Neurobiology of Aging 84 (2019) 189–199

Contents lists available at ScienceDirect

Neurobiology of Aging

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

The relationship of age and *DRD2* polymorphisms to frontostriatal brain activity and working memory performance

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ARTICLE INFO

Article history:
Received 26 February 2019
Received in revised form 8 August 2019
Accepted 24 August 2019
Available online 29 August 2019

Keywords:
Working memory
Dopamine
DRD2
C957T
Aging
fMRI

ABSTRACT

Dopamine (DA) in both prefrontal cortex (PFC) and caudate nucleus is critical for working memory (WM) function. The C957T and Taq1A polymorphisms of the *DRD2* gene are related to DA D2 receptor densities in PFC and striatum. Using functional MRI, we investigated the relationship of age and these 2 *DRD2* gene polymorphisms to WM function and examined possible age by gene interactions. Results demonstrated less caudate activity for older adults (70–80 years; n = 112) compared with the younger age group (25–65 years; n = 191), suggesting age-related functional differences in this region. Importantly, there was a gene-related difference regarding WM performance and frontostriatal brain activity. Specifically, better WM performance and greater activity in PFC were found among C957T C allele carriers. Combined genetic markers for increased DA D2 receptor density were associated with greater caudate activity and higher WM updating performance. The genetic effects on blood oxygen level–dependent activity were only observed in older participants, suggesting magnified genetic effects in aging. Our findings emphasize the importance of DA-related genes in regulating WM functioning in aging and demonstrate a positive link between DA and brain activation in the frontostriatal circuitry.

1. Introduction

Working memory (WM) involves holding task-related information for a short time and manipulation of this information to guide current behavior (D'Esposito, 2007; D'Esposito and Postle, 2015; Eriksson et al., 2015). A widespread network including prefrontal cortex (PFC), parietal cortex, basal ganglia, as well as other regions specialized for perception is implicated in WM. Compared with WM tasks that only require maintaining information for a short delay, tasks in which there is a need for manipulation of information require both stable storage and flexible executive processes. Dorsolateral PFC (DLPFC) and caudate nucleus are strongly implicated in these types of WM tasks. In particular, DLPFC is critical for cognitive control and for maintaining task-related information in WM (Chee, 2004; Curtis and D'Esposito, 2003; Rypma and D'Esposito, 2000). Caudate nucleus, on the other hand, may be more involved in updating and manipulation of task-related information (Aron et al., 2003; Cools et al., 2004; Dahlin et al., 2008; Lewis et al., 2004; O'Reilly and Frank, 2006).

The importance of prefrontal dopamine (DA) for WM functioning is well documented in molecular imaging and pharmacological studies in animals (Arnsten and Goldman-Rakic, 1998; Brozoski et al., 1979; Phillips, 2004; Seamans et al., 2001), normal adults (Diamond et al., 2004; Mattay et al., 2003), and patients with Parkinson's disease (Cools et al., 2002). However, accumulating evidence supports a complementary role of striatal DA in WM (Braver and Cohen, 2000; Clatworthy et al., 2009; Dodds et al., 2009; Frank et al., 2001; Frank and Reilly, 2006; Mehta et al., 2004), and suggests that prefrontal and striatal DA might be linked to different components of WM (Cools et al., 2007; Cools and D'Esposito, 2011; Frank et al., 2001; O'Reilly and Frank, 2006). Specifically, DA in PFC appears to be more associated with maintaining stable representations (Brozoski et al., 1979; Durstewitz et al., 2000; Phillips, 2004), whereas updating and shifting may be more dependent on DA levels in caudate nucleus (Bäckman et al., 2011; Dodds et al., 2009; Frank et al., 2001; Frank and Reilly, 2006; Kellendonk et al., 2006; Mehta et al., 2004; Nyberg et al., 2009; Stelzel et al., 2010).

The DA D2 receptor is one of the 2 major DA receptors, and has the highest density in striatum while being less expressed in cortical regions, such as PFC. Striatal DA D2 receptors have been associated with updating of WM representations (Bäckman et al., 2011; Salami et al., 2018; Stelzel et al., 2010; van Holstein et al., 2011). Despite the low density of D2 receptors outside the striatum, a recent study provided evidence for the importance of both striatal and extrastriatal D2 receptors for WM function by showing

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0197-4580/$ – see front matter
https://doi.org/10.1016/j.neurobiolaging.2019.08.022

a positive link between DA and blood oxygen level–dependent (BOLD) signal in the thalamo-striato-cortical circuit during a WM task (Salami et al., 2018).

Genetic variations in the DA D2 receptor gene, and the neighboring ankyrin repeat and kinase domain containing 1 (*ANKK1*) gene, affect dopaminergic activity and D2 receptor density. Two polymorphisms are of main interest in the present study: the C957T (rs6277) polymorphism, located within the *DRD2* gene, and the Taq1A (rs1800497) polymorphism, located within the *ANKK1* gene about 10kb downstream from the *DRD2* gene. Human PET studies have found that presence of the C allele of the C957T polymorphism is associated with lower striatal DA binding potential (CC<CT<TT; Hirvonen et al., 2004; Smith et al., 2017). Conversely, this allele has also been related to higher extrastriatal DA binding throughout the cortex and the thalamus (CC>CT>TT Hirvonen et al., 2009). The Taq1a A allele of the *ANKK1* gene has been linked to reduced striatal D2 receptor binding (Eisenstein et al., 2016; Jönsson et al., 1999; Pohjalainen et al., 1998; Thompson et al., 1997).

Several studies have investigated the effects of C957T on WM and executive function (Bolton et al., 2010; Byrne et al., 2016; Colzato et al., 2013; Huertas et al., 2012; Klaus et al., 2017; Li et al., 2013; Rodriguez-Jimenez et al., 2007), but results regarding the direction of the effects are mixed. For example, it has been demonstrated that C carriers have worse general cognitive ability compared with T carriers (Bolton et al., 2010) and that they score lower on the Wisconsin Card Sorting Test (Rodriguez-Jimenez et al., 2007). Reduced performance in spatial WM and planning performance has also been found among C carriers (Klaus et al., 2017). Relatedly, it was recently demonstrated that T carriers outperformed C carriers in a category-learning task (Byrne et al., 2016). By contrast, C carriers have been reported to have faster motor learning (mirror drawing) compared with T carriers (Huertas et al., 2012), and the C allele has been associated with better episodic memory in a backward serial recall task (Li et al., 2013). Furthermore, older C carriers were more efficient in inhibiting a behavioral response to a stop signal (Colzato et al., 2013).

These discrepant results most likely reflect the fact that effects from single polymorphisms only contribute a small portion of the cognitive variance, and most studies have had relatively small sample sizes resulting in low statistical power. Another reason for the inconsistent findings could be that many cognitive functions, including WM, rely on a dynamic balance between stable storage and flexible updating. DA in PFC and in striatum might contribute differently to these 2 components of WM function (Cools and D'Esposito, 2011). As the C allele of rs6277 has greater binding in PFC (Hirvonen et al., 2009), while the T allele has been associated with greater binding in striatum (Hirvonen et al., 2004; Smith et al., 2017), C carriers might be better at maintaining stable representations in WM, whereas T carriers might perform better in tasks requiring flexible updating of information. Therefore, the direction of the effect of the C957T polymorphism on cognition may depend on the balance between stability and flexibility required in a specific task.

Aging is associated with changes in frontostriatal DA functioning (for reviews, see Karrer et al., 2017; Reeves et al., 2002). There is a loss of DA D2 binding potential (BP) in both striatal and extrastriatal regions from early to late adulthood (Bäckman et al., 2000; Volkow et al., 1998a, b). Both cross-sectional (Park et al., 2002) and longitudinal (Hultsch et al., 1992) fMRI studies have shown that older adults had functional changes in both PFC and striatum during WM performance compared with younger adults (Kennedy et al., 2017; Nyberg et al., 2014; Rieckmann et al., 2017; Rypma and D'Esposito, 2000; Ziaei et al., 2017). The resource-modulation hypothesis assumes that relationship of neurochemical, anatomical, and functional brain resources to cognitive performance is nonlinear, and posits that genetic effects are larger when resources are limited such as in aging (Lindenberger et al., 2008). This hypothesis has been supported by behavioral, structural, and functional neuroimaging studies (Colzato et al., 2013; Li et al., 2013; Papenberg et al., 2015; Persson et al., 2015). So far, only one study has investigated the effects of the Taq1A polymorphism, and its interactions with age on WM performance and WM-related brain activity (Persson et al., 2015). This study demonstrated that A carriers had worse cognitive performance than noncarriers of this allele in an updating task, along with lower caudate BOLD signal during updating, and this genetic effect was only observed in older adults. Despite the large number of behavioral studies, no age-comparative fMRI study has investigated the effects of the C957T polymorphism on brain function related to WM.

Although some studies have reported an association between CC combined with A+ genotypes and alcohol dependence, and its association with psychopathic traits in alcohol-dependent patients (Ponce et al., 2008; Swagell et al., 2012; Voisey et al., 2012), the interaction of these 2 polymorphisms on brain activity and cognition has not been addressed. The C957T polymorphism is in high linkage disequilibrium with Taq1A (Duan et al., 2003; Hill et al., 2008), suggesting dependence of these polymorphisms. It is therefore of special interest to investigate the additive effects of these 2 polymorphisms on WM and WM-related brain activity.

Here we examine the relationship of age and *DRD2* gene polymorphisms to WM performance and WM-related activity in the dorsolateral frontostriatal network. Participants were scanned with fMRI while performing a WM task that included 3 conditions: manipulation, maintenance, and control. This particular task has been associated with activation in both DLPFC (Nyberg et al., 2014; Pudas et al., 2009) and caudate (Pudas et al., 2009) for the manipulation compared with the maintenance condition. Using an exploratory whole-brain analysis, Nyberg et al. (2014) identified DLPFC as an age-sensitive region in the current task showing that older adults had reduced DLPFC activity in the more demanding manipulation condition. Using the same participants and task, we focus on the age-related differences in caudate activation. We also investigated the single and additive effects of the 2 *DRD2* polymorphisms on brain volumes to examine whether volumetric differences between beneficial and nonbeneficial genotype groups contribute to the genetic effect on brain activation and WM performance. Given our particular interest in DLPFC and caudate activity, we use a region-of-interest approach to examine the relationship of age and *DRD2* polymorphisms on WM-related brain activation in these specific regions.

2. Methods

2.1. Participants

The initial sample consisted of 373 participants from a longitudinal population-based study, the Betula project. In this project, cognitive assessments were completed at 6 separate measurement occasions using an age-homogeneous, narrow age cohort design, where chronological age was held constant within each cohort (i.e., participants were, e.g., tested at ages 35, 40, 45 etc.). The purpose of the narrow age cohort design is to minimize the age heterogeneity and decrease the confounding effect introduced by cohort effects, such as schooling, economic level, and so on (Sternäng et al., 2008). Before imaging analyses, a total of 54 participants were excluded from the original sample for the following reasons: problems with visual acuity ($n = 1$), neurological conditions or dementia ($n = 14$), Mini-Mental State Examination (Folstein et al., 1975) < 24 ($n = 3$), missing behavioral data or performance at chance level ($n = 26$),

Table 1
Demographic and cognitive data across age groups

Demographic and cognitive data	25–35 y (n = 28)	40–50 y (n = 25)	55–65 y (n = 138)	70–80 y (n = 112)
Age[a]	29.82 (4.19)	45.20 (4.20)	59.86 (4.05)	73.44 (3.49)
Sex	13/15	12/13	66/72	46/66
Education[a]	15.50 (2.64)	14.26 (2.83)	14.10 (3.52)	10.84 (4.06)
MMSE	28.54 (1.29)	28.56 (1.29)	28.30 (1.38)	28.03 (1.52)
Fluid intelligence[a]	37.25 (7.64)	37.16 (7.30)	31.86 (8.58)	24.91 (8.55)
Verbal fluency	23.00 (6.80)	20.92 (7.33)	25.37 (7.36)	23.69 (8.35)
Processing speed[a]	36.04 (8.45)	37.20 (6.25)	32.63 (6.12)	26.10 (6.01)
WM (2-back)[a]	35.50 (3.25)	35.52 (2.89)	33.14 (3.15)	30.48 (4.65)
Episodic memory[a]	46.61 (8.43)	41.16 (8.76)	43.25 (7.90)	35.95 (8.32)
WM manipulation, accuracy[a]	16.89 (0.88)	16.76 (1.17)	15.88 (1.94)	13.96 (3.09)
WM maintenance, accuracy[a]	17.64 (0.68)	17.64 (0.64)	17.20 (1.28)	16.62 (1.59)
WM control, accuracy	17.82 (0.48)	17.80 (0.41)	17.60 (0.72)	17.34 (1.11)

Values represent the number of participants for sex and means (standard deviations) for all other variables.
Key: MMSE, Mini-Mental State Examination; WM, working memory.
[a] $p < 0.05$.

technical problems (n = 6), and measurement artifacts (n = 4). The final sample of 319 participants had all completed a ~2-h cognitive assessment. Genotyping data were missing for 16 participants, leaving 303 participants (age range = 25–80 years; mean age = 60.89 years) for the genetic analyses. To retain the diversity of the sample, exclusions were not made for handedness, diabetes, hypertension, mild depressive symptoms, and other moderately severe medical conditions, which are common among the elderly. The number of participants in each age and genotype group, along with demographics and cognitive performance for each group, are shown in Tables 1 and 2. The study was approved by the Regional Ethical Review Board in Umeå, Sweden. All participants provided signed written informed consent before testing.

2.2. MRI acquisition

Participants were scanned with a 32-channel phased array receiving head coil (Discovery MR750 3.0T scanner, General Electric). T1-weighted 3D SPGR images were obtained (TR: 8.2 ms, TE: 3.2 ms, field of view: 25 cm, 176 axial slices, flip angle of 12°). Task-related fMRI data were acquired using a gradient-echo-planar imaging sequence with the following scanner parameters: repetition time = 2000 ms, echo time = 30 ms, flip angle = 80°, field of view = 25 cm. Thirty-seven transaxial slices with a thickness of 3.4 mm (0.5 mm gap) were acquired. Ten initial dummy scans were collected to allow for the fMRI signal to reach equilibrium. The stimuli were presented on a computer screen seen through a tilted mirror. E-Prime (Psychology Software Tools, Inc, Pittsburgh, PA) was used for stimulus presentation and recordings.

2.3. Preprocessing

All fMRI data were preprocessed using the statistical parametric mapping software (SPM12; Wellcome Department of Cognitive Neurology, London, U.K.) implemented in MATLAB 7.13 (MathWorks, Inc, Natick, MA). An in-house developed software (DataZ) was used for batching and visualization of statistical maps and BOLD signal changes. Before analysis, the data were preprocessed in the following way: slice timing correction, movement correction by unwarping and realignment to the first image of each volume, normalization to a sample-specific template using DARTEL (Ashburner, 2007) and affine alignment to Montreal Neurological Institute standard space, and smoothing with an 8-mm FWHM Gaussian kernel. The final voxel size was 2 × 2 × 2 mm.

2.4. WM task for functional MRI

The fMRI task was presented in a blocked design and has been described in detail elsewhere (Nyberg et al., 2014; Pudas et al., 2009). In short, the task included 3 conditions: manipulation, maintenance, and control (Fig. 1). Each block consisted of 3 stimulus presentations of the same condition and lasted for 27 seconds. In

Table 2
Demographic and cognitive data for different genotype groups of the *DRD2/ANKK1*-Taq1A and *DRD2*-C957T polymorphisms

Demographic and cognitive data	*DRD2/ANKK1*-Taq1A		*DRD2*-C957T	
	Any A (n = 107)	GG (n = 196)	Any T (n = 209)	CC (n = 94)
Age	59.86 (14.43)	61.45 (13.05)	60.60 (14.04)	61.54 (12.44)
Sex	54/53	83/113	99/110	38/56
Education	12.86 (3.79)	13.16 (4.09)	12.99 (4.02)	13.18 (3.93)
MMSE	28.23 (1.36)	28.24 (1.46)	28.19 (1.43)	28.36 (1.40)
Fluid intelligence	31.38 (9.73)	29.59 (9.31)	30.22 (9.64)	30.23 (9.18)
Verbal fluency	23.59 (7.36)	24.47 (7.98)	23.61 (7.41)	25.38 (8.42)
Processing speed	31.81 (8.07)	30.44 (7.08)	31.16 (7.56)	30.40 (7.26)
WM (2-back)[a]	32.84 (4.39)	32.42 (4.03)	32.93 (4.00)	31.77 (4.42)
Episodic memory	41.05 (8.64)	40.83 (9.03)	40.82 (8.94)	41.09 (8.80)
WM manipulation, accuracy[b]	15.24 (2.66)	15.39 (2.53)	15.19 (2.65)	15.67 (2.37)
WM maintenance, accuracy	17.01 (1.59)	17.09 (1.24)	17.06 (1.43)	17.07 (1.26)
WM control, accuracy	17.50 (1.06)	17.57 (0.75)	17.56 (0.90)	17.51 (0.79)

Values represent the number of participants for sex and means (standard deviations) for all other variables.
Key: MMSE, Mini-Mental State Examination; WM, working memory.
[a] Bonferroni corrected $p = 0.12$ for the difference between the any T and CC groups.
[b] $p = 0.039$ for pairwise comparison for the difference between the any T and CC groups.

the control condition, participants were shown 4 identical target letters for 2 seconds, followed by a fixation star for 3.5 seconds and a probe letter with a question mark for 2.5 seconds. Participants were asked to keep the target letter in memory and to decide whether it was the same as the probe letter. The maintenance condition was similar to the control condition, but involved 4 different letters as targets. In the manipulation condition, participants were shown 2 target letters and were instructed to generate and keep the subsequent letters in the alphabet in memory. After fixation, participants were asked to respond as to whether the probe letter was the subsequent letter to any of the 2 target letters in the alphabet. Participants were instructed to give a response for each item. Target letters were presented in lower case and probe letters in capital letters to minimize memorization purely based on visual representation. There were 6 blocks each of the maintenance, manipulation, and control conditions, presented in a randomized order. The experiment lasted for about 10 minutes and comprised a total of 290 whole-brain acquisitions.

2.5. Genotyping

Genotyping of *DRD2* was performed on the same platform as described previously (Kauppi et al., 2011). Primers for PCR amplification were designed using the Sequenom MassARRAY System Designer software and are available on request. Participants with a sample call rate of <0.9 (MIND 0.10) or indications of genotyping errors were excluded. The frequencies of the *DRD2/ANKK1*-Taq1A genotypes were 4.3% AA, 31% AG and 64.7% GG. For the C957T polymorphism, genotype frequencies were 31% CC, 52.1% CT, and 16.8% TT. The genotype distributions for both polymorphisms did not deviate from Hardy–Weinberg equilibrium ($p = 0.21$ and 0.49, respectively). The linkage disequilibrium, D′, between these 2 polymorphisms is 0.84.

2.6. Offline cognitive tasks

All participants underwent a series of offline cognitive tests, including block design, verbal fluency, letter-digit substitution, 2-back, and episodic memory, which are described in the following.

2.6.1. Fluid intelligence

Fluid intelligence was measured using the block design task. In this task, subjects need to rearrange a set of white and red blocks so that they can form a pattern given by the experimenter. The allowed time for each pattern depends on the number of blocks. The block design task is a subtest of the Wechsler Adult Intelligence Scale (Wechsler, 1981).

2.6.2. Verbal fluency

The verbal fluency score was the average score of 3 verbal fluency tasks, in which participants were asked to generate as many words as possible during one minute according to different instructions. The first task was to generate words beginning with the letter A. The second task was to generate as many words as possible with 5 letters beginning with the letter M. The third task was to name as many professions as possible starting with the letter B.

2.6.3. Processing speed

Processing speed was measured using a composite score of 3 tests. The first test was letter-digit substitution in which participants are required to pair letters with digits according to a letter-digit transformation key, which was given on the top of the paper form. The score was the number of correct digits that the participant managed to fill in during 1 minute (maximum = 125). The second measure was pattern comparison, in which participants were instructed to compare pairs of abstract line figures during 30 seconds (maximum = 30). Finally, a letter comparison test was used where participants were asked to compare pairs of nonword strings of 3–9 letters, judging whether they were the same or different. The score was the number of correctly judged pairs during 30 seconds (maximum = 21).

2.6.4. Working memory

WM was measured using a 2-back task. Words were presented one at a time continuously on a computer screen. Each word was presented for 2.5 seconds with a 2 seconds interstimulus interval. Participants were instructed to decide whether the currently presented word was the same as the one presented 2 words earlier. The task includes 40 test words, of which 9 were target items. The 2-back task requires constant updating.

2.6.5. Episodic memory

Episodic memory was measured using a composite score from 5 tasks (maximum = 76; Josefsson et al., 2012): (1) Immediately after presentation of 16 verbal commands that were enacted by the participants, they were requested to recall as many of them orally, in any order. (2) In a second condition, participants were asked to study the commands without enactment. Number of sentences recalled (correct verb and noun) in the enacted and nonenacted conditions were used in the present analysis. (3 & 4) After a brief retention interval, participants were asked to recall as many nouns as possible from the sentences described earlier. The 4 categories to which each noun belonged served as cues to remember the nouns. Number of nouns recalled from the enacted and nonenacted sentences served as separate measures. (5) Participants were presented auditorily with a list of 12 common

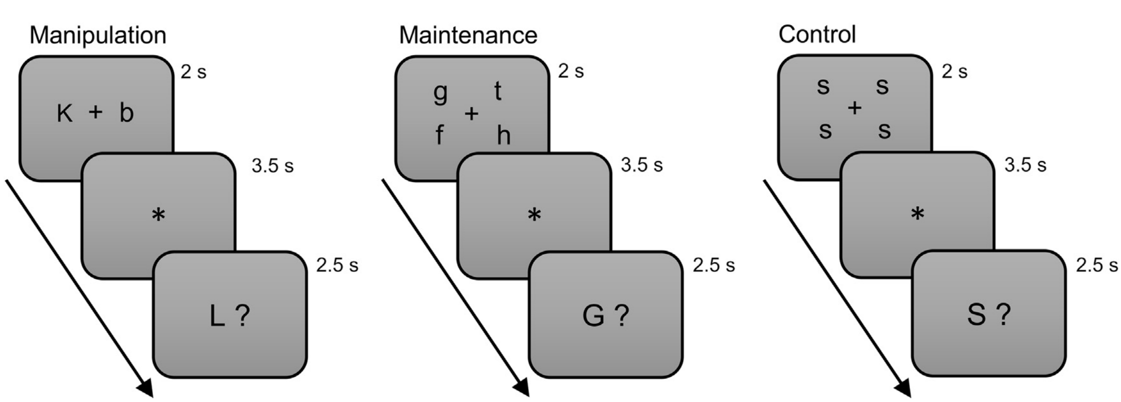

Fig. 1. Schematic overview of the fMRI working memory (WM) task.

unrelated nouns and instructed to learn these words for an immediate free recall test.

2.7. Behavioral data analysis

To investigate the effect of age on WM performance, we included 16 individuals without genetic data and separated the whole sample into 4 age groups with 10-year intervals (25–35 years, n = 28; 40–50 years, n = 25; 55–65 years, n =146; and 70–80 years, n = 120). Two participants were excluded due to missing data on educational level. First, we investigated the effects of age and WM condition on task performance using a 4 (age group) × 3 (condition: manipulation, maintenance, control) repeated-measures ANCOVA, controlling for sex and education. There was a significant main effect of age [$F(3, 311) = 8.75$, $p < 0.001$] and an age × condition interaction [$F(4.45, 461.01) = 5.88$, $p < 0.001$]. Follow-up tests revealed that WM performance was significantly worse in the oldest age group (70–80 years) compared with the other age groups in the manipulation condition (Bonferroni corrected $p < 0.005$). The remaining 3 groups did not differ reliably (Bonferroni corrected p values >0.05). The interaction reflected the fact that the age effect in the manipulation condition was larger than that in the maintenance condition [$F(3, 311) = 4.76$, $p < 0.005$]. No age effect was observed in the maintenance or control conditions (Bonferroni corrected p values >0.05). Because of the finding that oldest age groups had worse performance along with the lack of significant performance differences between the other 3 age groups, we divided participants into 2 age groups: a younger group (25–65 years) and an older group (70+ years) for all subsequent behavioral and fMRI analyses.

We then examined the interaction of age and genes in WM performance. This was performed by conducting 3 separate 2 (age group) × 2 (genetic group) × 3 (condition: manipulation, maintenance, control) repeated-measures ANCOVAs for each of the 2 genetic polymorphisms and their combination. Sex and education were included as covariates. In addition, we investigated the genetic effects on cognitive performance in the other tasks included in the Betula cognitive battery, using independent t-tests with Bonferroni corrected p values reported.

2.8. fMRI data analysis

The first-level analysis was performed separately for each scan, and a general linear model was set up to include regressors for each condition, convolved with a canonical hemodynamic response function. The manipulation-maintenance contrast for each participant was entered into a random-effects group analysis.

In the group-level analysis, we first investigated single-gene effects, the main effect of age and their interactions on brain activation by conducting a 2 (age) × 2 (gene) ANOVA for each of the 2 *DRD2* polymorphisms. Because the A allele was associated with lower striatal DA availability, for the analysis of the *DRD2/ANKK1*-Taq1A polymorphism, G/G participants were considered as the beneficial gene group; the A/A and A/G genotypes were considered nonbeneficial. For the *DRD2*-C957T polymorphism, C/C carriers were compared with C/T and T/T carriers. As the C allele is associated with greater frontal DA availability, and the T allele is linked to greater striatal DA binding, we did not classify these 2 groups as beneficial or nonbeneficial.

The effects of the combined genes and the interaction with age on brain activity were examined by means of a 2 (age) × 2 (gene group) ANOVA. As both the T allele of *DRD2*-C957T and the G allele of *DRD2/ANKK1*-Taq1A have been associated with higher striatal DA binding potential, we coded any T in combination with any G carriers as the beneficial group. Demographic data, cognitive performance, and allelic distributions of the combinations of the 2 polymorphisms are shown in Table 3.

Table 3
Demographic and cognitive data for the combined genotype groups of the *DRD2/ANKK1*-Taq1A and *DRD2*-C957T polymorphisms

Demographic and cognitive data	AA or CC carriers	Any G and any T carriers
	(n = 107)	(n = 196)
Age	61.40 (12.59)	60.61 (14.07)
Sex	47/60	90/106
Education	13.15 (3.88)	13.00 (4.05)
MMSE	28.34 (1.35)	28.19 (1.46)
Fluid intelligence	30.37 (9.41)	30.14 (9.54)
Verbal fluency	25.04 (8.08)	23.68 (7.57)
Processing speed	30.35 (7.40)	31.24 (7.50)
WM (2-back)[a]	31.52 (4.75)	33.14 (3.69)
Episodic memory	40.76 (8.75)	40.98 (8.97)
WM manipulation, accuracy	15.57 (2.42)	15.21 (2.65)
WM maintenance, accuracy	17.04 (1.33)	17.08 (1.40)
WM control, accuracy	17.49 (0.88)	17.57 (0.86)

Values represent the number of participants for sex and means (standard deviations) for all other variables.
Key: MMSE, Mini-Mental State Examination; WM, working memory.
[a] Bonferroni corrected $p = 0.005$.

For all ANOVAs, we first set an uncorrected $p < 0.005$, with a 10-voxel extent threshold, as recommended by Lieberman et al. for the whole brain. Given our hypothesis regarding DLPFC and caudate involvement, the threshold applied here would be more sensitive in detecting small genetic effects and provides an adequate balance between type-I and type-II errors (Lieberman and Cunningham, 2009). The retained suprathreshold voxels were small-volume corrected using a 6 mm radius sphere around the peak coordinates of caudate and DLPFC. Results that survived a peak-level familywise error (FWE) threshold of $p < 0.05$ were considered as significant. We inspected the main effects of age and genotype, along with their interactions. If the interactions were significant, t-tests were performed for each of the 2 age groups to compare the genetic effects in younger and older adults.

To examine brain regions associated with WM performance, we conducted a multiple linear regression with WM accuracy for the manipulation condition as independent variable, and the contrasts between manipulation and maintenance as dependent variable across the whole sample. Results that survived a cluster-level FWE-corrected threshold of $p < 0.05$ were considered as significant.

2.9. Volumetric measurements

T1-weighted MR images were segmented into gray matter, white matter, and cerebrospinal fluid using the unified segmentation approach (Ashburner, 2007) in SPM12b (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/) implemented in MATLAB 10 (The MathWorks, Inc). The "light cleanup" option was used to remove odd voxels from the segments. Volumes of bilateral caudate and DLPFC (including Brodmann area 8 and 9) were extracted using masks defined by the Automated Anatomical Labeling atlas, and the Brodmann anatomical template as implemented in the WFU_pickatlas. We used intracranial volume (ICV) to adjust volumetric data based on the analysis of covariance approach: adjusted volume = raw volume × b (ICV−mean ICV), where b is the slope of regression of volume on ICV (Jack et al., 1989; Raz et al., 2005).

3. Results

3.1. Behavioral data

3.1.1. Performance on the fMRI WM task

A repeated-measures ANOVA for *DRD2/ANKK1*-Taq1A showed significant main effects of age [younger adults > older adults; F (1,

296) = 16.49, $p < 0.001$], and of condition [manipulation < maintenance < control; F (1.48, 439.09) = 71.02, $p < 0.001$]. A significant age by condition interaction [F (1.48, 439.09) = 14.04, $p < 0.001$] reflected that the age effect was largest in the most difficult manipulation condition compared with the maintenance and control conditions. Follow-up comparisons showed that the effect of age was significant for all 3 conditions (manipulation: $p < 0.001$; maintenance: $p = 0.005$; control: $p = 0.032$). No other main effects or interactions were significant (all p values >0.05).

Similarly, the 2 other ANOVAs for *DRD2*/C957T and the combination of *DRD2/ANKK1*-Taq1A and *DRD2*/C957T revealed main effects of age (younger adults > older adults; p values <0.001), and of condition, and an age by condition interaction (p values <0.001), but no genetic effect or any gene by age interaction. For illustrative purposes, we plotted only the age effect on WM performance shown in Fig. 2A.

Because age did not interact with genotype, we included age as a covariate in subsequent behavioral data analyses to examine effects of genotype on WM performance using 2 (gene group) × 3 (condition) ANOVAs for each polymorphism separately and for the gene combination. Only the main effects of gene and the gene by condition interactions are reported here. For the *DRD2/ANKK1-Taq1A* polymorphism, the main effect of gene and the gene by condition interaction were nonsignificant (all Bonferroni corrected p-values > 0.1; Table 2). For the *DRD2*-C957T polymorphism, the main effect of gene group was not significant (all Bonferroni corrected p-values > 0.1; Table 2). However, the gene × condition interaction was significant [F (2, 441.06) = 3.801, $p = 0.035$]: CC carriers performed significantly better on the WM task compared with T carriers, and this effect was significant in the manipulation ($p = 0.039$), but not in maintenance ($p > 0.1$) or control ($p > 0.1$) conditions (Table 2). For the analyses of the combined gene score, we did not find any significant main effects or interactions for WM performance ($p > 0.05$; Table 3).

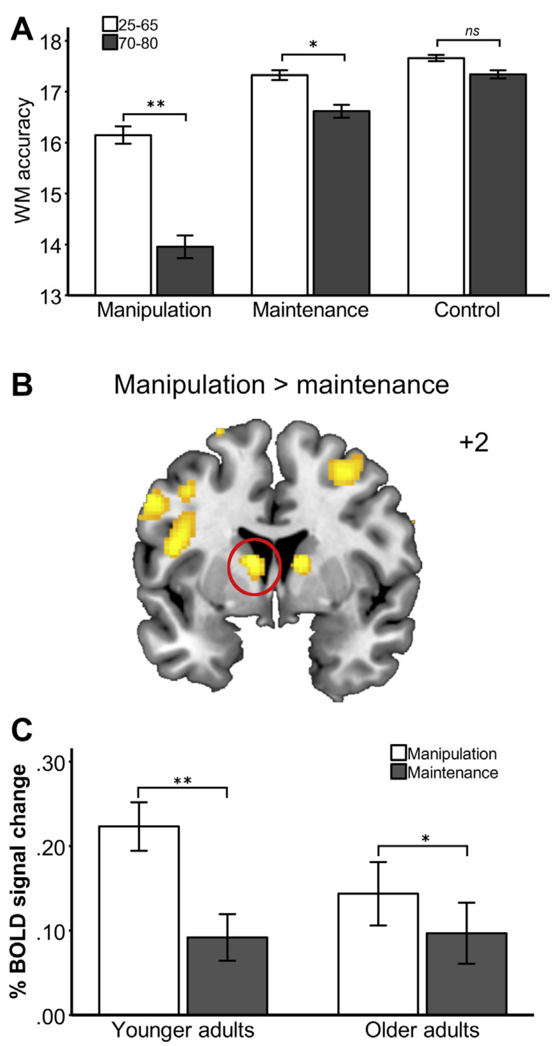

Fig. 2. Age differences in WM accuracy (A) and left caudate BOLD signal (B, C). Percentage BOLD signal change is derived from local maxima of left caudate (x y z = -10 -2 12). Error bars show standard error of the means. $^{**}p < 0.001$, $^{*}p < 0.05$. Abbreviations: WM, working memory; BOLD, blood oxygen level–dependent.

3.1.2. The effect of the DRD2 gene polymorphisms in other cognitive tasks

For the single-gene analysis on the Taq1A polymorphism, there were no differences between A carriers and noncarriers in any of the cognitive tasks. However, there was a trend of better performance on the 2-back WM task for the C957T polymorphism, with T carriers, who have higher DA availability in striatum, performing slightly better than CC carriers (Bonferroni corrected $p = 0.12$). For the combined gene analysis, G and T carriers (striatally associated beneficial gene combination) had significantly better 2-back performance than AA-CC carriers (Bonferroni corrected $p = 0.005$).

3.2. fMRI data

3.2.1. Single-gene analysis

Results from the ANOVAs on the *DRD2*-C957T polymorphism revealed a significant effect of age on caudate activity (x y z = -10 -2 12, k = 93, T = 3.50, SVC $P^{FWE\text{-}peak\ level} = 0.005$). Fig. 2B shows the location of the age effect and Fig. 2C illustrates the % BOLD signal change in this cluster. If we lower the initial threshold to an uncorrected level of $p < 0.01$, we found the main effect of age on caudate activity in the same cluster from the ANOVA for *DRD2/ANKK1*-Taq1A (x y z = -10 -4 12, k = 32, T = 2.69, SVC $P^{FWE\text{-}peak\ level} = 0.041$).

The main effect of gene and the age by gene interaction for the *DRD2/ANKK1*-Taq1A polymorphism were both nonsignificant. However, for the C957T polymorphism, there was a reliable age × gene interaction in right DLPFC (x y z = 32 48 38, k = 18, T = 2.91, SVC $P^{FWE\text{-}peak\ level} = 0.025$). Although older C allele carriers showed more activity in this region compared with noncarriers (x y z = 32 48 38, k = 10, T = 2.74, SVC $P^{FWE\text{-}peak\ level} = 0.038$), this effect was not observed in the younger age group (Fig. 3).

3.2.2. Combined gene analysis

We found significant main effects of age (x y z = -10 -2 12, k = 100, T = 3.65, SVC $P^{FWE\text{-}peak\ level} = 0.003$), and of gene (x y z = -6 4 18, k = 116, T = 4.12, SVC $P^{FWE\text{-}peak\ level} = 0.001$), along with a significant age × gene interaction for left caudate activity (x y z = -10 2 18, k = 80, T = 3.22, SVC $P^{FWE\text{-}peak\ level} = 0.012$). Critically, follow-up analyses showed that brain activity in left caudate differed between beneficial and nonbeneficial carriers in the older group (x y z = -10 4 18, k = 119, T = 4.11, SVC $P^{FWE\text{-}peak\ level} = 0.001$), but not in the younger group (Fig. 4). The findings reported in the aforementioned combined-genetic analysis (i.e., main effect of gene, age × gene interaction, and simple genetic effect in older adults) also survived after a whole-brain cluster-level FWE correction ($p < 0.05$) with an initial voxel-level threshold of $p < 0.001$ (uncorrected).

3.3. Correlational analysis

To examine whether activation in frontostriatal regions were related to WM performance, we performed a multiple regression

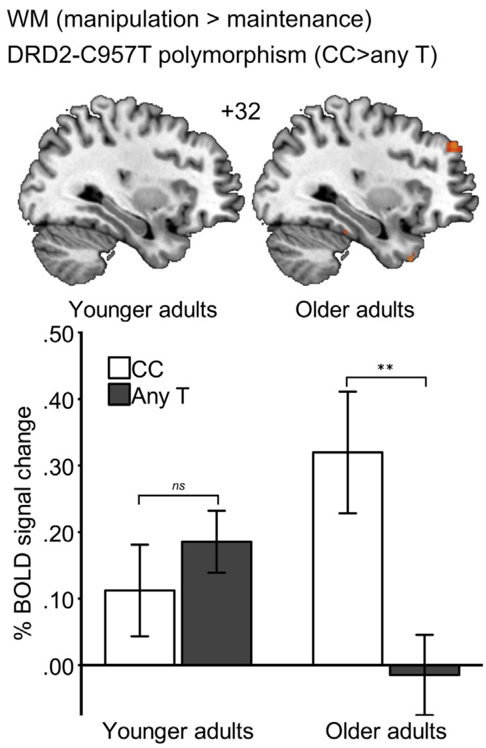

Fig. 3. Bar graph and brain regions showing the effects of the *DRD2*-C957T polymorphism (CC > any T) in the younger and older groups on cortical BOLD activity during WM (manipulation-maintenance). Percentage BOLD signal change is derived from local maxima of right DLPFC (x y z = 32 48 38). Abbreviations: WM, working memory; BOLD, blood oxygen level–dependent; DLPFC, dorsolateral prefrontal cortex. $^{**}p < 0.001$.

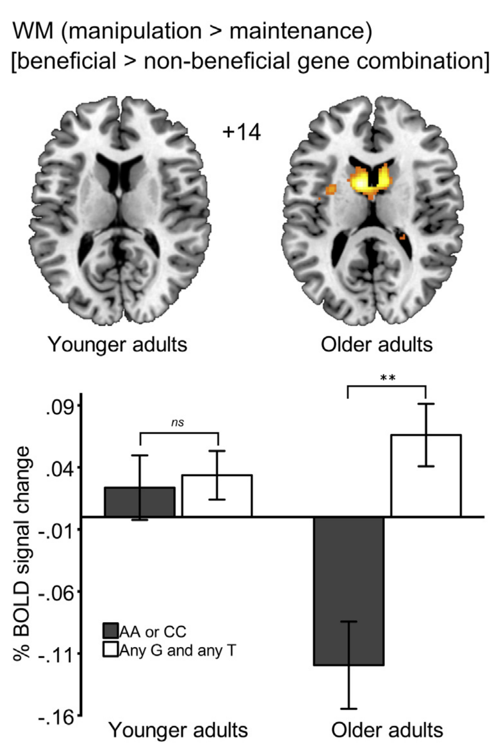

Fig. 4. Bar graph and brain regions showing the additive effect of 2 *DRD2* polymorphisms on striatal BOLD activity in younger and older groups during WM (manipulation-maintenance). Percentage BOLD signal change is derived from local maxima of left caudate (x y z = -10 4 18). Abbreviations: WM, working memory; BOLD, blood oxygen level–dependent. $^{**}p < 0.001$.

analysis. As shown in Fig. 5, this analysis revealed a significant relationship between brain activation and WM manipulation accuracy. The identified brain areas included left (x y z = -36 -46 34, T = 7.05; x y z = -28 -70 40, T = 6.73; x y z = -6 -70 54, T = 6.73. $P^{FWE\text{-}cluster\ level} < 0.001$) and right (x y z = 36 -44 36 T = 5.26, $P^{FWE\text{-}cluster\ level} < 0.005$) parietal lobe, left DLPFC (x y z = -38 26 22 T = 6.63, $P^{FWE\text{-}cluster\ level} < 0.001$), and dorsomedial PFC (x y z = 6 20 46 T = 6.57; x y z = -4 14 46 T = 6.02, $P^{FWE\text{-}cluster\ level} < 0.001$). Activation in left caudate (x y z = 14 -4 10 T = 4.79, $P^{FWE\text{-}cluster\ level} < 0.05$) was demonstrated, using an uncorrected threshold of $p < 0.001$.

3.4. Volumetric data

Volumetric data analysis showed a main effect of age on volume of all region of interest, with older individuals having significantly smaller regional brain volumes bilaterally compared with younger persons (all p values <0.001). No main effects of gene and interactions were significant (all p values >0.1). There were no significant correlations between volumes of any brain region and WM accuracy (all p values >0.1).

4. Discussion

The current results demonstrated that participants in the older age group (70–80 years) had poorer WM performance compared with the younger age group (25–65 years), and this deficit was specific to the manipulation condition. Furthermore, brain activity in caudate nucleus during WM manipulation was lower in the older group. Importantly, for the first time, we found that 2 polymorphisms of the *DRD2* and *DRD2/ANKK1* genes, which have been related to DA D2 receptor densities in PFC or striatum, were associated with WM performance and frontostriatal activity. Brain activity in this network was related to WM performance. Genotypes associated with higher DA signaling were beneficial to WM performance and related to greater brain activity. Finally, we observed magnified genetic effects on brain activity in aging, which is consistent with the resource-modulation hypothesis (Lindenberger et al., 2008).

First, we showed that modulation of striatal activity during manipulation was reduced in older compared with younger adults. There is evidence for reduced positive (Kennedy et al., 2017; Rieck et al., 2017) and negative (Kennedy et al., 2017; Park, 2010; Persson et al., 2007; Turner and Spreng, 2015) task modulation with increasing age. However, studies on age-related reduction in positive BOLD modulation to parametrically increasing task difficulty have typically focused on frontal regions, with striatal regions receiving less attention. The current observation adds new evidence to these findings by showing a reduced age-related range of modulation of striatal response by WM task demands. There are data indicating that maintaining a greater dynamic range of brain activation underlies efficient task performance (Kennedy et al., 2017), and deficits in this ability may serve as a marker for age-related cognitive impairment. However, it should be noted that the age range for the younger group (25–65 years) in the present study was wider and therefore atypical relative to most other aging studies. Previous cross-sectional studies commonly assessed age differences by using either extreme age groups (younger adults and older adults), or by including participants from the entire adult age range. While participants were sampled from the entire adult age range also in the present study, because WM performance was found significantly worse only in the oldest age group (70–80 years), we combined all other groups into a younger age group to increase statistical power. Our results regarding the age differences on striatal activity should be considered within the context of

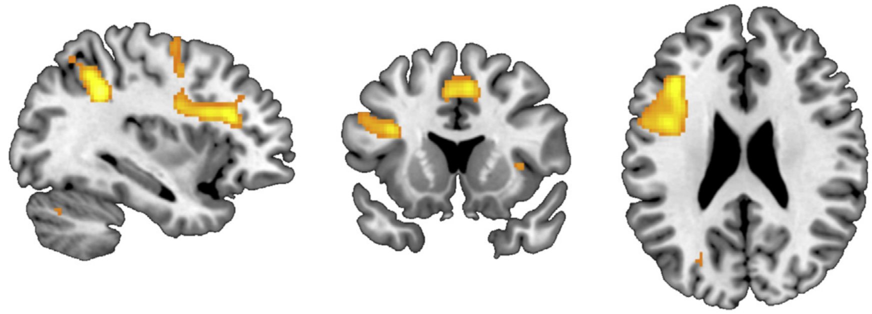

Fig. 5. Regression analysis revealed positive correlation between brain activity in parietal lobe, dorsolateral, and dorsomedial PFC and WM performance in manipulation condition. Abbreviations: PFC, prefrontal cortex; WM, working memory. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

comparisons between older adults in 70–80 years and all other adults under 70 years.

The behavioral results showed that the C957T polymorphism was associated with WM performance, but that the associations differed across different WM tasks. C carriers performed better than T carriers in the fMRI WM task, especially in the most demanding condition, whereas carriers of the T allele performed better in the offline 2-back task. These results are consistent with the notion that a balance of DA signaling between PFC and striatum is critical for WM performance. In particular, PFC DA has been more associated with keeping stable memory representations (Brozoski et al., 1979; Durstewitz et al., 2000; Phillips, 2004), whereas striatal DA has been more linked to flexible updating (Bäckman et al., 2011; Dodds et al., 2009; Frank et al., 2001; Frank and Reilly, 2006; Kellendonk et al., 2006; Mehta et al., 2004; Nyberg et al., 2009; Stelzel et al., 2010). For the in-scanner WM task, manipulation of WM representations, compared with maintenance, was related to increased brain activation in both DLPFC and caudate nucleus (Nyberg et al., 2014; Pudas et al., 2009), suggesting that the manipulation condition relies on both cognitive stability and flexibility. Indeed, the manipulation condition requires not only WM updating, but also unbinding of no longer relevant information, and maintaining stable representations of this updated information in the face of distraction from no longer relevant information. It has been shown that C957TC carriers have higher DA D2 BP throughout neocortex (Hirvonen et al., 2009), and therefore their better performance during the fMRI WM task might reflect a larger influence of PFC DA functioning in this task. In comparison, performance on the offline 2-back task relies more on memory updating. The C957TT and *ANKK1* G alleles are associated with higher caudate DA D2 BP (Hirvonen et al., 2004; Jönsson et al., 1999; Pohjalainen et al., 1998; Smith et al., 2017; Thompson et al., 1997). This might contribute to our finding that carriers of their combination had better performance in the offline 2-back task.

In addition to the effect of *DRD2* polymorphisms on WM performance, we found that the C957T polymorphism, in combination with Taq1A, was selectively linked to the WM-related BOLD response in specific brain regions. C carriers exhibited stronger brain activity than T carriers in DLPFC, whereas carriers of the T (C957T) combined with the G (*DRD2/ANKK1*-Taq1A) allele activated the caudate nucleus to a larger extent compared with noncarriers of these alleles. Although the present study cannot address the underlying mechanisms of these gene-related differences in brain function, one possibility is that they are linked to individual differences in frontostriatal DA availability. Consistent with this explanation, a pharmacological fMRI study has revealed that the DA D2 receptor agonist bromocriptine can modulate striatal activity during task switching, but does not seem to affect processes related to distraction from irrelevant information in WM. By contrast, this agonist has been shown to modulate PFC activity during distraction, but not during task-switching (Cools et al., 2007). In line with these findings, the current results suggest that frontostriatal involvement in cognitive flexibility and stability may be differentially modulated by PFC and striatal DA systems. Other studies directly link DA measurement with brain imaging data showing that brain activity was influenced by DA function in the same region. For example, reward-induced DA release in nucleus accumbens is associated with increased BOLD signal in this particular region (Knutson and Gibbs, 2007). This view is also supported by training studies showing that WM updating training can increase caudate BOLD response (Dahlin et al., 2008), as well as DA release in caudate (Bäckman et al., 2011). Salami et al. (2018) found a DA-BOLD association in both striatal and extrastriatal brain regions during WM performance, especially under highly demanding conditions. Consistent with these findings, our genetic data provide indirect evidence for a relationship of DA availability in PFC and striatum to functional brain activity in these regions during WM performance.

The link between DA and local BOLD activity has also been supported by several other genetic imaging studies. For example, Persson et al. (2015) found that older A allele carriers of the *DRD2/ANKK1*-Taq1A polymorphism performed worse on a memory updating task and had a corresponding reduction in left caudate BOLD activation compared with noncarriers. An association between the COMT gene, which has been related to prefrontal DA D1 receptor availability, BOLD response in prefrontal regions, and WM performance has also been observed (Nyberg et al., 2014). However, note that, in our study, the effect size of the C957T polymorphism on DLPFC activation was relatively small. This may reflect the relatively sparse distribution of DA D2 receptors in cortical and limbic areas compared with striatum.

The exact roles of PFC and striatum in WM still remain unclear. However, extant findings suggest that PFC is more associated with maintaining stable representations in WM (Chee, 2004; Curtis and D'Esposito, 2003; Rypma and D'Esposito, 2000), whereas striatum is key region in dynamic updating and switching mechanisms (Aron et al., 2003; Cools et al., 2004; Dahlin et al., 2008; Lewis et al., 2004; O'Reilly and Frank, 2006). Computational work reveals that PFC maintains current goal-relevant information in the face of distraction, until basal ganglia sends updating or shifting signals, which enables PFC to rapidly update new representations at the appropriate time (Frank et al., 2001; O'Reilly, 2006; O'Reilly and Frank, 2006). It is possible that DA function in PFC and striatum may modulate this WM maintaining/updating mechanism through its influence on frontostriatal brain activity during WM. Because there is no measurement of DA signaling in the present study, we cannot test the correlative triad among DA, frontostriatal network, and WM performance. Future studies with both PET-derived DA data and WM-related fMRI data are needed to fully address the contributions of PFC and striatal DA systems to WM.

BOLD signal analyses for the maintenance and manipulation conditions revealed a significant hypoactivation of the left caudate in older carriers of the nonbeneficial gene combination. The current observation of striatal hypoactivation in the caudate is supported by demonstrations of reduced striatal activation with increased task difficulty in individuals with limited brain resources, such as older compared with younger participants (Eppinger et al., 2018). These results suggest that when facing enhanced demands on a limited resource (DA availability), carriers of the nonbeneficial gene combination may default to using less efficient strategies that do not rely on the striatum to solve the task. Alternatively, it could be argued that independently of their cognitive control limitations, older nonbeneficial carriers may be less willing to engage in cognitively demanding WM processes, and this is why they show reduced recruitment of the striatum during the high-demanding manipulation condition. This interpretation is in line with evidence showing that, in addition to being implicated in higher-order cognitive functions, the striatum is linked to evaluation of effort-related cost-benefit decisions about the effort invested in a task and the value of persisting with a course of action given expected rewards (Croxson et al., 2009; Prévost et al., 2010; Treadway et al., 2012), and that the neurotransmitter DA significantly impacts cost/benefit decision-making (Wardle et al., 2011).

Volumetric data showed smaller caudate volume in older compared with younger adults, which was consistent with several studies (Gunning-Dixon et al., 1998; Papenberg et al., 2016; Raz et al., 2003, 2005; Taki et al., 2013). However, no genetic effects or interactions between age and genetic polymorphisms were found for brain volumes. This result indicates that the relationship between these particular *DRD2* genes and brain function was not confounded by structural alterations.

Some limitations need to be considered in interpreting our findings. First, the analyses are based on cross-sectional data, and therefore we cannot draw any conclusions as to how the genes examined relate to within-person changes in WM functions. Similarly, we analyzed differences between 2 groups carrying different genotypes, without allowing a temporal relationship to be examined, so our data cannot establish any causal influence of genes on cognition and brain functioning. Second, this study did not include a direct measure of DA system integrity, which prevents firm conclusions about the effect of age and the *DRD2/ANKK1*-TaqIA and *DRD2*-C957T polymorphisms on WM performance, and striatal BOLD response. Indeed, it has proven difficult to predict whether higher or lower DA levels results in increased or decreased brain activity (Bäckman et al., 2011; Braskie et al., 2008; Landau et al., 2009). For example, memory-related BOLD activation has been associated with both striatal D2 binding (Nyberg et al., 2009), and D1 binding potential (Rypma et al., 2015). In addition, changing DA availability by DA antagonists/agonists can modulate resting-state network efficiency (Achard and Bullmore, 2007), and task-related BOLD activation (Alavash et al., 2018). That said, our results revealed a positive link between genetic proxies of DA availability and regional BOLD response. The effects of the genetic variation in the present study were small. This is a common finding, as single polymorphisms typically have small effects on brain structure and function, as well as on cognitive performance (Colzato et al., 2013; Li et al., 2013, 2018; Papenberg et al., 2015; Persson et al., 2015). The candidate gene approach may be helpful in understanding the functional role of certain polymorphisms at neural and behavioral levels. However, owing to the small effect sizes of single polymorphisms, we set a relatively liberal threshold and conducted small-volume corrections to restrict our multiple comparisons within small regions of interests to minimize the volume tested; the results therefore should be interpreted with caution.

In conclusion, our study showed reduced dynamic striatal modulation in older adults, and also demonstrated that 2 polymorphisms of the *DRD2* and *DRD2/ANKK1* genes were associated with WM performance and WM-related frontostriatal brain activity. The current results also revealed a reliable interaction of age and gene by showing significant genetic effects only in older adults. The differential effects of the 2 alleles of C957T on cognition and brain activation might be related to different roles of striatal and cortical DA systems in 2 different WM components: cognitive stability and cognitive flexibility. The current results provide novel evidence pertaining to the roles of DA functions in PFC and striatum for brain integrity and WM and demonstrate a positive association between DA and WM-related BOLD responses in the frontostriatal brain circuitry.

Disclosure

The authors state that there are no actual or potential conflicts of interest associated with the research. Study participants provided written informed consent, and the protocol was approved by Ethical Review Board in Umeå. All authors have reviewed the contents of the article being submitted, approve of its contents and validate the accuracy of the data.

Acknowledgements

The authors thank Alireza Salami, Micael Andersson, and the staff at the Umeå Center for Functional Brain Imaging for collecting and preprocessing the imaging data. This work was supported by the Swedish Research Council [421-2013-1039] and Hjärnfonden [F02014-0224] to J.P. Grants from the Swedish Research Council supported the BETULA Project (Lars-Göran Nilsson and Lars Nyberg). L. B. was supported by grants from the Swedish Research Council for Health, Working Life, and Welfare; an Alexander von Humboldt Research Award; and a donation from the af Jochnick Foundation.

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