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Research Report

The influence of hippocampal dopamine D2 receptor losses on episodic-memory decline across 5 years is moderated by *BDNF* and *KIBRA* polymorphisms

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ABSTRACT

Losses in dopamine (DA) functioning may contribute to aging-related decline in cognition. Hippocampal DA is necessary for successful episodic memory formation. Previously, we reported that higher DA D2 receptor (D2DR) availability in hippocampus is beneficial for episodic memory only in older carriers of more advantageous genotypes of well-established plasticity-related genetic variations, the brain-derived neurotrophic factor (*BDNF*, rs6265) and the kidney and brain expressed protein (*KIBRA*, rs17070145) polymorphisms. Extending our observations to the longitudinal level, the current data show that individuals with one or no beneficial *BDNF* and *KIBRA* genotype ($n = 80$) decline more in episodic memory across five years, without any contribution of losses in hippocampal D2DR availability to memory decline. Although carriers of two beneficial genotypes ($n = 39$) did not decline overall in episodic memory, losses of hippocampal D2DR availability were predictive of episodic-memory decline among these individuals. Our findings have implications for interventions targeting DA modulation to enhance episodic memory in aging, which may not benefit all older individuals.

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1. Introduction

Individual differences in episodic memory (EM) due to, for example, age, sex, education, vascular status, and genetic background are routinely reported (Nyberg et al., 2012). These differences may partly reflect variations in the molecular mechanisms underlying successful long-term memory formation. We reported that hippocampal D2 dopamine (DA) receptor (D2DR) availability is positively related to EM performance (Nyberg et al., 2016). These findings are in line with DA's role in EM formation and consolidation (Lisman et al., 2011; Lisman & Grace, 2005). Novelty-related activity of dopaminergic neurons and DA release in the hippocampus result in an enhancement of plasticity-related molecular mechanisms, such as long-term potentiation (LTP). Intriguingly, the positive link between D2DR availability and episodic memory was only observed in individuals with beneficial genotypes of the *BDNF* and *KIBRA* polymorphisms (Papenberg, Karalija, et al., 2019), two genetic variations with well-established roles in EM based on meta-analytic evidence (Kambeitz et al., 2012; Milnik et al., 2012). Thus, these data suggest that DA's role in hippocampus and EM is linked to *BDNF* and *KIBRA*. More specifically, the genetic variation rs17070145 is a common T → C substitution within the ninth intron of the *KIBRA* gene, with the T-allele being the minor one (around 25%) in populations with European ancestry (Papassotiropoulos et al., 2006). Similarly, the common exonic Val66Met substitution (rs6265) within the pro-region of *BDNF* has a minor allele frequency of about 20–30% in Caucasians (minor allele: T/Met), with about 4% being homozygotes (Shimizu et al., 2004). Both *BDNF* (Devlin et al., 2021; Hsu et al., 2015) and *KIBRA* (Piras et al., 2017) polymorphisms have been shown to influence gene expression, resulting in differences in protein levels between genotypes. High expressions of KIBRA and BDNF levels have consistently been shown in the hippocampus (Hofer et al., 1990; Papassotiropoulos et al., 2006; Piras et al., 2017), where they likely interact with the mesolimbic dopaminergic pathway innervating the hippocampus.

Cross-sectional estimation of individual differences in memory, however, may not reflect longitudinal changes and be uninformative of cognitive-aging trajectories (Raz & Lindenberger, 2011). Using the Cognition, Brain, and Aging (COBRA) sample of healthy older adults (64–68 years at baseline), we demonstrated longitudinal decline in hippocampal D2DR availability (Karalija et al., 2022). Here, we investigate whether losses of hippocampal D2DRs interact with plasticity-related polymorphisms (*KIBRA*, *BDNF*) to influence 5-year changes in EM. We hypothesize that individuals with less beneficial genotypes decline more in EM across five years. Based on our cross-sectional observations, we further predict that changes in hippocampal D2DR availability are particularly relevant to EM changes in individuals with more beneficial genotypes.

2. Methods

2.1. Participants

The initial sample included 181 healthy older individuals (64–68 years of age; mean = 66.2; SD = 1.2; 81 women), who were randomly selected from the population register of Umeå, a city in northern Sweden. The parent sample has been described in detail elsewhere (Karalija et al., 2022; Nevalainen et al., 2015). Exclusion criteria were neurological and psychiatric disorders, epilepsy, previous brain trauma, intellectual disability, a Mini- Mental State Examination (MMSE) score <27, structural brain abnormalities (inspection performed by neuroradiologists), cancer, diabetes, severe auditory and visual impairments, claustrophobia, and metal implants. From the baseline sample, 128 returned for the 5-year follow up (ages: 69–73 years, mean: 71.2 ± 1.2 SD, 60 women). A detailed description of the follow-up sample, including selectivity analysis, is described elsewhere (Karalija et al., 2022). No cases of neurological disorders (e.g., Alzheimer's disease, Parkinson's disease) were reported at follow-up. 67% of the sample were retired at baseline and 91% at follow-up.

This study was approved by the Swedish Ethical Review Authority (Umeå, Sweden; registration number: 2012-57-31M) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before testing. No part of the study procedures or analyses was pre-registered prior to the research being conducted. We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

2.2. Brain imaging: acquisition and analyses

The same scanners and protocols were used at both baseline and the 5-year follow-up. MRI was performed with a 3T Discovery MR 750 scanner (General Electric, WI, US), equipped with a 32-channel phased-array head coil. PET was acquired with a Discovery PET/CT 690 (General Electric, WI, US) and 250 MBq [^{11}C]raclopride.

2.2.1. Regional volumes

T1-weighted images were obtained with echo time 3.2 msec, flip angle 12°, repetition time 8.19 msec, 176 slices with thickness 1.0 mm, field of view 25.0 × 25.0 cm, with a resolution of .98 mm upsampled to .49 mm. The longitudinal image processing pipeline in Freesurfer, version 6.0 was used to process T1-weighted images and derive estimates of grey matter (GM), white matter, and lateral ventricle size. Subcortical GM segmentations (Fischl et al., 2002) were used to define regions-of-interest (ROIs) for hippocampal D2DR assessment. GM volume was calculated as the sum of the left and right hemispheres.

2.2.2. D2DR availability

A 55-min, 18-frame dynamic PET scan was acquired during rest starting at the time of intravenous bolus injection of 250 MBq [^{11}C]raclopride (baseline: 263.5 ± 19.0 MBq; follow-up: 260.2 ± 15.0 MBq). An attenuation CT scan (20 mA, 120 kV, 0.8 sec/revolution) preceded ligand injection. Attenuation- and decay-corrected images (47 slices, 25 cm field of view, 256 × 256-pixel transaxial images, voxel size = .977 × .977 × 3.27 mm^3) were reconstructed with the iterative algorithm VUE Point HD-SharpIR (GE; 6 iterations, 24 subsets, 3.0 mm post filtering; FWHM: 3.2 mm). PET images

were motion-corrected and co-registered to the structural T1-weighted images from the corresponding session (baseline and follow-up), using the Statistical Parametric Mapping software (SPM12). As source for co-registration, the mean of the first five time-frames were used. For three participants, PET images from both time points were co-registered with the baseline T1 image (no MRI at follow-up). D2DR binding potential (BP_{ND}), was estimated using reference-Logan analysis (Logan et al., 1996) from time–activity curves within T1-segmented ROIs (median of ROI voxel values, Logan regression starting at 18 min). Cerebellar GM served as the reference area.

DRD2 binding potential (BP_{ND}) was estimated with and without correction for partial volume effects (PVEs). Regional PVE correction was conducted using the symmetric geometric transfer matrix implemented in FreeSurfer (Greve et al., 2016). An incremental PVE-correction approach was used in which (1) the initial correction was achieved using resolution modeling in the iterative image reconstruction procedure (SHARP-IR), and (2) the remnant PVE was controlled using the ROI-based geometric transfer matrix approach. The size of the secondary correction kernel was estimated empirically (point spread function of 2.5 mm; isotropic) to achieve a similar level of correction as earlier (Smith et al., 2019). FreeSurfer segmentations and preprocessed PET data were used to estimate PVE-corrected regional radioactivity concentrations per ROI and time frame. PVE-corrected BP_{ND} estimates were calculated with the multilinear reference tissue model (MRTM) on dynamic PVE-corrected data, with cerebellar GM radioactivity as an indirect input function.

The 2 pipelines (MRTM *vs* Logan) allowed for comparisons of the robustness of the associations reported below.

Based on data from studies with few subjects, extrastriatal assessment of DRD2 BP_{ND} with the radioligand [^{11}C]raclopride was not considered reliable due to its lower signal-to-noise ratio as compared to other radioligands, such as [^{11}C]fallypride. However, in recent studies, we and others have reported high long-term test-retest reliability for extrastriatal [^{11}C]raclopride binding (Alakurtti et al., 2015; Karalija et al., 2020) and validity (Johansson et al., 2023; Papenberg, Jonasson, et al., 2019).

2.3. Episodic memory

The present work focuses on EM. Therefore, we restrict our description to the measures of EM (Nevalainen et al., 2015), which was tested with three separate tasks (verbal, numerical, and figural, as described below). Then, summary scores were computed across the total number of blocks or trials. From these, a composite score was created by averaging the T-scored measures (M = 50; SD = 10). Follow-up EM scores were standardized on performance at baseline.

2.3.1. Word recall

Participants were presented with 16 Swedish nouns that appeared consecutively on the screen. The nouns were concrete, easy to spell, and all differed in the first three letters. During study, nouns were presented for 6 sec each, with an ISI of 1 sec. After having seen the entire list of 16 items, participants reported the nouns they could recall by writing them down one-by-one in any order using a keyboard (maximum score = 32). Two test trials were administered.

2.3.2. Number-word recall

This task consisted of memorizing pairs of 2-digit numbers and concrete plural nouns (e.g., 46 dogs). During study, 8 number-word pairs were displayed for 6 sec each, with an ISI of 1 sec. Following study, participants were requested to report, using the keyboard, the 2-digit number associated with each noun shown on the screen (e.g., How many dogs?). During testing, words were presented one-by-one in a different order than during acquisition. If failing to recall the number, participants guessed. Two test trials were administered (maximum score = 16).

2.3.3. Object-position recall

Participants were presented with a grid of 6 × 6 squares. Twelve objects were shown, one at a time, each at separate locations in the grid. Presentation time of each object-position pair was 8 sec, with an ISI of 1 sec. At test, all objects were shown adjacent to the grid and the correct position of each object was reported by moving objects with the computer mouse (in any order) to the correct location in the grid. Again, participants were asked to guess for recall failures and two test trials were performed (maximum score = 24).

2.4. Genotyping

In conjunction with the PET session, blood samples were collected from all participants and stored at the local biobank. Deoxyribonucleic acid (DNA) extraction and genotyping services were performed by LGC genomics, using their in-house products (Hoddesdon, England, United Kingdom). In brief, DNA was extracted from the buffy-coat fraction of blood samples using the Kleargene™ XL nucleic acid extraction kits and genotyping was performed with KASPTM genotyping assays. In the genotyping analysis, the DNA template was mixed with a KASP master mix (containing KASP Taq polymerase, deoxynucleoside triphosphates, buffers, salts, two fluorescently-labeled (FAM and HEX) reporter cassettes), and a SNP-specific KASP Assay mix (containing two allele-specific forward primers that differed at one base in the 3′-end, and one common reverse primer). For analysis of the *BDNF* polymorphism (rs6265), the primer sequence was 5′-GGC TGA CAC TTT CGA ACAC G/A-3′ for the forward primers, and 5′-GGT CCT CAT CCA ACA GCT CTT CTA T-3′for the reverse primer. For the *KIBRA* polymorphism (rs17070145), the primer sequence was 5′-C CTT GAT CCT GGA CCT C/T-3′ for the forward primers and 5′-CAG TAT AAA AGG AAA GCT CAG GAA CAG TT-3′ for the reverse primer. Genotyping was carried out with polymerase chain-reaction sessions, during which primers bound to their target sequences, reporter cassettes were incorporated into the DNA product, and amplification of the product was achieved. Allelic variants were determined via detection of FAM or HEX fluorescence for homozygotes, or both for heterozygotes. DNA amplification failed for one sample.

The distributions of the *KIBRA* and *BDNF* alleles were in Hardy–Weinberg equilibrium (*KIBRA*: T/T: $n = 13$; C/T: $n = 47$; C/C: $n = 58$; $\chi^2 < 1$, $p > .1$; *BDNF*: Met/Met: $n = 4$; Met/Val: $n = 37$; Val/Val: $n = 78$; $\chi^2 < 1$, $p > .1$). The distribution of the genotypes

across the two gene score groups is: *KIBRA* C/C and *BDNF* Any MET: $n = 20$; *KIBRA* C/C and *BDNF* Any MET: $n = 22$; *KIBRA* C/C and *BDNF* Val/Val: $n = 38$; *KIBRA* CC and *BDNF* ValVal: $n = 39$.

2.5. Statistical analyses

Behavioral and demographic data were analyzed using SPSS for Windows 15 (SPSS, Chicago, IL, USA). No part of the study procedures was pre-registered prior to the research being conducted. To increase predictive power and optimize individual differences in synaptic efficacy and plasticity, we contrasted individuals carrying two advantageous genotypes (*BDNF* Val/Val and *KIBRA* T-allele carriers; $n = 39$) against the rest ($n = 80$). Table 1 displays demographic, cognitive and brain measures as a function of gene-score group. To examine whether the association between changes in hippocampal D2DR availability (PVE-corrected data) and changes in EM was moderated by gene score group, a regression analysis was conducted with changes in hippocampal D2DR availability, gene score group, and their interaction term as independent variables and EM changes as the outcome. Changes in D2DR availability and cognition were calculated as a simple linear slope (i.e., t2 − t1 or (t2 − t1/t1)*100 when % change is reported). All analyses were adjusted for the *DRD2 C957T* polymorphism (rs6277), which affects [^{11}C]raclopride affinity (Hirvonen et al., 2009), and thereby may inflate BP_{ND} in individuals with high affinity (Karalija et al., 2019). Given the well-established female superiority in EM (Herlitz et al., 1997; Maitland et al., 2004), sex was included as a covariate. We also adjusted for influences of baseline EM and D2DR availability. Given that both *KIBRA* and *BDNF* have been related to hippocampal volumes (Bueller et al., 2006; Witte et al., 2016), change in hippocampal GM volume was also entered as a covariate. The same regression analysis was repeated with data uncorrected for partial-volume effects. In addition, we report the same results for the two polymorphisms separately (with PVE-corrected PET data).

The Outlier Labeling Rule was used to identify outliers; the following formulas were computed to calculate the upper and lower limits, respectively, for outliers: Q3 + (2.2*(Q3 − Q1)) and Q1 − (2.2*(Q3 − Q1)), where Q1 is the lower quartile (25th percentile of the data), and Q3 is the upper quartile (75th percentile). The number 2.2 is the value of the tuning parameter, *g*, which was set to 2.2 following recommendations (Hoaglin & Iglewicz, 1987). Multivariate outliers within and across groups were determined using Mahalanobi's distance, with the recommended $p < .001$ threshold for the χ^2 value (Tabachnick & Fidell, 2006). There were no univariate or multivariate outliers. For all analyses, the alpha level was set to $p < .05$.

Table 1 – Demographic, cognitive and brain measures as a function of gene score group.

Beneficial genotypes	No/one	Two
	n = 80	n = 39
Age	66.0 (1.2)	66.4 (1.5)[a]
Women %	46.3	48.7[b]
Education (years)	13.3 (3.6)	13.6 (3.3)[a]
Episodic memory baseline	51.1 (7.1)	50.7 (8.4)[a]
Episodic memory 5 years	49.6 (7.5)	51.2 (7.8)[a]
BP_{ND} in hippocampus baseline (PVE-corrected)	.25 (.04)	.25 (.05)[a]
BP_{ND} in hippocampus 5 years (PVE-corrected)	.23 (.06)	.23 (.06)[a]
Hippocampal volume baseline	7818.0 (774.8)	7689.6 (747.8)[a]
Hippocampal volume 5 years	7598.7 (837.5)	7493.2 (807.4)[a]

[a] Univariate ANOVA = not significant. Hippocampal volume was adjusted for ICV.
[b] Chi-square test = not significant.

3. Results

The regression analysis revealed a significant effect of gene-score group on changes in EM ($\beta = .309$, $t(109) = 3.33$, $p < .001$; see Table A1 in the appendices for full model results), indicating more EM decline for carriers of one or no beneficial genotype (Fig. 1A). While changes in hippocampal D2DR availability per se were not a significant predictor of changes in EM, $\beta = -.135$, $t(109) = -1.325$, $p = .188$, the interaction between gene-score group and hippocampal D2DR availability was a significant predictor of EM changes, $\beta = .388$, $t(109) = 3.504$, $p = .001$. Follow-up partial correlations indicated no significant change–change correlation in carriers with one or no beneficial genotype ($r = -.152$, CI 95% [−.371, .094], $p = .193$, Fig. 3A for PVE-corrected data). By contrast, there was a reliable positive correlation among individuals carrying two beneficial genotypes ($r = .416$, CI 95% [.030, .730], $p = .016$, Fig. 3B), indicating that more losses of hippocampal D2DRs were related to more EM decline. Analyses involving working-memory changes are reported in the appendices (Table A2), suggesting that the patterns reported above were specific to episodic memory.

The exactly same pattern of results was obtained using uncorrected (for PVE) data, with a significant interaction between gene-score group and hippocampal D2DR availability ($\beta = .416$, $t(109) = 3.174$, $p = .002$), but no overall effect of changes in D2DR availability on changes in EM ($\beta = -.156$, $t(109) = -1.530$, $p = .129$). The corresponding correlation for carriers of one or no beneficial genotype was, $r = -.191$, CI 95% [−.423, .059], $p = .101$. As before, carriers of two beneficial genotypes showed a positive change–change correlation, $r = .351$, CI 95% [.041, .627], $p = .045$.

The gene-score groups did not differ in terms of changes in hippocampal D2DR availability, $\beta = -.032$, $t(117) = -.342$, $p = .733$ (Fig. 2; PVE-uncorrected data: $\beta = -.063$, $t(116) = -.700$, $p = .486$, after adjusting for changes in hippocampal volume).

Investigating the two polymorphisms separately, we did not find any *KIBRA* or *BDNF* effects on change in episodic memory (*KIBRA*: $\beta = .100$, $t(109) = 1.042$, $p = .300$; *BDNF*: $\beta = .159$, $t(109) = -1.693$, $p = .093$), and there were no interaction effects with hippocampal D2DRs (*KIBRA*: $\beta = .548$, $t(109) = 1.913$, $p = .058$; BDNF: $\beta = .538$, $t(109) = 1.644$, $p = .103$).

4. Discussion

We reported that only carriers of two beneficial *KIBRA* and *BDNF* genotypes benefit from greater hippocampal D2DR availability

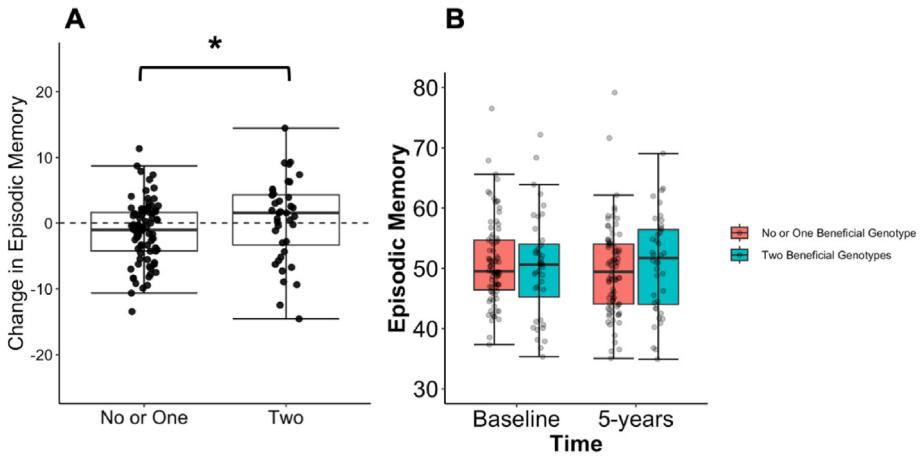

Fig. 1 – Change in episodic memory performance (A) and episodic memory performance at baseline and 5-year follow-up (B) as a function of gene-score grouping (no/one beneficial genotype, two beneficial genotypes). *$p < .05$.

when it comes to EM (Papenberg et al., 2019b). Motivated by these cross-sectional findings, the main goal of this study was to test whether changes in hippocampal D2DR availability interact with genetic status to influence EM decline across five years in an age-homogenous sample of older adults. Extending our cross-sectional observations, our results document that individuals with one or no beneficial genotype of plasticity-related genes (i.e., *KIBRA* and *BDNF*) decline more in EM across five years. The relative reduction of hippocampal D2DR availability, however, was not related to EM changes in this group. By contrast, carriers of two beneficial genotypes maintained episodic memory across five years. For this group, decline in EM was related to losses in hippocampal D2DR availability, although they, on average, exhibited no reliable overall EM decline. Notably, single polymorphisms did not influence changes in memory or moderate its association with changes in hippocampal D2DRs, highlighting the importance of synergistic effects of KIBRA and BDNF.

Our findings are consistent with meta-analytic evidence linking the *KIBRA* T and *BDNF* Val alleles to superior EM (Kambeitz et al., 2012; Milnik et al., 2012), contributing to individual differences in cognitive aging (for review, see Papenberg et al., 2015). Further, hippocampal DA has been related to EM formation both in animal (Frey et al., 1993;

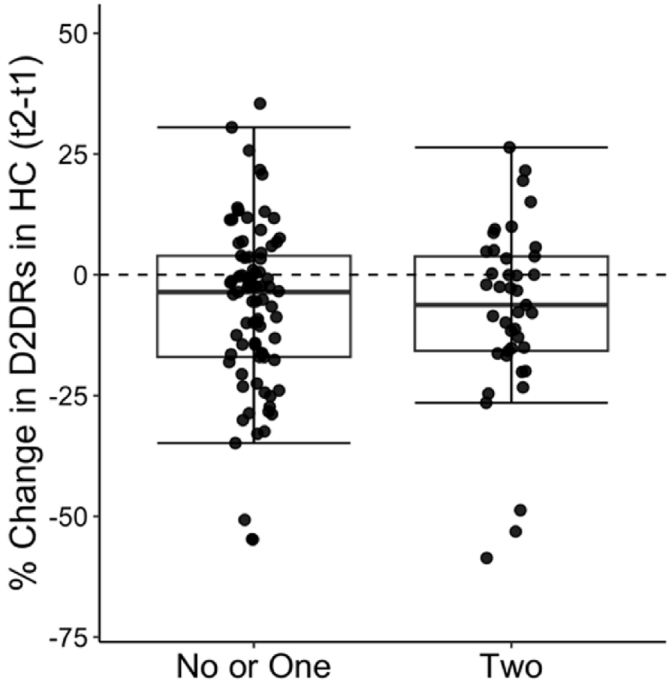

Fig. 2 – Percent change in hippocampal D2DRs (PVE-corrected data) as a function of gene-score grouping (no/one beneficial genotype, two beneficial genotypes). Group differences were not significant.

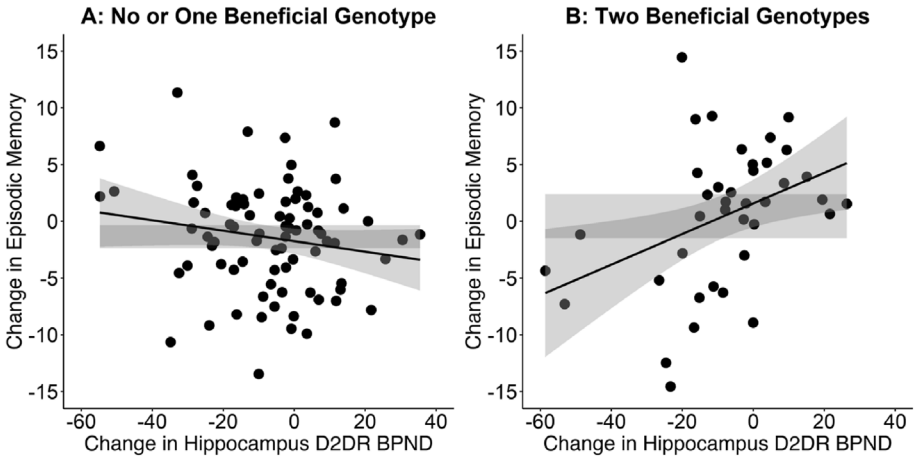

Fig. 3 – Relationship between changes in episodic memory performance and % changes in hippocampal D2DR BP_{ND} (PVE-corrected) as a function of gene-score grouping: (A) no/one beneficial genotype and (B) two beneficial genotypes (data unadjusted for covariates are plotted). Only the relationship in Figure B is significant (see text). 95% confidence bands are plotted around the regression lines.

Lisman & Grace, 2005) and human (Nyberg et al., 2016; Takahashi et al., 2007, 2008) studies. Importantly, the two gene-score groups did not differ with respect to hippocampal losses in D2DR availability. Together, this pattern underscores the relative importance of *BDNF* and *KIBRA* in the molecular cascades involved in successful EM functioning (Binder & Scharfman, 2004; Schneider et al., 2010). Based on in vitro data, it is conceivable that the KIBRA and BDNF proteins are limiting factors for D2DR's action on EM, all three factors being linked through the protein kinase Mzeta (PKMzeta). In vitro data show that PKMzeta is involved in synaptic tagging and capture (Sajikumar & Korte, 2011), creating the potential for a lasting change in synaptic efficacy (Redondo & Morris, 2011) and maintenance of episodic memories (for review, see Glanzman, 2013). Importantly, PKMzeta is involved in the induction and maintenance of DA-induced LTP in hippocampus (Navakkode et al., 2010). In turn, BDNF facilitates LTP maintenance through PKMzeta (Mei et al., 2011) and KIBRA regulates learning and memory through stabilization of PKMzeta (Vogt-Eisele et al., 2014). These patterns suggest a cascade of molecular events with DA's action depending and possibly succeeding the effects of KIBRA and BDNF on LTP. That said, further evidence is required to substantiate the ordering of these events.

Moreover, previous research has linked both disadvantageous genotypes of the KIBRA and BDNF polymorphisms with an increased risk for Alzheimer's disease (Lim et al., 2018, 2022). Increased BDNF levels may protect against tau-related neurodegeneration (Jiao et al., 2016). Similarly, increasing KIBRA levels in neurons can restore tau-related deficits in synaptic plasticity (Tracy et al., 2016). A recent animal study showed that the C-terminus of KIBRA restores plasticity and memory in transgenic mice expressing pathogenic human tau (Kauwe et al., 2023). Thus, tau pathology may be increased in carriers of more disadvantageous genotypes, thereby obscuring relationships between D2DR availability and memory.

It is noteworthy that our data show positive changes in D2DRs availability as well as cognition. Cognitive improvements are likely due to often observed practice effects, which may be particularly pronounced at the second follow-up (as compared to future follow-ups, Ronnlund et al., 2005). With respect to D2DRs, it is conceivable that positive changes in lifestyle variables may contribute to increases in D2DR availability across time, as shown in a study with a physical activity intervention in methamphetamine users (Robertson et al., 2015). In addition, aging-related increases in D2DRs may be due to decline in endogenous DA. Since [^{11}C]raclopride is sensitive to endogenous DA levels (Laruelle, 2000), aging-related DA decline may result in inflated D2DRs BP_{ND}, which we cannot differentiate with our assessment.

DA functioning has gained a lot of interest due to its modifiable nature through pharmacological treatment. Therefore, our results may have implications for intervention studies trying to manipulate DA modulation to enhance cognitive processes in aging. For example, it is likely that not all older adults may benefit from a DA agonist to the same extent, as DA's modulatory action on human EM may depend on other molecular cascades and genetic predispositions shaping its influence on EM.

Taken together, our data suggest that polymorphisms associated with plasticity-related mechanisms (1) contribute to maintenance of EM in old age, and (2) moderate the influence of aging-related losses in dopaminergic modulation on EM decline.

Data availability

The conditions of our ethics approval do not permit public archiving of pseudoanonymised study data. Readers seeking access to the data should contact the lead author Goran Papenberg. Access will be granted to named individuals in accordance with ethical procedures governing the reuse of

sensitive data. Specifically, requestors must meet the following conditions to obtain the data [completion of a formal data sharing agreement and ethical approval]. Codes behavioral tasks used to reproduce the main figures of the manuscript are available in the following repository (https://osf.io/szda4/).

Open practices

The study in this article has earned Open Material Badges for transparent practices. The materials used in this study is available at: https://osf.io/szda4.

CRediT authorship contribution statement

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

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Appendix

Table A1 – Results for multiple regression model investigating the moderator effect of the gene score grouping on the relation between changes in episodic memory and changes in hippocampal D2DRs.

	Variable	β	t	p
Analyses with hippocampal PVE-corrected BP_{ND} data				
Model:	Gene-score grouping	.309	3.33	**.001**
$F(8,109) = 4.96$	Change in hippocampal D2DRs	−.135	−1.33	.188
$p < .01$				
$R^2 = .27$	Interaction gene-score × change in hippocampal D2DRs	.388	3.50	**.001**
Adjusted $R^2 = .21$	**Episodic memory** (baseline)	−.281	−3.18	**.002**
	Hippocampal D2DRs (baseline)	−.207	−2.39	**.019**
	Sex	.032	.363	.717
	D2DR polymorphism (rs6277)	−.029	−.347	.729
	Change in hippocampal volume	.072	.832	.412

For all analyses, the alpha level was set to $p < .05$ is indicated in bold.

Table A2 – Results for multiple regression model investigating the moderator effect of the gene score grouping on the relation between changes in working memory and changes in hippocampal D2DRs.

	Variable	β	t	p
Analyses with hippocampal PVE-corrected BP_{ND} data				
Model:	Gene-score grouping	−.167	−1.673	.097
$F(8,109) = 2.44$	% Change in hippocampal D2DRs	.028	.252	.801
$p = .018$	Interaction gene-score × % change in hippocampal D2DRs	.085	.706	.482
$R^2 = .15$				
adjusted $R^2 = .091$	**Working memory** (baseline)	−.321	−3.29	.001
	Hippocampal D2DRs (baseline)	.109	1.12	.235
	Sex	−.008	−.083	.934
	D2DR polymorphism (rs6277)	.025	.268	.789
	Change in hippocampal volume	.031	.325	.746

Note. Working memory is based on a composite score of three tasks (a verbal, a numerical, and a figural task, see Nevalainen et al. (2015) for details).

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