 3.5	26.4 ± 3.8
MMSE	28.8 ± 1.0	29.3 ± 0.8	28.8 ± 1.4
Digit-symbol coding	42.9 ± 10.3	37.6 ± 8.1	37.6 ± 7.4

Note: All continuous values are given as mean ± standard deviation, or frequencies. MMSE: mini mental state examination; BMI: Body-Mass-Index.

Table 2
List of candidate genes and single-nucleotide polymorphisms (SNPs) that were assessed in the present work.

Gene	SNPs	Gene	SNPs
DRD1	rs265976	*PPP1R1B*	rs879606
	rs265977	(DARPP-32)	rs3764352
	rs863126		rs3764353
	rs835541		rs907094
	rs835616	*TH*	
	rs11746641		rs2070762
	rs686		rs6356
	rs11749676		rs11042962
	rs265981		rs10840490
	rs4532	*DDC*	
	rs5326		rs62445903
			rs6263
			rs10499695
DRD2	rs6279	*SLC18A2*	rs363387
	rs6275	(VMAT2)	rs363399
	rs6277		rs363338
	rs1076560		rs10082463
	rs2283265		rs363227
	rs1079598		rs363285
	rs4648317		
ANKK1	rs877138	*COMT*	rs737865
	rs1800497		rs5993883
DRD3	rs7631540		rs4680
	rs2046496		rs4646315
	rs3773678		rs165774
	rs324030		rs9332377
	rs6280		rs165599
LOC107986115	rs905568	*SLC6A3* (DAT)	rs6347
DRD4	rs3758653		rs3863145
	rs1800955		rs27072
	rs7124601		rs40184
	rs11246226		rs464049
	rs936465		rs456082
			rs463379
DRD5	rs7655090	*APOE*	rs7412
	rs2076907	*WWC1* (KIBRA)	rs429358
	rs6283		rs17070145
SLC2A9	rs10033951	*BDNF*	rs6265

Note: SNPs in gray were perfectly associated with the preceding SNP, and therefore excluded from analyses.

brief, the genotyping was performed using a multiplexed primer extension (SBE) chemistry of the iPLEX assay with detection of the incorporated allele by mass spectrometry with a MassARRAY analyzer from Agena Bioscience (Gabriel et al., 2009). Raw data from the mass reader were converted to genotype data using the Typer software (Agena Bioscience).

2.4. Working memory performance

WM tasks used in BASE-II and COBRA consisted of a letter-updating task, a columnized numerical 3-back task, and a spatial-updating task (max scores: 48, 108, and 24, respectively; (Nevalainen et al., 2015; Schmiedek et al., 2010). Scores were summarized across the number of trials per test and rescaled to a T-metric with a mean of 50 and a standard deviation (SD) of 10. The three T-standardized scores were then averaged to build a unit-weighted composite score for WM. WM distributions for samples are found in Supplementary Figure 1. In case of missing data for one WM task, the non-missing tasks were averaged. Data for all three tasks were missing for one person in COBRA at the follow-up session. Outliers defined as +/−3.29 SD from the mean (corresponding to $p<0.001$ in a t-test) were excluded from analyses ($n = 8$ for BASE-II; $n = 0$ for COBRA; (Tabachnick and Fidell, 2013)).

2.5. In vivo *DRD2 availability*

2.5.1. Magnetic resonance imaging

Regions of interest for DRD2 assessments were delineated from T1-weighted images acquired with magnetic resonance imaging (MRI) 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. Imaging 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. The longitudinal image processing pipeline in Freesurfer (http://surfer.nmr.mgh.harvard.edu), version 6, was used to process T1 images and obtain segmentations of regions-of-interest (ROIs) for the two time points.

2.5.2. Positron emission tomography

Following a CT scan (20 mA, 120 kV, 0.8 s/revolution), an intravenous bolus injection of 250 MBq ^{11}C-raclopride was administered, and a 55 min (18-frame) dynamic PET scan was acquired in resting-state conditions with a Discovery PET/CT 690 (General Electric, WI, US). Attenuation- and decay-corrected images (47 slices, field of view = 25 cm, 256 × 256-pixel transaxial images, voxel size = 0.977 × 0.977 × 3.27 mm^3) were reconstructed with the iterative 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.

DRD2 binding potential (BP_{ND}) was estimated via two separate pipelines where the first applied correction for partial volume effects (PVE), and the second yielded unadjusted BP_{ND} values. PET image data were converted from DICOM to NIfTI format and corrected for head movement. The PET and T1 images were co-registered with the Statistical Parametric Mapping software (SPM8). ^{11}C-raclopride BP_{ND} was calculated from time-activity curves within Freesurfer-segmented ROIs. Regional PVE correction was conducted using symmetric geometric transfer matrix implemented in Freesurfer (Greve et al., 2014). Briefly, the abovementioned Freesurfer segmentations, point-spread function (PSF) of 2.5 mm (isotropic, full-width-at-half-maximum), and the abovementioned preprocessed PET data were used to estimate PVE-corrected regional radioactivity concentrations in each ROI and time frame. Then, PVE-corrected BP_{ND} estimates were calculated using the multilinear reference-tissue model from dynamic PVE-corrected data, using cerebellar gray matter radioactivity as an indirect input function. The unadjusted ^{11}C-raclopride BP_{ND} values were estimated using Logan analysis (Logan et al., 1996) with median of ROI voxel values from time frames between 18 and 55 min. Cerebellar GM served as the reference area. BP_{ND} was calculated as distribution volume ratio – 1. Together, the two pipelines with different modeling methods (MRTM *vs*. Logan) allowed for comparisons of the robustness of genetic effects on DRD2 availability.

DRD2 assessments were carried out in *a priori* selected ROIs, including dorsal striatum (caudate nucleus and putamen) and hippocampus, in which DRD2 levels have previously been linked to updating of WM (Bäckman et al., 2011; Lövden et al., 2018; Takahashi et al., 2007). Values are expressed as mean ^{11}C-raclopride BP_{ND} across the left and right hemisphere for each brain region. Values for a few individuals were excluded because they either were classified as statistical outliers (±3.29 SD from the sample mean; (Tabachnick and Fidell, 2013)), or because of their unwillingness to undergo the PET regime at follow-up (*baseline:* n = 2 for caudate, and n = 3 for putamen and hippocampus; *follow-up:* n = 2 for all three regions; handled as pairwise exclusions). Multivariate outliers were assessed with Mahalanobis Distance, and concerned n = 1 at baseline and n = 1 at follow-up (handled as listwise exclusions).

2.6. Statistical analyses

Statistical analyses were conducted with R (R Core Team, 2018), using tidymodels (Kuhn and Wickham, 2020), and SPSS Statistics software (version 26). Descriptive data are presented with mean values and standard deviations (SDs) for continuous variables, and frequencies for nominal scales. Effect sizes for mean group differences are reported with Cohen's d and 95% confidence intervals (minimum; maximum).

The main objective was to identify dopaminergic SNPs (*cf.* Table 2) that best predict WM performance, while affording generalizability of findings, and considering potential correlations among SNPs. To this end, we applied a statistical learning approach referred to as regularized regression, in which variable selection was performed with Least Absolute Shrinkage and Selection Operator (LASSO (Helwig, 2017; McNeish, 2015; Tibshirani, 1996). This approach uses penalized regression, which yields linear regression estimates that best predict the outcome while shrinking the least-squares coefficients toward zero, such that ideally the unimportant predictors attain regression coefficient estimates of zero and only important predictors remain. It is conceptually closely related to Bayesian approaches with prior beliefs in simple models, that is, models with many regression coefficients set to zero. Estimation is performed by optimizing a loss function of the least-squares fit to the data and a penalty term consisting of the sum of the absolute value of each regression coefficient. The amount of penalization is guided by a hyperparameter (λ) which balances the influence of fit and penalty. Consequently, as the penalty increases, regression coefficients are shrunken toward zero, and only the most influential predictors are kept within the model. As there is no single generic optimal value for λ, we tested a range of fifty different λ values, performed bootstraps (with 200 draws each), and chose the penalty minimizing the expected prediction error (given as root-mean-squared error). The benefits of this approach include reduced risks of overfitting to noise due to excessive model complexity, and thus finding predictors with a higher likelihood of being non-zero in independent samples. In particular, LASSO can handle situations in which predictors are potentially highly correlated, which is often the case with genetic data. The full regression model included an intercept term, all 61 SNPs and three demographic covariates, age, sex, and education.

In a second step, the significant predictors from the regularized regression in the BASE-II sample were independently tested for their predictive accuracy of WM performance and DRD2 availability in the COBRA study at two consecutive time points (baseline and 5-year follow-up), using independent-samples t-tests, repeated-measures analysis of variance (RM-ANOVA), and ANOVA (Table 3; Supplementary Tables 1–4). WM scores and DRD2 measures were residualized for age, sex, and education, and presented as z-standardized estimates.

3. Results

3.1. Genetic predictors of working memory performance

Regularized regression with LASSO was carried out in the BASE-II sample with the SNPs from Table 2 as predictors, and a composite score of WM as the dependent variable. The bootstrap procedure yielded λ=0.037 as the optimal value. The regularized model has an intercept term and a total of seven predictors. Of these, largest effect sizes are seen for the three demographic covariates, where younger age, male sex, and higher education is associated with higher WM. In addition, four SNPs explained further variance above and beyond the demographic variables (Fig. 1). Next, we tested the robustness of the selected SNPs on WM performance in the COBRA sample (Supplementary Table 1). Of the four top SNPs from the regularized regressions in BASE-II, we found that T-carriers of the DAT polymorphism rs40184 were characterized by higher WM performance in both samples (Table 3). Approximately 70% of the COBRA cohort returned for a 5-year follow-up. Among the returnees, T-carriers of rs40184 demonstrated significantly higher performance also at the follow-up session. A RM-ANOVA for the returnees confirmed that WM performance was higher in T-carriers at both sessions ($F(1118)=4.75$, p = 0.031), yet, no genotype x time interaction was found ($F(1118)= 0.02$, p = 0.877). Hence, we found no evidence for differential WM change in the allelic groups.

3.2. Genetic effects on in vivo DRD2 availability

Next, we tested whether rs40184 was also linked to differences in caudate, hippocampal, and putamen DRD2 availability in the COBRA sample. Indeed, T-carriers were characterized by higher DRD2 levels in caudate at baseline and in hippocampus at both time points (Table 3).

Table 3
Working memory and *in vivo* D2-receptor (DRD2) availability (binding potential, with correction for partial volume effects) for allelic groups of the DAT polymorphism rs40184 in the BASE-II and COBRA samples. Values are presented as z-standardized estimates, residualized for age, sex, and education.

	BASE-II	COBRA	
		Baseline	5 years
Frequency			
CC	29%	36%	37%
T-carriers	71%	64%	63%
Working memory			
CC	-0.14 (0.94)	-0.20 (1.00)	-0.25 (0.94)
T-carriers	0.06 (1.02)	0.11 (0.98)	0.15 (0.99)
p	0.006	0.040	0.026
Cohen's d	0.20	0.32	0.41
95% CI	0.06; 0.35	0.01; 0.63	0.05; 0.77
Caudate DRD2			
CC		-0.23 (1.09)	-0.19 (0.98)
T-carriers		0.13 (0.91)	0.11 (0.98)
p		0.021	0.112
Cohen's d		0.36	0.31
95% CI		0.05; 0.67	-0.07; 0.68
Hippocampus DRD2			
CC		-0.20 (0.95)	-0.32 (0.85)
T-carriers		0.11 (1.00)	0.18 (1.02)
p		0.048	0.007
Cohen's d		0.31	0.52
95% CI		0.00; 0.62	0.14; 0.90
Putamen DRD2			
CC		-0.13 (1.00)	-0.06 (0.92)
T-carriers		0.07 (0.98)	0.03 (1.03)
p		0.205	0.634
Cohen's d		0.20	0.09
95% CI		-0.11; 0.51	-0.28; 0.46

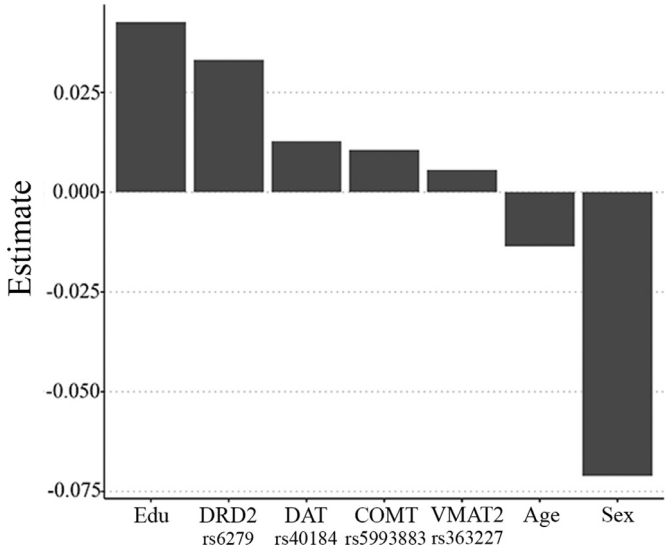

Fig. 1. Significant predictors of working memory performance in a sample of healthy, older adults (n = 1313, ages: 61–80 years; from the BASE-II study). 61 dopaminergic SNPs, and the covariates age, sex, and education were entered as independent variables in a Least Absolute Shrinkage and Selection Operator (LASSO) regression. Edu: education.

For the returnees, a RM-ANOVA confirmed that allelic groups of rs40184 differed in caudate (F(1, 118)=4.90, p = 0.029), and hippocampal (F(1, 118)=7.13, p = 0.009) DRD2 availability. Again, no interactions for genotype x time were found (*caudate:* F(1, 118)= 1.11, p = 0.295; *hippocampus*: F(1, 118)= 0.39, p = 0.533). C/C and T-carriers had comparable volumes for caudate, putamen, and hippocampus at baseline (F(3, 123)=2.2, p = 0.093), and similar 5-year volume changes (*putamen*: −2.5% for C/C and −2.2 for T-carriers; *caudate*: −1.1% for C/C and −0.6 for T-carriers; *hippocampus:* −3.1% for C/C and −2.5 for T-carriers; F(3, 120)=0.4, p = 0.740). Still, volumes had a slight influence on DRD2 levels, as volume-DRD2 correlations were noted at baseline for the PVE-corrected data (*r*s: −0.19 and −0.25 for caudate and putamen, p<0.05). At follow up, DRD2-volume associations were found for caudate (*rs*=−0.29 and −0.20 with and without PVE-correction), putamen (*r*=−0.23, without PVE-correction), and hippocampus (r = 0.21 and 0.26 with and without PVE-correction, p<0.05). Notably, results were consistent for DRD2 values estimated with or without PVE correction (Supplementary Tables 2 and 3). No DRD2 differences were found for allelic groups of the other SNPs in Fig. 1 (Supplementary Tables 2 and 3). We also present WM performance and DRD2 availability for the three allelic groups of rs40184 (Supplementary Table 4).

We have previously demonstrated the existence of three profiles with different DRD2-cognition-associations within the COBRA sample (Lövden et al., 2018). These consisted of individuals with (i) high cognitive and DRD2 measures, (ii) low cognitive and DRD2 measures, and (iii) low cognition and high DRD2 levels. Here, we further add to this finding by showing that rs40184 T-allele carriers are underrepresented in the two low-performing groups (17% and 22% in group 2 and 3 *versus* 60% in group 1; p = 0.033; chi-squared test).

4. Discussion

Increased knowledge of DA functions that predict individual differences in WM is warranted. Ethical concerns and high costs impede the assessment of multiple *in vivo* DA markers within the same sample. The present work combined a genetic approach with *in vivo* DA imaging to assess how individual differences in DA proteins relate to WM performance in old age. Generalizability of findings was verified by inclusion of a large sample, and confirmation in a second, smaller sample with DA imaging data. A polymorphism in the DAT gene (rs40184) reliably predicted WM performance in both samples, as well as *in vivo* DRD2 availability in the second sample.

WM is supported by several parallel and interactive processes and brain regions. Among these, a fronto-striatal DA-based gating mechanism presumably mediates maintenance via activation of DRD1s,

and updating via the DRD2 pathway (D'Esposito and Postle, 2015; Nyberg and Eriksson, 2015; O'Reilly, 2006). DAT is a protein located at nerve terminals and is commonly used as a presynaptic DA marker. It is abundantly expressed in striatum, where it regulates the reuptake of DA into presynaptic terminals, thus adjusting extracellular DA levels. The present work demonstrated higher WM performance and caudate and hippocampal DRD2 levels for T-homozygotes of the DAT SNP rs40184. Toward this end, it is of note that availability of striatal DRD2s and DAT are closely linked in healthy adults (Volkow et al., 1998), and show similar age differences (~8% per decade) (Karrer et al., 2017). This suggests that the expression of receptors and transporters may reflect adaptation of major components of the dopaminergic pathways. Although DAT has been assigned a minor role in extrastriatal DA clearance (Borgkvist et al., 2012), cortical DAT levels decline significantly upon dopaminergic cell loss in Parkinson's disease, and such losses are linked to cognitive deterioration (Sampedro et al., 2021). rs40184 T-allele carriers have been characterized by accelerated increases of WM performance during development (Nemmi et al., 2018). The current findings suggest that this advantage may persist into old age. However, allelic groups did not differ in terms of 5-year WM decline. Similar observations have been made for other variables, where *e.g.* education is found to predict individual difference in the level of cognition and cerebral gray matter density, while exerting very little to no influence on slopes of decline (Berggren et al., 2018; Lövdén et al., 2020; Nyberg et al., 2021). Furthermore, variability in DAT function has been associated with individual differences in WM performance and training-induced WM improvement (Brehmer et al., 2009; Stollstorff et al., 2010). We previously identified subgroups within the COBRA sample, which suggests non-linear DA-cognition associations (Lövden et al., 2018). Here, we found that T-homozygotes of rs40184 are underrepresented in groups showing low overall cognition (WM, episodic memory, and perceptual speed), thus, DAT function may have a central role for several cognitive processes.

Even though causality cannot be inferred from the current analyses, it is conceivable that higher DRD2 availability and WM function reflect higher DA availability in T-carriers of rs40184. Striatal DA integrity is partly reflected in extrastriatal regions (Papenberg et al., 2019; Zald et al., 2010), rhyming well with high DRD2 levels in caudate as well as the hippocampus of T-carriers as compared to non-carriers. Previous research has also established a link between caudate and hippocampal DRD2s and WM performance (Lövden et al., 2018; Rocchetti et al., 2015; Takahashi et al., 2007). The SNP rs40184 is located in intron 14 of the DAT (*SLC6A3*) gene. Even though it is located within a non-coding region, intronic SNPs may still exert effects on gene transcription and translation (Cooper, 2010). The Genotype Tissue Expression (GTEx; (Consortium., 2020)) project provide some evidence supporting this notion, where rs40184 shows evidence for a genome-wide significant eQTL effect in Testis (NES [normalized effect size] 0.29, $p<0.001$; URL https://www.gtexportal.org/home/snp/rs40184). In GTEx brain samples, effects appear to go in the same direction (however statistically non-significant), that is, the T-allele increases expression of *SLC6A3*. Other samples, *e.g.* BrainSeq (Schubert et al., 2015) and xQTL (Ng et al., 2017) did not reveal further insights for the functional role of rs40184. Its functional effects are indicated here via allelic group differences in cognitive performance as well as *in vivo* DA integrity. Still, the biological implications of carrying T- *versus* C-alleles are currently inconclusive.

The effects of individual SNPs are generally small, which may explain the exclusion of most SNPs at the optimal penalty level in the current LASSO regression. Several of the excluded polymorphisms consisted of well-assessed SNPs, including rs4680 in the *COMT* gene, which has been associated with WM performance, rs6277 and rs1800497 in the *DRD2* gene that have been linked to *in vivo* DRD2 availability, and ApoE (Bertolino et al., 2006; Bilder et al., 2004; Hirvonen et al., 2009; Karalija et al., 2019; Papenberg et al., 2015; Smith et al., 2017). As potential consequences of the statistical modeling approach, the candidate gene approach, and the design of the WM tasks, we may have overseen DA polymorphisms that are linked to different conceptualizations of WM performance. The WM tasks used here require the ability to maintain and manipulate information, and are considered to be indicators of the same theoretical construct. They do not, however, cover a wider range of executive function tasks, including inhibition or shifting tasks, which may be associated to different dopaminergic functions and SNPs (Friedman and Miyake, 2017). In interpreting the negligible effects of specific SNPs, it is important to note that we cannot conclude non-importance from their exclusion. SNPs may be not selected because of a lack of power to detect a weak effect, or because their predictive power may only show up non-linearly or in interaction with other SNPs. That said, it is possible that other SNPs had little or no unique predictive power over and above the selected set of SNPs. For these reasons, it is crucial to test the reliability of the present and other findings. To exemplify, the DRD2 polymorphism rs6279 was the strongest predictor of WM in the BASE-II sample, yet it did not replicate for WM performance and was unrelated to *in vivo* DRD2 availability in the COBRA sample. Apart from a few studies showing allelic differences for rs6279 with problem solving (Zhang and Zhang, 2016), and cognitive function following injury (Failla et al., 2015), no clear links have been found between this specific polymorphism and cognition.

5. Conclusions

The present work highlights the role of the DAT for individual differences in WM performance among older adults, which was reflected not only by individual differences in performance, but also for *in vivo* DRD2 availability. Additional work is needed to clarify the functional implications of rs40184 C/C vs- T-carriers, and overall, the implications of altered DAT function in normal aging for WM performance. Such lines of work could encompass genomically informed approaches, targeting linked SNPs across the DAT gene, and imaging studies of WM that use a DAT ligand.

Credit authorship contribution statement

Nina Karalija: Conceptualization, Formal analysis, Investigation, Writing – original draft. **Ylva Köhncke:** Formal analysis, Methodology, Writing – review & editing. **Sandra Düzel:** Data curation, Project administration, Writing – review & editing. **Lars Bertram:** Funding acquisition, Data curation, Methodology, Writing – review & editing. **Goran Papenberg:** Conceptualization, Writing – review & editing. **Ilja Demuth:** Funding acquisition, Data curation, Project administration, Writing – review & editing. **Christina M. Lill:** Funding acquisition, Data curation, Project administration, Writing – review & editing. **Jarkko Johansson:** Formal analysis, Methodology, Writing – review & editing. **Katrine Riklund:** Conceptualization, Funding acquisition, Writing – review & editing. **Martin Lövdén:** Conceptualization, Funding acquisition, Writing – review & editing. **Lars Bäckman:** Conceptualization, Funding acquisition, Writing – review & editing. **Lars Nyberg:** Conceptualization, Funding acquisition, Writing – review & editing. **Ulman Lindenberger:** Conceptualization, Funding acquisition, Writing – review & editing. **Andreas M. Brandmaier:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Funding

This work reports data from the BASE-II project, which was supported by the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF) under grant numbers #01UW0808; #16SV5536K, #16SV5537, #16SV5538, #16SV5837; #01GL1716A; and #01GL1716B). Another sources of funding are the Max Planck Institute for Human Development, Berlin, Germany, and the European Commission as part of the Lifebrain Consortium (grant number 732592) within the Horizon 2020 program. Additional contributions (*e.g.* equipment, logistics, and personnel) are made from each

of the other participating sites. Further details about the study can be obtained at www.base2.mpg.de. C.M. Lill was supported by the German Research Foundation (DFG, GZ LI 2654/2-1).

The COBRA study was funded by the Swedish Research Council, Umeå University, the Swedish Brain Foundation, Umeå University–Karolinska Institute Strategic Neuroscience Program, the Knut and Alice Wallenberg Foundation, the Torsten and Ragnar Söderberg Foundation, an Alexander von Humboldt Research award, a donation from the Jochnick Foundation, Swedish Brain Power, Västerbotten County Council, Innovation Fund of the Max Planck Society, and the and Gottfried Wilhelm Leibniz Research Award 2010 of the German Research Foundation (DFG). The Freesurfer analyses were performed on resources provided by the Swedish National Infrastructure for Computing (SNIC) at HPC2N in Umeå, partially funded by the Swedish Research Council through grant agreement no. 2018-05973.

Data and code availability statement

The data sets generated and analyzed during the current study are available from the corresponding author upon reasonable request. Conditions for such requests include the need for a formal data sharing agreement, and submission of a formal project outline. Research questions of the project outlines need approval from the local ethics committees.

Declarations of interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2021.118707.

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