ELSEVIER

Neurobiology of Aging 32 (2011) 1849–1856

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Dopamine D_1 receptors and age differences in brain activation during working memory

Lars Bäckman [a,*], Sari Karlsson [a], Håkan Fischer [a], Per Karlsson [b], Yvonne Brehmer [a], Anna Rieckmann [a], Stuart W.S. MacDonald [a,c], Lars Farde [b], Lars Nyberg [d,e]

[a] *Aging Research Center, Karolinska Institutet, Gävlegatan 16, SE-113 30 Stockholm, Sweden*
[b] *Department of Clinical Neuroscience, Psychiatry Section, Karolinska Institutet, Stockholm, Sweden*
[c] *Department of Psychology, University of Victoria, Canada*
[d] *Department of Radiation Sciences, Umeå University, Sweden*
[e] *Department of Integrative Medical Biology, Umeå Center for Functional Brain Imaging, Umeå University, Sweden*

Received 2 April 2009; received in revised form 30 October 2009; accepted 31 October 2009
Available online 4 December 2009

Abstract

In an fMRI study, 20 younger and 20 healthy older adults were scanned while performing a spatial working-memory task under two levels of load. On a separate occasion, the same subjects underwent PET measurements using the radioligand [^{11}C] SCH23390 to determine dopamine D_1 receptor binding potential (BP) in caudate nucleus and dorsolateral prefrontal cortex (DLPFC). The fMRI study revealed a significant load modulation of brain activity (higher load > lower load) in frontal and parietal regions for younger, but not older, adults. The PET measurements showed marked age-related reductions of D_1 BP in caudate and DLPFC. Statistical control of caudate and DLPFC D_1 binding eliminated the age-related reduction in load-dependent BOLD signal in left frontal cortex, and attenuated greatly the reduction in right frontal and left parietal cortex. These findings suggest that age-related alterations in dopaminergic neurotransmission may contribute to underrecruitment of task-relevant brain regions during working-memory performance in old age.

Keywords: Aging; Dopamine; D_1 receptors; fMRI; Load-dependent BOLD response; Multimodal brain imaging; PET; Spatial working memory

1. Introduction

Age-related differences in brain activation during working-memory (WM) performance are legion (for reviews, see Buckner, 2004; Cabeza, 2002). A common finding is that normal older adults show less strong activity increase in fronto-parietal regions typically recruited by younger adults (e.g., Holtzer et al., 2009; Jonides et al., 2000; Reuter-Lorenz and Lustig, 2005). This underrecruitment in aging is magnified under conditions of higher load, indicating an age-related deficit in modulating neural activity in response to increasing cognitive demands (e.g., Mattay et al., 2006; Nyberg et al., 2009b; Rypma and D'Esposito, 2000).

One potential mechanism underlying age-related underactivation of the fronto-parietal WM network is less efficient dopaminergic neurotransmission (Nyberg and Bäckman, 2004; Bäckman et al., 2006). The importance of the dopamine (DA) systems for WM functions is well established in both animal (e.g., Arnsten, 1997; Sawaguchi and Goldman-Rakic, 1991; Vijayraghavan et al., 2007) and human (Erixon-Lindroth et al., 2005; Kimberg and D'Esposito, 2003; Luciana and Collins, 1997) research. In particular, studies on non-human primates (e.g., Wang et al., 2004; Williams and Goldman-Rakic, 1995) as well as recent human research (McNab et al., 2009; Takahashi et al., 2008) suggest that D_1 receptors are especially critical to WM and executive functioning.

* Corresponding author. Tel.: +46 8 6905826; fax: +46 8 6906889.
E-mail address: lars.backman.1@ki.se (L. Bäckman).

0197-4580/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.neurobiolaging.2009.10.018

Further, there is ample empirical evidence that both presynaptic DA markers, such as the DA transporter (Rinne et al., 1998; Van Dyck et al., 1995) and postsynaptic DA markers such as D_1 (Suhara et al., 1991; Wang et al., 1998) and D_2 (Antonini et al., 1993; Nordström et al., 1992) receptors deteriorate markedly from early to late adulthood. The average loss of DA markers from the 20 s through the 80 s has been estimated between 7% and 13% per decade in striatal and extrastriatal regions alike (see Bäckman and Farde, 2005; Bäckman et al., 2006; Li et al., 2009, for reviews).

It has been proposed that dopaminergic activity in ventral striatum modulates local blood flow (Knutson and Gibbs, 2007). In support of this assertion, Schott et al. (2008) found a sizeable relationship between a PET-derived marker of DA D_2 release in ventral striatum and the magnitude of the blood-oxygenation-level-dependent (BOLD) signal during reward-related learning. Other current work has extended this local striatal DA–BOLD association to more distal brain regions. Landau et al. (2009) reported a link between a measure of caudate DA synthesis capacity and load-dependent (high load > low load) BOLD response in left prefrontal cortex during a verbal WM task. Relatedly, Nyberg et al. (2009a) observed a relationship between a marker of caudate D_2 receptor density and frontal BOLD activity during a task that taxes updating of long-term memory representations. These distal relationships are consistent with models of dopaminergic influx to neocortical regions via the striato-thalamo-cortical pathway (e.g., Alexander et al., 1986; Sánchez-González et al., 2005).

In this study, we specifically tested the hypothesis that aging-related underrecruitment of fronto-parietal regions during WM performance is related to age-related DA losses. Younger and older adults underwent PET measurements with the radioligand [^{11}C] SCH23390 to determine D_1 receptor binding potential (BP; Farde et al., 1987). On a separate occasion, the same subjects took part in an fMRI study where a spatial WM task was administered during two conditions varying in memory load. Of chief interest was whether the predicted fronto-parietal underactivation of older adults during higher load could be empirically linked to age-related reductions in D_1 BP. D_1 receptor densities were quantified in the caudate nucleus and the dorsolateral prefrontal cortex (DLPFC). The caudate was selected because of previous reports of an association between caudate DA function and load-dependent frontal blood flow during WM (Landau et al., 2009), and the DLPFC region was selected because of (a) its strong involvement in WM functioning in general (Callicott et al., 1999; Curtis and D'Esposito, 2003; and (b) the fact that age-related differences in activation patterns during WM are routinely found there (e.g., Nyberg et al., 2009b; Rypma and D'Esposito, 2000). Given that two regions were targeted, an additional aim was to examine whether striatal vs. frontal DA losses contribute differentially to the reduced fronto-parietal BOLD signal during WM performance in aging.

2. Methods

2.1. Participants

Twenty younger (mean age = 25.2 years, range = 22–30; 10 male, 10 female) and 20 older (mean age = 70.3 years, range = 65–75; 10 male, 10 female) persons were recruited through a newspaper advertisement. Exclusion criteria included mental disorders, brain damage, other significant medical conditions, actual or previous drug or alcohol abuse, nicotine use, and hormone therapy. Vision was corrected to normal by means of MR-compatible glasses for participants normally wearing glasses. All participants were included in a larger study with several examinations, including (1) health screening and off-line cognitive testing; (2) resting state PET examination; (3) PET examination during performance of a cognitive task; (4) fMRI examination; (5) fMRI examination with a DA antagonist (younger participants only); and (6) pharmacological PET examination (five younger participants only), all performed on separate occasions. The whole study protocol was completed within 2 months. Participants were paid 4000–6000 SEK for their participation, depending on which examinations they took part in. This study includes data from examinations 1, 2, and 4. The 40 subjects in this study participated in all examinations, with the exception that only young subjects received the dopaminergic antagonist. Written informed consent was obtained from all participants, and the Ethics and Radiation Safety Committees of the Karolinska Hospital, Stockholm, Sweden, approved the study.

2.2. Off-line cognitive testing

Two tests of fluid intelligence (free recall of words, digit symbol) and two tests of crystallized intelligence (vocabulary, information) were administered. Free recall of words involved recalling 16 words presented at a rate of 5 s/word immediately after presentation of the last word in the series. Digit symbol, vocabulary, and information are all standardized tests taken from the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981).

2.3. Cognitive assessment during the fMRI examination

We used a spatial WM task, modeled after Klingberg et al. (2002). Participants were asked to remember the location of filled red circles that were presented sequentially in a 4×4 grid on a display. In the target condition, the circles (cues) were presented sequentially during 7000 ms. The task was to remember the locations in which the cues were presented. After a delay (1500 ms), a response phase of 1500 ms followed. During the response phase, an unfilled probe circle appeared on the screen. Participants had to judge whether the probe was in the same location as any of the cues. If the location matched, the participant pressed a button with their right index finger to indicate "yes" if not, they pressed another button, using the right middle finger, to indicate "no"

WM load was manipulated by presenting 4 circles (WM/low) or 6 circles (WM/high) during the sample period. The total number of trials (i.e., the maximum score) in each condition was 15.

In the control condition, participants were also instructed to watch 4 (WM/low) or 6 (WM/high) green filled circles that were presented one-by-one in each of the four corners of the grid. After a 1500 ms delay, an unfilled green circle (probe) appeared in the middle of the grid, and participants responded by pressing the button with their index finger each time the probe appeared. Before entering the scanner, participants practiced the task to be acquainted with the experimental situation. During scanning, 35 s epochs of the 2 WM tasks and the 2 control tasks were alternated, with the order counterbalanced between two 6 min runs.

The stimuli were presented by means of standard software (E-prime; Psychology Software Tools). The pictures were projected via a Philips Hopper HG 20 Impact LCD projector (Philips Corp., Netherlands) positioned inside the scanner room onto a rectangular screen, approximately 3 m in front of the subject. Stimuli were presented via a mirror system (prism and oculars) mounted on top of a head coil positioned approximately 2 cm from the participant's eyes.

2.4. Acquisition and processing of brain imaging data

2.4.1. fMRI

Whole-brain imaging data were acquired on a 1.5 T GE Signa Echospeed MR scanner (GE Medical Systems, USA), using a standard circular one-channel head coil. T1 weighted 3D-SPGR images (TR = 24 ms, TE = 6 ms, flip angle = 35°) were acquired for anatomical co-registration in 124 contiguous 1.5 mm coronal slices (image resolution = 256 mm × 256 mm × 186 mm, voxel size = 0.9 mm × 0.9 mm × 1.5 mm). Functional images were acquired using a T2*-sensitive gradient echo-EPI sequence (TR = 2.5 s, TE = 40 ms, flip angle = 90°). The image volumes had a field of view of 220 mm × 220 mm, an in plane resolution of 3.44 mm × 3.44 mm, and contained 32 horizontal 4 mm thick slices with a 0.5 mm gap in between each slice. All images were acquired interleaved. During the fMRI session, 140 image volumes were obtained during each of the two runs. To account for magnetic saturation effects, 4 dummy scans in the beginning of each session were discarded in the statistical analysis.

All data processing was carried out using SPM2 (Wellcome Department of Cognitive Neurology, UK). Functional images were first spatially realigned to the first volume in each time series. Inspection of movement parameters generated during the spatial realignment showed that no participant had moved more than 3 mm or 3° in any direction during task performance. Volumes were then normalized to a standard T1 template. Normalized images were spatially smoothed with a Gaussian filter of 12 mm full width at half maximum (FWHM). High-and low-frequency noise was removed using a high-pass filter and a low-pass filter, respectively.

BOLD effects were modeled using a box-car model convolved with the canonical hemodynamic response function on the data from the WM/low and WM/high conditions. The analysis was performed in two steps. First, the WM load contrast (WM/high–WM/low) was analyzed for each subject using a fixed-effects model. This created a single contrast image per subject that was subsequently used together with images from the other participants in a random-effects model to analyze the load effect separately within each age group by means of one-sample *t*-tests. Second, the load contrasts in the two age groups were directly compared using two sample *t*-tests. Those regions where a significant ($p < .001$, uncorrected) age difference in the load-dependent BOLD signal (WM/high > WM/low) was obtained were used as the outcome measures in subsequent analyses relating the load-dependent BOLD signal to the D_1 binding data. For these analyses, beta values from a 4 mm sphere around the peak activations were extracted from the relevant age contrast.

2.4.2. PET

The PET assessment was made using an ECAT Exact HR 47 system (CTI/Siemens, Knoxville, TN) run in 3D mode. The transaxial resolution was 3.8 mm FWHM at the center of the field of view, 4.5 mm FWHM tangentially, and 7.4 mm FVHM radially at 20 cm from the center. Prior to each emission measurement, a transmission measurement of 10 min was performed using three rotating 68Ge–68Ga sources. This information was used for attenuation correction. [^{11}C] SCH23390 was prepared as described previously (Halldin et al., 1986) and injected into the left antecubital vein as a rapid bolus. Emission data were acquired over a period of 51 min in 13 frames of progressively increasing duration.

2.4.2.1. Regions of interest. T1-weighted MR images were reconstructed into a 256 × 256 × 156 matrix, with a resolution of 1.02 mm × 1.02 mm × 1 mm. The MR images were spatially normalized using SPM2. The line defined by the anterior and posterior commissures was parallel to the horizontal plane, and the inter-hemispheric plane was parallel to the sagittal plane. The regions of interest (ROIs) were then manually delineated on each individual MR image using the Human Brain Atlas software (Roland et al., 1994). This software enables ROIs to be delineated in any of the three orthogonal planes in the same dataset. The caudate nucleus was delineated in all sagittal planes. The DLPFC was defined as the medial-inferior and the lateral part of the superior frontal gyrus delineated in all coronal planes anterior to the corpus callosum. The cerebellum was manually traced in the six central planes of that region in order to consider gray matter only.

2.4.2.2. Regions of interest and BP. The regional [^{11}C] SCH23390 BP was used as an index for D_1 receptor density in caudate nucleus and DLPFC. The cerebellum, where dopamine D_1 receptor density is negligible, served as reference region (Hall et al., 1998). The PET images were

coregistered to the structural MR images and re-sliced to a voxel size of 2 mm × 2 mm × 2 mm. The MRI-defined ROIs were displayed on the corresponding PET images. To obtain time–activity curves, regional radioactivity was calculated for each frame, corrected for decay and plotted versus time. BP, which represents the product of receptor density (B_{max}), apparent affinity ($1/K_d$) and the free fraction of free and non-specific bound ligand (f2; Mintun et al., 1984), was calculated for [^{11}C] SCH23390 according to the Simplified Reference Tissue model (Gunn et al., 1997). D_1 BP in left and right caudate ($r = .87$, $p < .001$) and left and right DLPFC ($r = .92$, $p < .001$) were highly correlated, and thus, the BP data were pooled across hemispheres.

2.4.3. PET-fMRI integration

To analyze whether D_1 receptor availability accounted for weaker load-dependent BOLD responses in older adults, a regression approach was adopted. We first conducted simple regression analyses with chronological age as the only predictor variable and beta values for regions showing significant age × load BOLD effects as the dependent measures. In the second step, D_1 BP was entered as a predictor prior to age. Regression analyses were performed separately for the caudate and the DLPFC. The main question of interest was whether the age differences in BOLD would be eliminated or attenuated when D_1 binding was entered into the equations.

3. Results

3.1. Demographics and off-line cognitive data

Mean years of education were 14.67 for the young ($SD = 1.97$) and 14.30 for the old ($SD = 2.96$, $p > .70$). Results from the off-line cognitive testing revealed that the two samples were highly representative of their respective birth cohorts. There was a clear advantage for the young in tests of fluid abilities (free recall of words: $M_{young} = 11.90$ [$SD = 2.31$], $M_{old} = 9.60$ [$SD = 2.46$], $t = 3.05$, $p < .01$; digit symbol: $M_{young} = 35.75$ [$SD = 13.90$], $M_{old} = 20.30$ [$SD = 5.90$], $t = 4.57$, $p < .01$). By contrast, the old outperformed the young in tests of crystallized abilities (vocabulary: $M_{young} = 29.30$ [$SD = 2.49$], $M_{old} = 33.30$ [$SD = 2.00$], $t = 5.59$, $p < .01$; information: $M_{young} = 23.20$ [$SD = 2.28$], $M_{old} = 25.30$ [$SD = 3.08$], $t = 2.45$, $p = .02$). No participant had a deviant score on any cognitive test, as evidenced by mean scores and measures of variability.

3.2. Cognitive data during fMRI assessment

Analyses of the cognitive data acquired during fMRI scanning revealed an age-related deficit for both accuracy and reaction times ($ps < .001$; Table 1). In general, the behavioral effects of the load manipulation were weak ($ps > .05$). For younger adults, a slight decrease in accuracy along with a somewhat slower reaction time with increasing load was seen.

Table 1
Mean spatial working-memory performance across age and load.

	Young ($n = 20$)	Old ($n = 20$)	*p-value*
WM/low accuracy	14.56 (0.70)	11.37 (1.93)	<.001
WM/high accuracy	14.17 (1.04)	11.37 (2.45)	<.001
WM/low RT (ms)	818 (175)	1113 (171)	<.001
WM/high RT (ms)	844 (166)	1066 (240)	<.001

Note: Standard deviations are given in parentheses.

In contrast, the elderly persons responded marginally faster in the WM/high than in the WM/low condition. Together with previous observations (e.g., Mattay et al., 2006; Nyberg et al., 2009b), this behavioral pattern indicates that older adults were close to their maximum capacity already in the WM/low condition.

3.3. Effects of the load manipulation on BOLD activity

In younger adults, a comparison of the WM/high condition with the WM/low condition revealed increased activity in regions that previously have been associated with greater WM demands. These include dorsolateral prefrontal ($x, y, z = -56$, 12, 32; 44, 10, 38) and parietal (x, y, $z = -40$, -48, 52; 50, -28, 38) areas bilaterally ($p < .05$, FDR-corrected, cluster size >15 voxels). In older adults, no significant increase of BOLD activity by the load manipulation was found. Even after lowering the statistical threshold ($p < .01$ uncorrected), no load effect was detected in frontal or parietal cortex for the older adults. Beta values for younger and older adults in these brain regions across the two load conditions are portrayed in Fig. 1.

Direct age group comparisons revealed a greater load effect ($p < .001$, uncorrected) for the young in bilateral frontal cortex ($x, y, z = -52$, 8, 32; 44, 12, 38) and left parietal cortex (x, y, $z = -46$, -44, 48). As can be seen from the figure, all significant interaction effects (panels A–C) reflected the fact that younger adults showed an increased BOLD response in the WM/high condition, whereas older adults showed negligible effects of the load manipulation. The interaction effect did not attain conventional significance for right parietal cortex ($p = .11$; panel D), because of a non-significant activation increase in the WM/high condition also for the old.

In several brain regions, an interaction in the direction of greater load-dependent modulation of the BOLD signal in the old was observed ($p < .001$). These include superior temporal gyrus ($x, y, z = -56$, -56, 20), posterior cingulate (x, y, $z = -10$, -48, 22), precuneus ($x, y, z = -6$, -60, 20), and cerebellum (x, y, $z = -12$, -50, -28). These regions are not part of the typical spatial working-memory network identified in several studies. Further, in all cases the interactions reflected the fact that the young showed greater reductions of activity with increasing load, although the old exhibited such reductions too. As these data were regarded as less meaningful in the present context, they will not be discussed further.

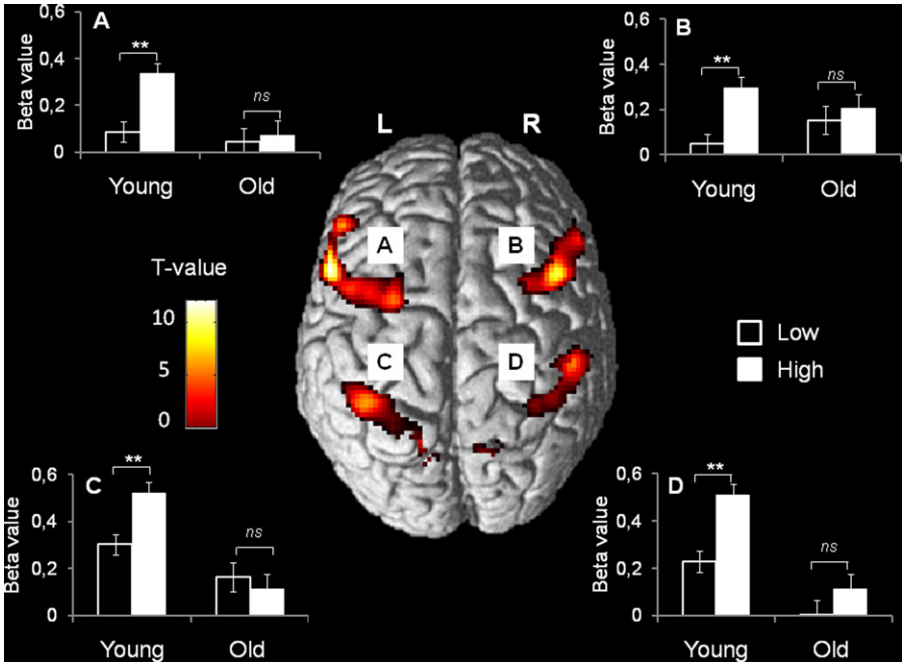

Fig. 1. Brain regions showing load-dependent BOLD effects (WM/high > WM/low) in younger but not older adults during spatial working memory. (A) Left frontal cortex (−56, 12, 32). (B) Right frontal cortex (44, 10, 38). (C) Left parietal cortex (−40, −48, 52). (D) Right parietal cortex (50, −28, 38). *Note*: L = left; R = right. The beta values in the bar graphs are derived by contrasting WM/high–baseline to WM/low–baseline in the two age groups. $^{**}p < .001$.

3.4. Dopamine D_1 BP

Analyses of D_1 BP in caudate and DLPFC revealed a significant age difference for the caudate ($M_{young} = 1.44$, $SD = .26$; $M_{old} = 1.02$, $SD = .18$; age correlation = −.69, $p < .005$) as well as for the DLPFC ($M_{young} = .30$, $SD = .07$; $M_{old} = .15$, $SD = .05$; age correlation = −.74, $p < .001$). The average age-related loss of D_1 BP per decade was estimated to 8% for the caudate and 14% for the DLPFC. In the total sample, there was a strong correlation between D_1 binding in caudate and DLPFC ($r = .87$, $p < .001$). This correlation remained highly significant after partialing out age ($r = .73$, $p < .001$).

3.5. Dopamine–BOLD relationship

The DA–BOLD analyses were restricted to regions showing a significantly greater load effect ($p < .001$, uncorrected) in young compared to old subjects. These analyses addressed whether the age × load interaction for the BOLD signal in bilateral frontal cortex and left parietal cortex was attenuated when individual differences in D_1 BP in caudate and DLPFC

Table 2
Strength of the relationship between age and load-dependent modulation of the BOLD signal (entries marked with 1). The same relationship after statistical control of caudate D_1 receptor density (entries marked with 2) and DLPFC D_1 receptor density (entries marked with 3). The outcome measures are the load-dependent BOLD signal (higher load > lower load) in brain regions showing a significant ($p < .001$, uncorrected) age difference in the load effect.

Outcome measures	Predictors	R^2	*p-value*
L inferior frontal gyrus (BA 9; −52 8 32)	1. Age only	.23	.01
	2. Caudate D_1	.19	.01
	Age	.06	ns
	3. DLPFC D_1	.16	.01
	Age	.07	ns
R middle frontal gyrus (BA 9; 44 12 38)	1. Age only	.23	.01
	2. Caudate D_1	.12	.02
	Age	.11	.03
	3. DLPFC D_1	.13	.02
	Age	.10	.03
L inferior parietal lobe (BA 40; −46 −44 48)	1. Age only	.30	.001
	2. Caudate D_1	.14	.02
	Age	.16	.01
	3. DLPFC D_1	.14	.02
	Age	.16	.01

Note: The *p-values* were computed from SPSS-based regression analyses in which age was used as a continuous variable.

were controlled for (Table 2). When entered in isolation, chronological age accounted for between 23% and 30% of the variance in BOLD response across the three brain regions. However, when entered after D_1 binding levels in caudate and DLPFC, the effect of age on the BOLD response in left frontal cortex was non-significant, accounting for only 6–7% of the variance. In the corresponding analysis for right frontal and left parietal cortex, the influence of age remained stronger and continued to account for significant portions of the variance, although an attenuation of around 50% was observed. D_1 binding in caudate and DLPFC equally contributed to the age-related BOLD variance in the three brain regions.

Finally, to verify the mediational impact of caudate and DLPFC D1 binding, we compared statistically the magnitude of the relationship between age and the load-dependent BOLD signal in left and right frontal cortex and left parietal cortex, before and after controlling for D1 binding. As noted, statistical control of D1 binding fully mediated the age-related reduction in load-dependent BOLD signal in left frontal cortex, and partially mediated the reduction in right frontal and left parietal cortex. Direct inferential comparison of correlations for dependent samples (Meng et al., 1992) confirmed these observations; the correlations in the left inferior frontal region after controlling for caudate or DLPFC D1 binding were significantly attenuated compared to the simple age-BOLD correlations ($p = .02$ and $p = .04$, respectively). Further, there were clear trends in the same direction for right frontal cortex ($p = .11$ and $p = .08$, respectively) and left parietal cortex ($p = .10$ and $p = .10$, respectively).

4. Discussion

Consistent with the bulk of past research (e.g., D'Esposito et al., 1999; Jonides et al., 2000; Reuter-Lorenz et al., 2000), the present data showed an age-related deficit in spatial WM performance. The older sample had lower accuracy and required longer time to respond than their younger counterparts.

The behavioral effects of the load manipulation were weak. Although the younger adults performed close to the ceiling in both conditions, they showed non-significant tendencies of lower accuracy and longer response times in the WM/high condition. Nevertheless, the young showed selective activity increases in DLPFC bilaterally and left parietal cortex in the WM/high condition, indicating modulation of the BOLD signal in response to increasing cognitive demands in regions typically activated during WM performance (e.g., Braver et al., 1997; Callicott et al., 1999; Nyberg et al., 2009b; Rypma et al., 1999). In other words, although the performance levels were similar, increased WM demands modulated neural activity in the young. A stronger influence of the load manipulation on brain activity than on behavioral performance is consistent with past research indicating that neurobiological effects can co-occur with no behavioral differences. (e.g., Dreher et al., 2009; Mattay et al., 2003; Schott et al., 2006). By contrast, older adults showed no alteration of the BOLD signal in response to the load manipulation. This apparent age-related deficit in neural modulation is in accord with much previous research (e.g., Mattay et al., 2006; Nyberg et al., 2009b; Reuter-Lorenz, 2002).

The findings from the PET assessment of DA D_1 BP were also in excellent agreement with prior work (Suhara et al., 1991; Wang et al., 1998). There were clear age-related losses of D_1 receptors in both caudate and DLPFC. Interestingly, the relative age-related loss was somewhat greater in DLPFC (on average 14% per decade) than in caudate (on average 8% per decade). These estimates mirror closely those reported in an early age-comparative study using the same radioligand to quantify D_1 BP (Suhara et al., 1991).

The age-related patterns observed in the fMRI and PET data open up for examining the key issue addressed in this study: Could the load-dependent fronto-parietal underrecruitment in older adults be linked to age-related losses in D_1 BP? In general, the answer to that question is affirmative. For the three regions that revealed reliable age × load interactions in the BOLD data, chronological age accounted for slightly less than one third of the load-dependent BOLD variation. Of chief importance, for the left prefrontal region statistical control of D_1 binding in both caudate and DLPFC eliminated the age-related BOLD variation. For the right prefrontal and left parietal regions, age contributed unique variance to the load-dependent BOLD response over and above D_1 binding, although controlling for the D_1 data in caudate and DLPFC attenuated the age-related BOLD variance by 50%. The fact that D_1 binding did not fully account for age-related differences in BOLD is only to be expected, given extant evidence that several factors can contribute to underrecruitment in aging, including resting-state cerebral blood flow and cerebrovascular pathology (D'Esposito et al., 2003). That said, it is interesting to note that the strongest DA-related mediation of the age-related difference in BOLD signal was seen in left prefrontal cortex, given that previous research has found a marked relationship between striatal DA activity and left prefrontal blood flow during both WM (Landau et al., 2009) and episodic memory (Nyberg et al., 2009a) performance.

Of further note is that the current research extends previous observations of a local DA-BOLD link in the striatum during cognitive processing (Schott et al., 2008) to extrastriatal regions. To our knowledge, this is the first demonstration that frontal DA activity is related to frontal BOLD signal and mediates age-related differences in frontal blood flow in a load-dependent manner.

In general, the size of the predictive relationship to age-related underactivation in frontal and parietal regions was similar for caudate and DLPFC D_1 binding. Frontal DA activity commonly reflects input from the mesocortical DA pathway that originates from a diffuse collection of nerve cells in the ventral tegmentum (e.g., Gurden et al., 2000; Lavin et al., 2005). However, there is also DA input to extrastriatal regions that belongs to the nigrostriatal basal ganglia-thalamo-cortical circuitry (e.g., Alexander et al.,

1986; Sánchez-González et al., 2005). Although the current study cannot disentangle these origins, the fact that D_1 binding in caudate and DLPFC was strongly related even after controlling for age may indicate that the relationships of caudate and DLPFC D_1 binding to age-related differences in load-dependent frontal blood flow may originate from the same nigrostriatal source.

It should be emphasized that even though our findings demonstrate that age-related dopaminergic losses and underrecruitment of task-relevant regions show a proportional age-related decline, they do not allow strong conclusions regarding causality. Still, in related work we have recently found that administration of a DA D_1 antagonist lead to a reduced load-dependent fronto-parietal BOLD response in younger adults (Fischer et al., manuscript submitted for publication). This observation is consistent with a model in which age-related DA losses drive age-related changes in functional brain activity.

Conceivably, the relationships observed in this study are not unique to spatial WM. Specifically, an association between a measure of DA synthesis capacity in caudate and the load-dependent BOLD signal during verbal WM has been documented in an age-homogenous sample (Landau et al., 2009), and an age-related attenuation of the load-dependent BOLD signal has been reported for verbal WM (e.g., Mattay et al., 2006; Nyberg et al., 2009b). Thus, there are good reasons to believe that the present pattern of findings would generalize to verbal WM and likely to other executively demanding tasks. As to the latter, altered DA functions have been linked to age-related deficits in several cognitive domains, including speed of processing, episodic memory, and verbal fluency (Bäckman et al., 2000; Erixon-Lindroth et al., 2005; Mozley et al., 2001; Volkow et al., 1998; Wang et al., 1998). Future studies may extend the approach adopted in this research to other cognitive domains, thereby assessing the generality of the DA–BOLD association in neurocognitive aging.

Conflict of interest statement

The authors declare no actual or potential conflicts of interest.

Acknowledgments

This research was supported by grants from the Swedish Research Council and Swedish Brain Power, and by an Alexander von Humboldt Research Award to Lars Bäckman, from the Swedish Research Council and the Joint Committee for Nordic Research Councils in the Humanities and the Social Science to Lars Nyberg for a Nordic Center of Excellence in Cognitive Control (NOS-HS), and from the Swedish Research Council to Lars Farde. Sari Karlsson was supported by a postdoctoral fellowship from the Swedish Research Council.

References

Alexander, G.E., DeLong, M.R., Strick, P.L., 1986. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu. Rev. Neurosci. 9, 357–381.

Antonini, A., Leenders, K.L., Reist, H., Thomann, R., Beer, H.F., Locher, L., 1993. Effect of age on D_2 dopamine receptors in normal human brain measured by positron emission tomography and [11C]raclopride. Arch. Neurol. 50, 474–480.

Arnsten, A.F.T., 1997. Catecholamine regulation of the prefrontal cortex. J. Psychopharmacol. 11, 151–162.

Bäckman, L., Farde, L., 2005. The role of dopamine functions in cognitive aging. In: Cabeza, R., Nyberg, L., Park, D.C. (Eds.), Cognitive Neuroscience of Aging: Linking Cognitive and Cerebral Aging. Oxford University Press, New York, pp. 58–84.

Bäckman, L., Ginovart, N., Dixon, R.A., Robins Wahlin, T.B., Wahlin, Å., Halldin, C., Farde, L., 2000. Age-related cognitive deficits mediated by changes in the striatal dopamine system. Am. J. Psychiatry 157, 635–637.

Bäckman, L., Nyberg, L., Lindenberger, U., Li, S.C., Farde, L., 2006. The correlative triad among aging, dopamine, and cognition: current status and future prospects. Neurosci. Biobehav. Rev. 30, 791–807.

Braver, T.S., Cohen, J.D., Nystrom, L.E., Jonides, J., Smith, E.E., Noll, D.C., 1997. A parametric study of prefrontal cortex involvement in human working memory. Neuroimage 5, 49–62.

Buckner, R.L., 2004. Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. Neuron 44, 195–208.

Cabeza, R., 2002. Hemispheric asymmetry reduction in old adults: the HAROLD model. Psychol. Aging 17, 85–100.

Callicott, J.H., Mattay, V.S., Bertolino, A., Finn, K., Frank, J.A., Goldberg, T.E., Weinberger, D.R., 1999. Physiological characteristics of capacity constraints in working memory as revealed by functional MRI. Cereb. Cortex 9, 20–26.

Curtis, C.E., D'Esposito, M., 2003. Persistent activity in the prefrontal cortex during working memory. Trends Cogn. Sci. 7, 415–423.

D'Esposito, M., Deouell, L.Y., Gazzaley, A., 2003. Alterations in the BOLD fMRI signal with aging and disease: a challenge for neuroimaging. Nat. Rev. Neurosci. 4, 863–872.

D'Esposito, M., Zarahn, E., Aguirre, G.K., Rypma, B., 1999. The effect of normal aging on the coupling of neural activity to the bold hemodynamic response. Neuroimage 10, 6–14.

Dreher, J.C., Kohn, P., Kolachana, B., Weinberger, D.R., Berman, K.F., 2009. Variation in dopamine genes influences responsivity of the human reward system. Proc. Natl. Acad. Sci. 106, 617–622.

Erixon-Lindroth, N., Farde, L., Robins Wahlin, T.B., Sovago, J., Halldin, C., Bäckman, L., 2005. The role of the striatal dopamine transporter in cognitive aging. Psychiatry Res. Neuroimag. 138, 1–12.

Farde, L., Halldin, C., Stone-Elander, S., Sedvall, G., 1987. PET analysis of human dopamine receptor subtypes using ^{11}C-SCH 23390 and ^{11}C-raclopride. Psychopharmacology 92, 278–284.

Fischer, H., Nyberg, L., Karlsson, S., Karlsson, P., Brehmer, Y., Rieckmann, A., MacDonald, S.W.S., Farde, L., Bäckman, L., Manuscript submitted for publication. Simulating neurocognitive aging: effects of a dopaminergic antagonist on brain activity during working memory. 2009.

Gunn, R.N., Lammerstma, A.A., Hume, S.P., Cunningham, V.J., 1997. Parametric imaging of ligand–receptor binding in PET using a simplified reference region model. Neuroimage 6, 279–287.

Gurden, H., Takita, M., Jay, T.M., 2000. Essential role of D1 but not D2 receptors in the NMDA receptor-dependent long-term potentiation at hippocampal–prefrontal cortex synapses in vivo. J. Neurosci. 20, 1–5, RC106.

Hall, H., Farde, L., Sedvall, G., 1998. Human dopamine receptor subtypes – in vitro binding analysis using 3H-SCH 23390 and 3H-raclopride. J. Neur. Transm. 73, 7–21.

Halldin, C., Stone-Elander, S., Farde, L., Ehrin, E., Fasth, K.J., Långström, B., Sedvall, G., 1986. Preparation of ^{11}C-labeled SCH 23390 for the in

vivo study of dopamine D_1 receptors using positron emission tomography. Appl. Radiat. Isot. 37, 1039–1043.

Holtzer, R., Rakitin, B.C., Steffener, J., Flynn, J., Kumar, A., Stern, Y., 2009. Age effects on load-dependent brain activations in working memory. Brain Res. 1249, 148–161.

Jonides, J., Marshuetz, C., Smith, E.E., Reuter-Lorenz, P.A., Koeppe, R.A., Hartley, A., 2000. Age differences in behavior and PET activation reveal differences in interference resolution in verbal working memory. J. Cognit. Neurosci. 12, 188–196.

Kimberg, D.Y., D'Esposito, M., 2003. Cognitive effects of the dopamine receptor agonist pergolide. Neuropsychologia 41, 1020–1027.

Klingberg, T., Forssberg, H., Westerberg, H., 2002. Increased brain activity in frontal and parietal cortex underlies the development of visuospatial working memory during childhood. J. Cognit. Neurosci. 14, 1–10.

Knutson, B., Gibbs, S.E.B., 2007. Linking nucleus accumbens dopamine and blood oxygenation. Psychopharmacology 191, 813–822.

Landau, S.M., Lal, R., O'Neil, J.P., Baker, S., Jagust, W.J., 2009. Striatal dopamine and working memory. Cereb. Cortex 19, 445–454.

Lavin, A., Nogueira, L., Lapish, C.C., Wightman, R.M., Philips, P.E.M., Seamans, P.K., 2005. Mesocortical dopamine neurons operate in distinct temporal domains using multimodal signaling. J. Neurosci. 25, 5013–5023.

Li, S.-C., Lindenberger, U., Nyberg, L., Heekeren, H.R., Bäckman, L., 2009. Dopaminergic Modulation of Cognition in Human Aging. In: Jagust, W., D'Esposito, M. (Eds.), Imaging the Aging Brain. Oxford University Press, New York, pp. 71–91.

Luciana, M., Collins, P.F., 1997. Dopamine modulates working memory for spatial but not object cues in normal humans. J. Cognit. Neurosci. 9, 330–347.

Mattay, V.S., Fera, F., Tessitore, A., Hariri, A.R., Berman, K.F., Das, S., Meyer-Lindenberg, A., Goldberg, T.E., Callicott, J.H., Weinberger, D.R., 2006. Neurophysiological correlates of age-related changes in working-memory capacity. Neurosci. Lett. 392, 32–37.

Mattay, V.S., Goldberg, T.E., Fera, F., Hariri, A.R., Tessitore, A., Egan, M.F., Kolachana, B., Callicott, J.H., Weinberger, D.R., 2003. Catechol-O-methyltransferase val(258)-met genotype and individual variation in the brain response to amphetamine. Proc. Natl. Acad. Sci. U.S.A. 100, 6186–6191.

McNab, F., Varrone, A., Farde, L., Jucaite, A., Bystritsky, P., Forssberg, H., Klingberg, T., 2009. Changes in cortical dopamine binding associated with cognitive training. Science 323, 800–802.

Meng, X.-L., Rosenthal, R., Rubin, D.B., 1992. Comparing correlated correlation coefficients. Psychol. Bull. 111, 172–175.

Mintun, M.A., Raichle, M.E., Kilbourn, M.R., Wooten, G.F., Welch, M.J., 1984. A quantitative model for the in vivo assessement of drug binding sites with poistron emission tomography. Ann. Neurol. 15, 217–227.

Mozley, L.H., Gur, R.C., Mozley, P.D., Gur, R.E., 2001. Striatal dopamine transporters and cognitive functioning in healthy men and women. Am. J. Psychiatry 158, 1492–1499.

Nordström, A.L., Farde, L., Pauli, S., Litton, J.E., Halldin, C., 1992. PET analysis of [^{11}C] raclopride binding in healthy young adults and schizophrenic patients: reliability and age effects. Hum. Psychopharmacol. 7, 157–165.

Nyberg, L., Andersson, M., Forsgren, L., Jakobsson-Mo, S., Larsson, A., Marklund, P., Nilsson, L.-G., Riklund, K., Bäckman, L., 2009a. Striatal dopamine D_2 binding is related to frontal BOLD response during updating of long-term memory representations. Neuroimage 46, 1194–1199.

Nyberg, L., Bäckman, L., 2004. Cognitive aging: a view from brain imaging. In: Dixon, R.A., Bäckman, L., Nilsson, L.G. (Eds.), New Frontiers in Cognitive Aging. Oxford University Press, New York, pp. 135–159.

Nyberg, L., Dahlin, E., Stigsdotter Neely, A., Bäckman, L., 2009b. Neural correlates of variable working memory load across adult age and skill: dissociative patterns within the fronto-pariatal network. Scand. J. Psychol. 50, 41–46.

Reuter-Lorenz, P.A., 2002. New visions of the aging mind and brain. Trends Cognit. Sci. 6, 394–400.

Reuter-Lorenz, P.A., Lustig, C., 2005. Brain aging: reorganizing discoveries about the aging mind. Curr. Opin. Neurobiol. 15, 245–251.

Reuter-Lorenz, P.A., Jonides, J., Smith, E.E., Hartley, A., Miller, A., Marshuetz, C., Koeppe, R.A., 2000. Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. J Cognit. Neurosci. 12, 174–187.

Rinne, J.O., Sahlberg, N., Ruottinen, H., Någren, K., Lehikoinen, P., 1998. Striatal uptake of the dopamine reuptake ligand subtypes using [^{11}C]b-CFT is reduced in Alzheimer's disease assessed by positron emission tomography. Neurology 50, 152–156.

Roland, P.E., Graufelds, C.J., Wåhlin, J., Ingelman, L., Andersson, M., Ledberg, A., Pedersen, J., Åkerman, S., Dabringhaus, A., Zilles, K., 1994. Human brain atlas for high resolution functional and anatomical mapping. Hum. Brain Mapp. 1, 173–184.

Rypma, B., D'Esposito, M., 2000. Isolating the neural mechanisms of age-related changes in human working memory. Nat. Neurosci. 3, 509–515.

Rypma, B., Prabhakaran, V., Desmond, J.E., Glover, G.H., Gabrieli, J.D., 1999. Load-dependent roles of frontal brain regions in the maintenance of working memory. Neuroimage 9, 216–226.

Sánchez-González, M.A., García-Cabezas, M.A., Rico, B., Cavada, C., 2005. The primate thalamus is a key target for brain dopamine. J. Neurosci. 25, 6076–6083.

Sawaguchi, T., Goldman-Rakic, P.S., 1991. D_1 dopamine receptors in prefrontal cortex: involvement in working memory. Science 251, 947–950.

Schott, B.H., Seidenbecher, C.I., Fenker, D.B., Lauer, C.J., Bunzeck, N., Bernstein, H.G., Tischmeyer, W., Gundelfinger, E.D., Heinze, H.J., Düzel, E., 2006. The dopaminergic midbrain participates in human episodic memory formation: evidence from genetic imaging. J. Neurosci. 26, 1407–1417.

Schott, B.H., Minuzzi, L., Krebs, R.M., Elmenhorst, D., Lang, M., Winz, O.H., Seidenbecher, C.I., Coenen, H.H., Heinze, H.J., Zilles, K., Düzel, E., 2008. Mesolimbic fMRI activations during reward anticipation correlate with reward-related ventral striatal dopamine release. J. Neurosci. 28, 14311–14319.

Suhara, T., Fukuda, H., Inoue, O., Itoh, T., Suzuki, K., Yamasaki, T., Tateno, Y., 1991. Age-related changes in human D_1 dopamine receptors measured by positron emission tomography. Psychopharmacology 103, 41–45.

Takahashi, H., Kato, M., Takano, H., Arakawa, R., Okumura, M., Otsuka, T., Kodaka, F., Hayashi, M., Okubo, Y., Ito, H., Suhara, T., 2008. Differential contributions of prefrontal and hippocampal dopamine D_1 and D_2 receptors in human cognitive functions. J. Neurosci. 28, 12032–12038.

Van Dyck, C.H., Seibyl, J.P., Malison, R.T., Laurelle, M., Wallace, E., Zoghbi, S.S., Zeaponce, Y., Baldwin, R.M., Charney, D.S., Hoffer, P.B., Innis, R.B., 1995. Age-related decline in striatal dopamine transporter binding with iodine-123-b-CIT. J. Nucl. Med. 36, 1175–1181.

Vijayraghavan, S., Wang, M., Birnbaum, S.G., Williams, G.V., Ansten, A.F.T., 2007. Inverted-U dopamine D_1 receptor actions on prefrontal neurons engaged in working memory. Nat. Neurosci. 10, 376–384.

Volkow, N.D., Gur, R.C., Wang, G.J., Fowler, J.S., Moberg, P.J., Ding, Y.S., Hitzemann, R., Smith, G., Logan, J., 1998. Association between decline in brain dopamine activity with age and cognitive and motor impairment in healthy individuals. Am. J. Psychiatry 157, 344–349.

Wang, Y., Chan, G.L.Y., Holden, J.E., Dobko, T., Mak, E., Schulzer, M., Huser, J.M., Snow, B.J., Ruth, T.J., Calne, D.B., Stoessl, A.J., 1998. Age-dependent decline of dopamine D_1 receptors in human brain: a PET study. Synapse 30, 56–61.

Wang, M., Vijayraghavan, S., Goldman-Rakic, P.S., 2004. Selective D_1 receptor actions on the functional circuitry of working memory. Science 303, 853–856.

Wechsler, D., 1981. Manual for the WechslerAdult Intelligence Scale-Revised. The Psychological Corporation, New York.

Williams, G.V., Goldman-Rakic, P.S., 1995. Modulation of memory fields by dopamine D_1 receptors in prefrontal cortex. Nature 376, 572–575.