Dopamine Receptor Genes Modulate Associative Memory in Old Age

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Abstract

■ Previous research shows that associative memory declines more than item memory in aging. Although the underlying mechanisms of this selective impairment remain poorly understood, animal and human data suggest that dopaminergic modulation may be particularly relevant for associative binding. We investigated the influence of dopamine (DA) receptor genes on item and associative memory in a population-based sample of older adults (n = 525, aged 60 years), assessed with a face–scene item associative memory task. The effects of single-nucleotide polymorphisms of DA D1 (*DRD1*; rs4532), D2 (*DRD2/ANKK1/Taq1A*; rs1800497), and D3 (*DRD3/Ser9Gly*; rs6280) receptor genes were examined and combined into a single genetic score. Individuals carrying more beneficial alleles, presumably associated with higher DA receptor efficacy (*DRD1* C allele; *DRD2* A2 allele; *DRD3* T allele), performed better on associative memory than persons with less beneficial genotypes. There were no effects of these genes on item memory or other cognitive measures, such as working memory, executive functioning, fluency, and perceptual speed, indicating a selective association between DA genes and associative memory. By contrast, genetic risk for Alzheimer disease (AD) was associated with worse item and associative memory, indicating adverse effects of *APOE* ε4 and a genetic risk score for AD (*PICALM*, *BIN1*, *CLU*) on episodic memory in general. Taken together, our results suggest that DA may be particularly important for associative memory, whereas AD-related genetic variations may influence overall episodic memory in older adults without dementia. ■

INTRODUCTION

Episodic memory refers to the ability to remember specific past events, situations, or experiences (Tulving, 1972), and it requires binding of different components of the episode at encoding, as well as access to these associations at retrieval. Compared with younger adults, older adults exhibit disproportionate difficulties in remembering associative episodic information, such as combining a face and a name, relative to remembering item information (e.g., a face or a name; Old & Naveh-Benjamin, 2008). In addition to age-related differences, large interindividual differences in associative memory performance have been observed among older adults. Whereas some older adults have severe problems in binding information, others show quite proficient performance (e.g., Becker et al., 2015; Brehmer, Li, Müller, von Oertzen, & Lindenberger, 2007; Nyberg et al., 2003). However, the mechanisms behind age-related associative memory deficits and interindividual differences in binding among older adults remain unclear. Imaging data suggest that associative memory draws on PFC and medial-temporal lobe regions, specifically the hippocampus (e.g., Becker et al., 2015; Bergmann et al., 2015; Bender, Daugherty, & Raz, 2013; Shing et al., 2011; Mayes, Montaldi, & Migo, 2007). Individual differences in neurochemistry have also been associated with between-person differences in episodic memory (e.g., Bäckman, Lindenberger, Li, & Nyberg, 2010).

At the molecular level, a large number of animal studies have shown that memory performance is impaired when dopamine (DA) receptors are blocked in hippocampus and enhanced when DA agonists are injected in the hippocampus (Lisman, Grace, & Düzel, 2011; Lisman & Grace, 2005). More specifically, D1 receptor activation in hippocampus is associated with enhancement of plasticity-related molecular mechanisms, such as long-term potentiation (Huang & Kandel, 1995; Frey, Huang, & Kandel, 1993; for a review, see Lisman & Grace, 2005). Also, a recent human PET study showed a relationship of D1 binding in fusiform gyrus to BOLD activity in the same brain region and episodic face recognition performance (Rypma et al., 2015). In terms of associative memory, animal data suggest that DA receptor activation is necessary for various episodic-like memory tasks, requiring learning and recall of different associations (e.g., reward-location, flavor-location; for a review, see Lisman et al., 2011). Furthermore, human studies have documented that higher D2 receptor binding in hippocampus is related to better verbal (Takahashi et al., 2007) and pictorial (Takahashi et al., 2008) recall. In line with these findings, one study reported a relationship

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between striatal D2 receptor availability and delayed memory after 30 min (Chen et al., 2005). Similarly, density of the striatal DA transporter has been related to episodic word recall and face recognition (Erixon-Lindroth et al., 2005). Moreover, D2 receptor availability in ventral striatum was positively associated with episodic memory in tasks assessing word recognition, pattern recognition, and paired-associate learning (Cervenka, Bäckman, Cselényi, Halldin, & Farde, 2008). Interestingly, when comparing the item and associative memory tasks, D2 binding was associated more strongly with paired-associate learning than with item recognition, suggesting a crucial role of DA in modulating associative binding (Cervenka et al., 2008). In line with this view, neurocomputational simulations have linked deficient dopaminergic neuromodulation with impairment in associative memory (Li, Naveh-Benjamin, & Lindenberger, 2005). More specifically, the simulations indicated that suboptimal dopaminergic neuromodulation affected the representational distinctiveness of distributed activation patterns, coding for stimulus- and response-related neuronal activities.

Despite the link between DA and associative memory, it is not clear whether this relationship would be stronger for associative than for item memory and whether the association is independent of item memory. For example, although Cervenka et al. (2008) reported stronger effects of a PET-derived DA measure for associative than for item memory, these measures were assessed in separate tasks rather than in the same experimental paradigm. In addition, whether the DA effects on associative memory were independent from those of item memory was not examined. Using a candidate gene approach, we explored whether individual differences in dopaminergic neuromodulation affect associative memory more than item memory in a sample of older adults. Importantly, we used the same task (i.e., face–scene recognition) to assess both item and associative memory. Rather than focusing on a single gene, three candidate genes that cover different DA receptors were selected to capture individual differences in the efficacy of DA modulation. Specifically, we examined the effects of single-nucleotide polymorphisms (SNPs) in DA D1 (*DRD1*; rs4532), D2 (*DRD2/ANKK1*; rs1800497), and D3 (*DRD3/Ser9Gly*; rs6280) receptor genes on item and associative memory. We hypothesized that individuals carrying more beneficial genotypes (see Methods for further details), presumably associated with greater DA receptor efficacy resulting in more proficient DA signaling, would show better episodic memory performance and that these effects would be stronger for associative than for item memory. As previous research has shown that polymorphisms associated with Alzheimer disease (AD) also affect episodic memory in elderly persons without dementia (Ferencz et al., 2014; Laukka et al., 2013), we also examined potential effects of several candidate genes for AD on item and associative memory: Apolipoprotein E (*APOE*; rs429358), phosphatidylinositol binding clathrin assembly protein (*PICALM*; rs3851179 and rs541458), bridging integrator 1 (*BIN1*; rs744373), and clusterin (*CLU*; rs111360000). Finally, to investigate the specificity of the influence of DA-relevant genes on cognitive functioning, we also examined their effects on speed, executive functioning, fluency, and working memory.

METHODS

Participants

Data were collected within the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), a population-based study targeting people 60 years and older living in the Kungsholmen district in central Stockholm. The current sample was taken from a cohort added in 2010–2013 (Wave 4 in SNAC-K). All 678 participants in this new cohort were 60 years old and randomly selected from population registries. The examination in SNAC-K took about 6 hr and consisted of three parts: a nurse interview, a medical examination, and a neuropsychological testing session. In addition to the standard cognitive test battery of SNAC-K (Laukka et al., 2013), this new cohort was assessed with an item associative memory task (Becker et al., 2015). From the total sample, participants with data on the item associative memory task and genetic data were included (n = 542). Moreover, we excluded persons with epilepsy (n = 2), Parkinson disease (n = 4), schizophrenia (n = 6), developmental disorder (n = 3), and questionable dementia according to DSM-IV (n = 2), resulting in an effective sample of 525 individuals (57.5% female).

The ethical committee at Karolinska Institutet has approved all parts of the SNAC-K project. Informed consent was collected from all participants.

Genotyping

DNA was extracted from peripheral blood samples using standard methods. The SNPs were genotyped using MALDI-TOF analysis on the Sequenom MassARRAY platform at the Mutation Analysis Facility, Karolinska Institutet (Darki, Peyrard-Janvid, Matsson, Kere, & Klingberg, 2012). Quality control was performed at DNA sample level, assay level, and the level of multiplex assay pool. All genotype distributions were in Hardy–Weinberg equilibrium (ps > .1). More specifically, the genotype frequencies of the *DRD1* polymorphism (rs4532) were 201 for T/T, 252 for C/T, and 72 for C/C. For *DRD2* (*ANKK1/TaqIA*; rs1800497), the distributions were 362 (A2/A2), 142 (A2/A1), and 21 (A1/A1), and the corresponding distributions for *DRD3* (*Ser9Gly*, rs6280) were 238 (T/T), 237 (T/C), and 50 (C/C). The following AD-related genetic variations were also included in the analyses: *APOE* (rs429358; e2/e2: n = 4; e2/e3: n = 57; e2/e4: n = 16; e3/e3: n = 264; e3/e4: n = 150; e4/e4: n = 11), *PICALM* (rs3851179; C/C: n = 230; T/C: n = 233; T/T: n = 62), *PICALM* (rs541458; T/T: n = 262; C/T: n = 212; C/C: n = 51), *BIN1* (rs744373; A/A: n = 251; G/A: n = 209;

G/G: $n = 50$), and *CLU* (rs11136000; C/C: $n = 186$; T/C: $n = 246$; T/T: $n = 92$).

Defining DA Gene-score Groups

To capture individual differences in DA modulation in terms of receptor efficacy, we computed a genetic score that corresponded to the number of beneficial genotypes of the three DA-related genes (*DRD1*, *DRD2*, *DRD3*). Similar gene-score approaches have been used and have proven to be more predictive of cognitive phenotypes than focusing on single genes (e.g., Ferencz et al., 2014; Papenberg et al., 2013; Hamrefors et al., 2010; de Quervain & Papassotiropoulos, 2006). Genotypes were defined as beneficial for memory if they had been associated with higher receptor availability or better behavioral performance in previous studies.

For the *DRD1* polymorphism, evidence suggests that the C allele is associated with higher D1 receptor efficiency. In healthy adults, C homozygotes showed more interference-resistant and effective action-cascading strategies than carriers of the T allele (Stock, Arning, Epplen, & Beste, 2014). Furthermore, the C allele is more common in persons with bipolar disorder (Dmitrzak-Weglarz et al., 2006) who are characterized by increased DA signaling (Whitton, Treadway, & Pizzagalli, 2015). Similarly, the C allele is associated with an increased rate of nicotine dependence (Huang et al., 2008), thought to reflect stronger reinforcing effects of nicotine, again because of increased DA signaling (D'Souza & Markou, 2011). The second polymorphism included in the DA gene score is a genetic variation in the *DRD2* gene (rs1800497), also known as Taq1A, which is associated with interindividual differences in D2 receptor density. The A1 allele has been related to a reduced number of DA binding sites in the brain (Gluskin & Mickey, 2016; Hirvonen et al., 2009; Jonsson et al., 1999; Pohjalainen et al., 1998) and worse outcomes in reversal learning (Jocham et al., 2009), performance monitoring (Klein et al., 2007), episodic memory (Persson, Rieckmann, Kalpouzos, Fischer, & Bäckman, 2014), and working memory (Berryhill, Wiener, Stephens, Lohoff, & Coslett, 2013). Finally, the third genetic variation included in the DA gene score codes for the D3 receptor (Lannfelt et al., 1992). Results from studies involving cognitive functions suggest that the T/T genotype of the *DRD3* polymorphism is beneficial. These include research on executive functioning (Bombin et al., 2008), prepulse inhibition (Roussos, Giakoumaki, & Bitsios, 2008), episodic memory (Papenberg et al., 2013; Yeh et al., 2012), and an electroencephalographic study on attentional regulation (Mulert et al., 2006).

In line with previous research (e.g., Ferencz et al., 2014; Pearson-Fuhrhop et al., 2014; Hamrefors et al., 2010), for each SNP, carriers of two disadvantageous alleles were assigned a value of 3, whereas carriers of one or no disadvantageous allele were assigned values of 2 and 1, respectively. On the basis of the literature reviewed above, the *DRD1* T allele, the *DRD2* A1 allele, and the *DRD3* C allele were considered disadvantageous. Hence, the genetic risk score ranged from 3 to 9, with higher values being more disadvantageous. Participants were further categorized into two subgroups, contrasting participants with low (3–6) versus high (7–9) risk profiles. Given the distribution of the genotypes, this particular cutoff was chosen to ensure that the frequency of disadvantageous alleles is high for all three polymorphisms in the high-risk group. Individuals with a risk score of 6 were already characterized by higher frequency of the beneficial *DRD2* allele than individuals carrying a risk score of 7, suggesting a cutoff at six separated individuals best in terms of low versus high DA receptor efficacy. Moreover, the DA gene score was not normally distributed and dichotomizing the score should increase the power to detect even small effects (Preacher, Rucker, MacCallum, & Nicewander, 2005). Notably, the two gene-score groups did not differ with respect to any of the demographic characteristics or regarding genetic risk for AD (see Table 1).

Table 1. Demographic Variables and Genetic Risk for AD across DA Gene-score Groups ($M \pm SD$)

	DA Gene Score	
	Normal DA Receptor Efficacy ($n = 456$)	*Reduced DA Receptor Efficacy ($n = 69$)*
Age	60.4 (.25)	60.4 (.25)[a]
Women/men	259/197	26/43[b]
Years of education	14.91 (3.2)	15.09 (2.5)[a]
MMSE	28.9 (1.19)	28.9 (1.23)[a]
APOE any e4, %	34.4	40.9[b]
AD genetic risk score	1.43 (.49)	1.42 (.50)[a]

[a]ANOVAs = *ns*.

[b]Chi-square test = *ns*.

AD Risk Score

Following the procedures of Ferencz and colleagues (2014), a genetic risk score for AD was computed by integrating the risk alleles for *PICALM* (rs3851179 G allele, rs541458 T allele), *BIN1* (rs744373 G allele), and *CLU* (rs11136000 T allele). The risk alleles of these candidate genes have been related to alterations in lipid metabolism, oxidative insult, and amyloid accumulation (Elias-Sonnenschein, Bertram, & Visser, 2012; Schjeide et al., 2011; Jones, Harold, & Williams, 2010). In previous studies, the risk alleles have also been linked to poorer episodic memory (Ferencz et al., 2014; Barral et al., 2012). Participants with no risk allele were assigned a score of 1, whereas participants with one and two risk alleles were assigned values of 2 and 3, respectively. Again, a cumulative score was calculated based on the sum of the individual scores. In line with Ferencz et al. (2014), we contrasted individuals with a low (4–8; $n = 279$) and high genetic risk scores (9–12, $n = 208$).

APOE

In addition to the two gene scores, the effects of *APOE* on item and associative memory were investigated. Previous studies showed that *APOE* ε4 explains a large part of the genetic variance in AD onset (Ferencz & Gerritsen, 2015) and is associated with cognitive deficits in normal aging (Wisdom, Callahan, & Hawkins, 2011; Small, Rosnick, Fratiglioni, & Bäckman, 2004).

Behavioral Measures

Item Associative Memory Task

The item associative memory task was described by Becker and colleagues (2015). During encoding, participants saw 24 face–scene picture pairs, each presented for 4 sec with an ISI of 1 sec. Items were male and female faces portraying older and younger adults, with neutral or happy expressions (Ebner, Riedeger, & Lindenberger, 2010). Scene stimuli were colored photographs of indoor and outdoor scenes (Chen & Naveh-Benjamin, 2012). Participants were instructed to memorize both the single pictures and their combinations. The encoding phase was followed by a distractor task, in which participants had to count backwards from 89 in steps of two for 1 min. Afterwards, three self-paced recognition tasks were administered: two item memory and one associative memory task. In each item memory task (one for the faces and one for the scenes), participants were presented with eight old and eight new pictures and asked to indicate whether or not they had seen a particular face or scene during encoding. During the associative memory test, participants were presented with 16 face–scene pairs where all pictures had been presented. Half of the pairs were "old," and the other half consisted of recombined pairs of faces and scenes that had all appeared in the study phase. Again, participants indicated whether or not they had seen a particular face–scene combination during encoding. Each picture appeared only once during encoding and once during testing. For further analyses, we aggregated the two measures of item memory (i.e., face, scene), as these showed identical results.

Free Recall Task

To control for differences in task difficulty between item and associative memory in the item associative memory task, a separate and more difficult item memory task was included and used as regressor in the analyses. Here, participants studied 16 concrete Swedish nouns, presented in black on white paper. Each word was shown and read out aloud by the experimenter. Immediately after presentation of the last word in the series, participants were given 2 min to recall the words orally (Laukka et al., 2013).

Perceptual Speed

Perceptual speed was assessed using two paper-and-pencil tests: digit cancellation (Zazzo, 1974) and pattern comparison (Salthouse & Babcock, 1991). For digit cancellation, participants were instructed to sequentially go through 11 rows of random digits as quickly as possible and cross out every "4" they encountered. For pattern comparison, they were asked to sequentially go through line segment patterns as rapidly as possible and mark whether the patterns were "same" or "different." The score used for both tests was based on the mean of two trials and reflected the number of correct responses in 30 sec.

Letter Fluency

For letter fluency, participants were asked to orally generate as many words as possible within 60 sec, beginning with the letters F and A, respectively. They were instructed that proper names, numbers, or words with a different suffix were not credited.

Category Fluency

For category fluency, participants were asked to orally generate as many words as possible within 60 sec, belonging to the categories animals and professions, respectively.

Executive Functioning

The Trail Making Test (TMT; Lezak, 2004) assessed executive functioning. The TMT-A and TMT-B versions each consisted of 13 circles with the same distance between them. For TMT-A, participants were required to connect encircled digits in numerical order (1, 2, 3, etc.). In TMT-B, circles included both digits and letters, and the task

was to connect these in alternating order (1-A, 2-B, 3-C, etc.). One careless connection was allowed, and the test leader corrected the first mistake without resulting in a lower score. The outcome variable for this task was the difference in completion time between TMT-B and TMT-A for participants with 12 correct connections.

Working Memory

In Digit Span forward, participants repeated lists of one-digit numbers (starting with list length 3). In Digit Span backwards, participants repeated the lists of numbers in reversed order (starting with list length 2). If a participant failed to repeat two trials of a certain list length, the task was terminated. The outcome variables were number of correct repetitions for forward and backward digit span.

Statistical Analyses

Behavioral and demographic data were analyzed using SPSS for Windows 15 (SPSS, Chicago, IL). We conducted a repeated-measures ANCOVA with DA gene-score group (normal DA receptor efficacy, reduced DA receptor efficacy) as between-subject factor and Test condition (item memory, associative memory) as within-subject factor. Given the well-established female superiority in episodic memory (Maitland, Herlitz, Nyberg, Bäckman, & Nilsson, 2004; Herlitz, Nilsson, & Bäckman, 1997) and the impact of education on episodic memory (Nyberg, Lövden, Riklund, Lindenberger, & Bäckman, 2012; Rönnlund, Nyberg, Bäckman, & Nilsson, 2005), sex and education were included as covariates in all analyses. To ensure that potential selective genetic effects were not due to differences in task difficulty between item and associative memory, analyses were adjusted for another item memory task (i.e., free recall). When comparing the tasks, it is evident that the free recall task (M = .54, SD = .15, based on proportion of correctly recalled items) is similarly difficult as the associative memory task (M = .42; SD = .32, based on proportion of hits minus false alarms) and considerably more difficult than item recognition in the face–scene task (M = .76, SD = .15, based on proportion of hits minus false alarms). In addition, we investigated whether genes related to risk for AD would show a similar pattern. Here, participants were grouped as *APOE* non-ε4 versus any ε4 carriers (cf. Laukka et al., 2013). We conducted another ANCOVA, keeping the same covariates as described above, with *APOE* (no ε4, any ε4) and the Genetic risk score for AD (low risk, high risk) as described by Ferencz and colleagues (2014) as between-subject factors. Moreover, to ensure that effects of the DA gene score are specifically related to episodic memory, we conducted univariate ANCOVAs with respect to other cognitive domains and DA gene-score group (normal DA receptor efficacy, reduced DA receptor efficacy) as between-subject factor, including sex and education as covariates.

For all analyses, the alpha level was set to $p < .05$. Effect sizes are indicated by partial eta-squared.

RESULTS

We found a main effect of Condition, $F(1, 519) = 30.27, p < .001$, partial eta-squared = .055, indicating that both DA gene-score groups showed worse performance in the associative than in the item condition (Figure 1A). Moreover, the main effect of DA gene-score group was reliable, $F(1, 519) = 4.70, p = .03$, partial eta-squared = .009, reflecting worse overall memory performance for individuals carrying less beneficial genotypes in terms of DA receptor efficacy. Critically, the DA gene-score group × Condition interaction was significant, $F(1, 519) = 4.35, p = .04$, partial eta-squared = .008. Follow-up comparisons showed no differences between DA gene-score groups with respect to item memory ($p > .10$). However, for associative memory, persons carrying less beneficial DA genotypes performed worse than carriers of more beneficial genotypes, $F(1, 519) = 5.44, p = .02$, partial eta-squared = .010.

Regarding genes associated with AD, analyses revealed main effects for both *APOE*, $F(1, 480) = 5.41, p = .02$, partial eta-squared = .011, and the Genetic risk score (*PICALM, BIN1, CLU*), $F(1, 480) = 5.14, p = .02$, partial eta-squared = .011, reflecting worse overall performance in *APOE* ε4 carriers and in individuals with more genotypes related to increased risk for AD. Importantly, in these two cases the Gene × Condition interaction fell far short of significance (ps > .10; Figure 1B and 1C). Apart from *APOE*, effects were only observable for the risk scores; none of the other single genes related to DA or AD risk modulated memory performance (ps > .10).

Notably, the significant DA gene-score group × Condition interaction reported above remained reliable, after *APOE* and the genetic risk score for AD were entered into the analysis as additional covariates to sex, education, and free recall, $F(1, 479) = 4.11, p = .04$, partial eta-squared = .009. Moreover, the DA gene score was unrelated to measures of perceptual speed (digit cancellation: $F(1, 521) = .78, p = .38$; pattern comparison: $F(1, 521) = .50, p > .10$), fluency (verbal fluency composite score: $F(1, 521) = .15, p = .70$; category fluency composite score: $F(1, 521) = .06, p = .81$), executive functioning ($F(1, 501) = 1.06, p = .31$), and working memory (digit span forward: $F(1, 519) = .30, p = .59$; digit span backward ($F(1, 501) = .28, p = 59$), suggesting a unique association between DA and associative memory in the present sample.

DISCUSSION

We investigated whether individual differences in DA modulation are related to item and associative memory in a population-based sample of 60-year-old adults. Our results show that genetic predisposition for greater DA receptor efficacy, captured by a score based on three DA receptor genes (i.e., *DRD*1, *DRD*2, and *DRD*3), was related to higher associative memory in older adults but did not modulate item memory. These differential patterns are unlikely to be due to differences in task difficulty

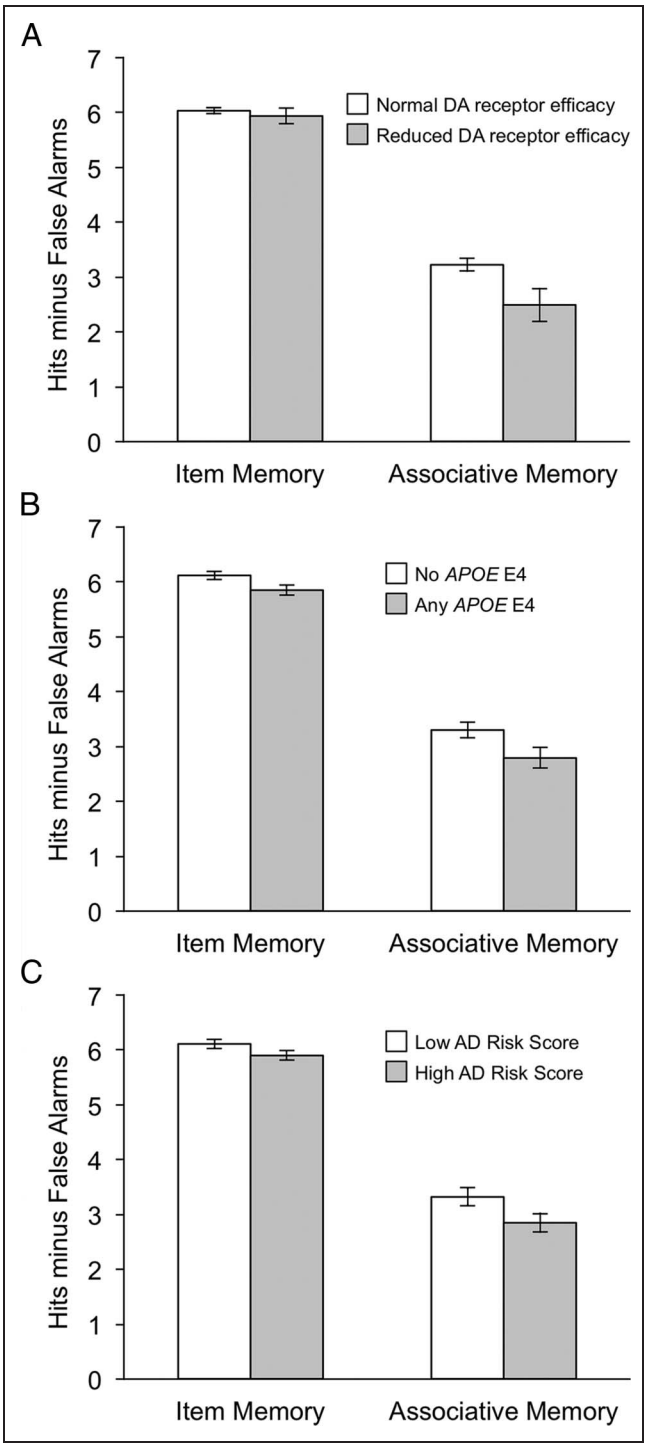

Figure 1. Item and associative memory performance for (A) carriers of genetic predispositions for normal (n = 456) and reduced (n = 69) DA receptor efficacy, (B) noncarriers (n = 325) and carriers (n = 177) of the *APOE* ε4 allele, and (C) persons with low (n = 279) and high (n = 208) AD risk scores. The range of the hits minus false alarm scale is from 0 to 8. The maximal number of hits in both conditions is 8. Error bars represent 1 standard error around the means.

between the two conditions, as we controlled for a more difficult item memory task, which required free recall of items (cf. Becker et al., 2015; Glisky, Rubin, & Davidson, 2001). Given that aging is characterized by both a specific impairment in associative memory (e.g., Naveh-Benjamin, 2000) and reduced dopaminergic neuromodulation (Bäckman et al., 2010), age-related decline in DA modulation may contribute to the often-observed disproportionate associative memory impairment in old age.

Our findings are in accordance with evidence from different lines of research, suggesting a critical role of DA in associative binding. Animal data show that activation of DA receptors is critical for learning associations in the environment (e.g., reward-location, object-location, flavor-location; Lisman et al., 2011). A receptor imaging study in humans that contrasted item and associative memory tasks revealed that DA D2 receptor densities in ventral striatum were more strongly related to associative than to item memory (Cervenka et al., 2008). Finally, our data are in line with results from neurocomputational simulations suggesting that deficient DA modulation plays an important role in age-related associative memory deficits (Li et al., 2005). The simulation work implicates DA in associative binding by affecting the efficacy of distributed conjunctive coding. The exact details of how DA modulates conjunctive coding of memory representations and consequently the binding between items remain to be determined in future studies. Taken together, our data support the notion that individual differences in dopaminergic modulation may be associated with individual differences in associative binding in old age.

Importantly, genetic predispositions for reduced DA receptor efficacy were unrelated not only to item memory but also to other measures of cognition, such as working memory, executive functioning, fluency, and perceptual speed, indicating a selective association between DA genes and associative memory. Ample evidence accumulated over the past decades points to the involvement of DA in working memory and executive tasks that draw on the PFC (e.g., Erixon-Lindroth et al., 2005; Goldman-Rakic, 1996). The fact that the DA gene-score groups did not differ in executive functioning and working memory in our study may be due to the relatively smaller expression of D2/D3 receptors in frontal cortex compared with hippocampus (Shohamy & Adcock, 2010). Thus, the current genetic risk score may largely reflect interindividual differences in dopaminergic modulation associated with the medial-temporal lobe. Although D1 receptor activation is necessary for hippocampal-dependent encoding and consolidation of episodic memories (de Lima et al., 2011; Bethus, Tse, & Morris, 2010; Rossato, Bevilaqua, Izquierdo, Medina, & Cammarota, 2009; O'Carroll, Martin, Sandin, Frenguelli, & Morris, 2006), human PET imaging studies suggest that D2 receptor densities may contribute more strongly to episodic memory (Cervenka et al., 2008; Takahashi et al., 2007, 2008; Bäckman et al., 2000), whereas D1 receptors may be more crucial for working memory (Bäckman et al., 2011; Rieckmann, Karlsson, Fischer, & Bäckman, 2011; McNab et al., 2009).

In addition, we replicated the effects of genes related to AD risk on overall episodic memory in a homogenous

sample of relatively young older adults (i.e., 60 years) without dementia. First, *APOE* ε4 was associated with adverse item and associative memory, replicating the well-established effects of *APOE* on episodic memory in general (Wisdom et al., 2011; Small et al., 2004). Moreover, we applied the same genetic score as Ferencz and colleagues (2014) and replicated the detrimental effects of carrying other disadvantageous risk genotypes for AD (*PICALM, BIN1, CLU*) on episodic memory (Ferencz et al., 2014; Barral et al., 2012) in a new cohort. As with *APOE*, the effects of this genetic score modulated both item and associative memory. Note that *APOE* and the AD genetic risk score affected episodic memory independently from each other. Importantly, given the homogenous and relatively young age of our sample, it is unlikely that the prodromal stage of dementia associated with the risk genotypes drove our effects.

None of the single polymorphism related to the DA (*DRD1*, *DRD2*, *DRD3*) or AD risk scores (*BIN*, *CLU*, *PICALM*) modulated item or associative memory. Thus, our data highlight the relatively strong effect of *APOE* on human episodic memory and the fact that a genetic score approach captures interindividual differences in dopaminergic modulation and AD risk more efficiently than a single-gene approach. Note that the relative contributions of the different mechanisms associated with each of the contributing polymorphisms to the observed behavioral effects cannot be delineated with a gene-score approach. That said, the aim of our study was to examine the association between DA modulation and associative memory using a candidate gene approach (Raz & Lustig, 2014), rather than to investigate the relative contributions of single genes to associative memory. Despite using a genetic score approach, the effect sizes observed in our study were relatively small, which is common in behavioral genetic studies (Papenberg, Lindenberger, & Bäckman, 2015; Barnett, Jones, Robbins, & Muller, 2007). To be sure, it would be biologically implausible to expect large contributions of a few genes on variation in complex, polygenic phenotypes such as episodic memory. Although we replicate the effects of AD-related genes on episodic memory (Ferencz et al., 2014; Barral et al., 2012; Small et al., 2004), future behavioral genetic studies are needed to replicate our main finding that DA genes are selectively linked to associative memory in independent samples.

Taken together, our results provide novel information regarding the influence of DA-related genes on associative memory. Older adults with genetic predispositions associated with better DA receptor efficacy performed better in associative memory, suggesting that individual differences in DA modulation may specifically contribute to associative-binding deficits in aging.

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