Simulating Neurocognitive Aging: Effects of a Dopaminergic Antagonist on Brain Activity During Working Memory

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Background: Previous correlational studies have indirectly linked dysfunctional dopaminergic neurotransmission to age-related cognitive deficits and associated reductions in task-induced functional brain activity.

Methods: We used an experimental-pharmacological functional magnetic resonance imaging (fMRI) approach to more directly examine the role of dopamine in neurocognitive aging. Twenty younger and 20 healthy older adults were included. During fMRI scanning, a spatial working memory (SWM) task was administered under two conditions, varying in cognitive load. Positron emission tomography measurements with the D1 receptor antagonist [^{11}C]SCH23390 confirmed that a given experimental dose of unlabeled solution occupied 50% of D1 receptors in younger adults.

Results: An age-related reduction in SWM performance was observed, and fMRI data revealed that, relative to younger adults under placebo conditions, elderly persons under-recruited load-sensitive fronto-parietal regions during SWM. Critically, in younger adults, the D1 antagonist resulted in a similar reduction in SWM performance and fMRI response.

Conclusions: These results suggest that depletion of dopamine, whether ontogenetically or pharmacologically, results in decreased SWM performance as well as reduced load-dependent modulation of the blood oxygen level dependent signal in fronto-parietal regions, possibly by decreasing the signal-to-noise ratio in relevant neural networks.

Key Words: Aging, antagonist, D1 receptors, dopamine, fMRI, pharmacology, spatial working memory

Human aging is associated with deficits in working memory (1), and functional brain-imaging studies have related such deficits to reductions in brain activity, particularly in the frontal and parietal cortices (2–4). It has been suggested that alterations in the dopamine (DA) systems contribute to these age-related neurocognitive changes (5). This suggestion is supported by the "correlative triad" among chronological age, in vivo measurements of DA functions, and cognitive performance (6). However, although the support for such a correlative triad is substantial (7–10), more direct experimental evidence has been called for to substantiate the causative link (6).

Pharmacological challenges provide a means to link DA neurotransmission to cognitive deficits and associated underactivation of neural networks (11–13). Previous studies have shown that DA antagonists might impair performance across a variety of cognitive tasks, including those tapping executive functioning and speed (14,15). Conversely, DA agonists have been found to boost performance in the same cognitive domains (14,16,17). Furthermore, there is evidence that pharmacological manipulations might affect functional brain activity patterns (18,19). Of particular relevance here is the finding that a dopaminergic agonist led to increased striatal brain activity and facilitation of motor memory in older adults (20). In the present study, we address the complementary question of whether administration of a DA antagonist to younger adults would lower their performance in a spatial working-memory (SWM) task and correspondingly lead to reduced functional brain activity as measured by functional magnetic resonance imaging (fMRI). In other words, would younger adults under the influence of a DA antagonist look more similar to elderly persons in terms of cognitive performance and functional brain activity?

Previous working-memory studies have shown that fMRI activity in frontal and parietal regions is increased under more executively demanding conditions (21–22). However, older adults show a markedly reduced load effect in fronto-parietal regions (23–25). If this weaker response, at least in part, results from a dysfunctional DA system in old age, it follows that younger adults under the influence of a DA antagonist might show a weaker load response in fronto-parietal regions. Here we tested this prediction by administering the DA D1 antagonist ([^{11}C]SCH23390) to a group of younger adults and compared their SWM performance and associated fMRI activity with younger adults under placebo conditions as well as with a group of healthy elderly adults.

Methods and Materials

Subjects

Twenty right-handed younger (mean age = 25.2 years, range = 22–30; 10 men, 10 women) and 20 right-handed older (mean age = 70.3 years, range = 65–75; 10 men, 10 women) persons were recruited through a newspaper advertisement. Mean years of education were 14.67 for the younger (SD = 1.97) and 14.30 for the older subjects (SD = 2.96, $p > .70$). Exclusion criteria included mental disorders, brain disorders, and other significant medical conditions; actual or previous drug or alcohol abuse; nicotine use; and hormone therapy. Off-line cognitive testing

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Received Apr 30, 2009; revised Dec 11, 2009; accepted Dec 14, 2009.

0006-3223/10/$36.00
doi:10.1016/j.biopsych.2009.12.013

revealed that the two samples were highly representative of their respective birth cohorts: there was a clear advantage of the younger subjects 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 older subjects 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, $p < .01$; General knowledge: M_{young} = 23.20 [SD = 2.28], M_{old} = 25.30 [SD = 3.08], t = 2.45, $p = .02$). Vision was corrected to normal by means of magnetic resonance (MR)-compatible glasses for participants requiring glasses outside of the scanner. Written informed consent was obtained from all participants, and the Regional Ethical Review Board in Stockholm, Sweden approved the study. The Radiation Safety Committee of the Karolinska Hospital approved the doses of [^{11}C]SCH23390.

Study Design and Procedure

Study Design. All participants were included in a larger study with several examinations comprising: 1) health screening and off-line cognitive testing; 2) resting state positron emission tomography (PET) examination; 3) PET examination during a cognitive challenge; 4) fMRI examination; 5) fMRI examination with a DA antagonist (younger persons only); and 6) pharmacological PET examination (five younger participants only). The five younger subjects who underwent the pharmacological PET examination (# 6) were part of the larger group of younger subjects that participated in this study. From the resting state PET examination (# 2), only data from these five younger subjects were included in the present study. The examinations were 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, 4, 5 and 6. Older participants underwent one fMRI examination, whereas younger participants underwent two fMRI examinations (under placebo and antagonist conditions) in a counterbalanced fashion. Importantly, there were no significant behavioral or brain effects related to order of presentation. The younger/placebo (YP) and younger/antagonist (YA) groups included the same subjects (i.e., drug condition was a within-subjects factor for the younger subjects).

Pharmacological Intervention. A blinded design was used, with the younger participants being unaware of the content of the injected solution. Before each of the two counterbalanced fMRI sessions (# 4 and # 5 in study design section), a solution containing either saline or .5 mg of unlabeled SCH23390 in saline was injected intravenously by the responsible physician (PK). To reduce the risk for peak-related adverse events, the dose was divided such that .25 mg was given 5 min before and .25 mg was given 1 min before the scanning session. The dose was estimated to result in 50% occupancy of D1 receptors (26). This D1 antagonist has a mean half-life of approximately 30 min. Older participants did not receive any injected liquid. The SWM task lasted for 12 min divided into two runs. Each of the two runs lasted for 6 min. The two fMRI sessions (# 4 and # 5) were separated by 2–6 days.

To confirm the effects of the pharmacological challenge, we used PET to quantify D1 receptor binding in five younger subjects with (Session # 6) and without (Session # 2) the antagonist.

Cognitive Assessment During the fMRI Examination. We used a spatial delayed-matching task, modeled after Klingberg *et al.* (27). Participants were asked to remember the location of filled red circles that were presented sequentially in a 4 × 4 grid on a display (Figure 1). In the target condition, the circles (cues) were presented sequentially during 7000 msec. The task was to remember the locations in which the cues were presented. After a delay (1500 msec), a response phase of 1500 msec 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, with the right middle finger, to indicate "no." Working-memory load was manipulated by presenting four circles (WM/low) or six circles (WM/high) during the sample period (Figure 1).

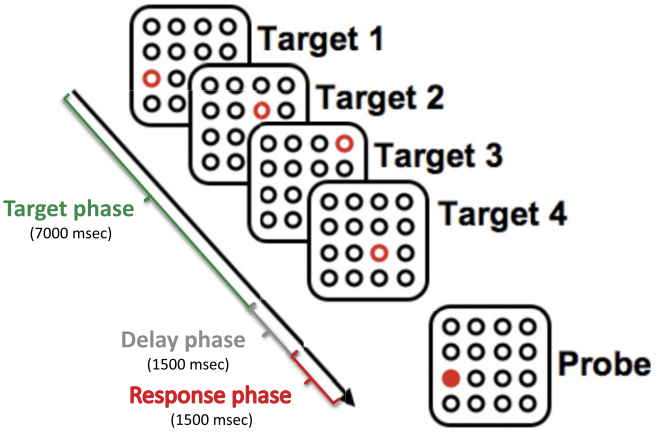

Figure 1. The spatial working memory task in the scanner used a blocked design (2 × 6 min) with randomized order of working memory–low (4-targets; see example above), working memory– high (6-targets), and two appearance-adjusted control tasks. In this example a "yes" response is required by pressing a button with the right index finger.

In the control condition, participants were also instructed to watch four (WM/low) or six (WM/high) green filled circles that were presented one-by-one in each of the four corners of the grid. After a 1500-msec 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 one to three times to become acquainted with the experimental task. During scanning, 35-sec epochs of the two SWM tasks and the two 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, Pittsburgh, Pennsylvania). The pictures were projected via a Philips Hopper HG 20 Impact LCD projector (Philips Corporation, Eindhoven, The 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.

Data Acquisition

MRI. Whole-brain imaging data were acquired at the Karolinska Hospital MR center on a 1.5-T GE Signa Echospeed MR scanner (GE Medical Systems, Milwaukee, Wisconsin), with a standard circular one-channel head coil. The T1-weighted three-dimensional spoiled gradient recalled images (repetition time = 24 msec, echo time = 6 msec, flip angle = 35°) were acquired for

anatomical coregistration in 124 contiguous 1.5-mm coronal slices (image resolution = 256 × 256 × 186 mm, voxel size = .9 × .9 × 1.5 mm). Functional images were acquired with a T2*-sensitive gradient echo-planar-imaging sequence (repetition time = 2.5 sec, echo time = 40 msec, flip angel = 90°). The image volumes had a field of view of 220 × 220 mm and an in-plane resolution of 3.44 × 3.44 mm and contained 32 horizontal 4-mm-thick slices with a .5-mm gap in between each slice. All images were acquired interleaved. During the functional MRI session, 140 image volumes were obtained during each of the two runs. To account for magnetic saturation effects, four dummy scans at the beginning of each session were discarded in the statistical analysis.

PET. Five younger subjects underwent PET examinations under normal conditions (# 2) and under the influence of the antagonist (# 6) with the same dosage as in the fMRI assessment. The PET assessment was made with an ECAT Exact HR 47 system (CTI/Siemens, Knoxville, Tennessee) run in three-dimensional mode. The transaxial resolution was 3.8 mm full-width-at-half-maximum (FWHM) at the center of the field of view, 4.5 mm FWHM tangentially, and 7.4 mm full-volume-width-at-half-maximal radially at 20 cm from the center. Before each emission measurement, a transmission measurement of 10 min was performed with three rotating 68Ge–68 Ga sources. This information was used for attenuation correction. The receptor antagonist [^{11}C]SCH23390 was prepared as described previously (28) and injected into the left antecubital vein as a rapid bolus injection. Emission data were acquired over a period of 51 min in 13 frames of progressively increasing duration. Data from the whole 51-min interval were used to determine D1 binding potential (BP). The second PET assessment (# 6) was identical to the first (# 2), with the addition of an intravenous injection of .5 mg SCH23390 as a bolus 5 min before the injection of [11C]SCH23390.

Data Analysis

Behavioral Data. The SPSS 15.0 software (SPSS, Chicago, Illinois) was used to analyze behavioral data by means of analyses of variance (ANOVAs). Two repeated-measures ANOVAs were conducted, one with intervention group (YP, YA) and load (four vs. six circles) as within-subjects factors. The second ANOVA included age group (YP, older subjects) and load (four vs. six circles) as factors, with repeated measures on load. Analyses of variance were conducted separately for accuracy and response latencies. Responses for trials where latencies deviated more than ± 2 SD from the mean or were shorter than 200 msec were discarded (both latency and accuracy). For latency, 4.2% of trials were discarded (3.2% for the older subjects; 5.2% for the younger subjects). For accuracy, 3.6% of trials were discarded (2.5% for the older subjects; 4.8% for the younger subjects).

MRI Data. All data processing was carried out with Statistical Parametric Mapping (SPM2; http://www.fil.ion.ucl.ac.uk/spm). 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 degrees 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 FWHM. High- and low-frequency noise and differences in global signal between subjects were removed with a high-pass filter, a low-pass filter, and global scaling, respectively. Blood oxygen level dependent (BOLD) effects were modeled with a box-car convolved with the canonical hemodynamic response function.

The working-memory load contrast (WM/high–WM/low) was used to create a single contrast image/subject that subsequently was used together with contrast images from the other participants in the three study groups (YP, YA, older subjects) in random-effects models. Thereafter, load-dependent WM-related brain activation in the YP group was determined ($p < .005$, uncorrected, $k > 5$ contiguous voxels). To investigate the effects of reduced D1 receptor availability on functional brain-activity patterns due to the influence of the antagonist or to older age, we used a functional masking strategy where the SPM for the YP group was used to define an inclusive mask (thresholded at $p < .05$ uncorrected). Within that mask, ANOVAs were conducted across the three groups. For regions where significant (nondirectional) F values were found ($p < .005$), t tests were performed on extracted β values with StatView 4.1 for Macintosh to identify regions with a reduced BOLD response as a function of lower DA function (YP > YA ≥ older subjects). Finally, we considered regions outside the load-dependent network where significant effects of group were observed ($p < .005$, uncorrected).

In a second step of the fMRI analyses, performance (accuracy) was included as a nuisance variable (i.e., covariate of no interest) to test whether this would alter the results. Critically, the observed patterns of brain activity were similar when potential effects of performance differences were covaried.

PET Data. Three regions of interest—the striatum, the dorsolateral prefrontal cortex (DLPFC), and the cerebellum—were manually delineated on each individual T1 MR image with the Human Brain Atlas software (29). The MR images were spatially normalized to the horizontal plane defined by the anterior and posterior commissure and the interhemispheric plane. The PET images were coregistered to the MR images and resliced to a

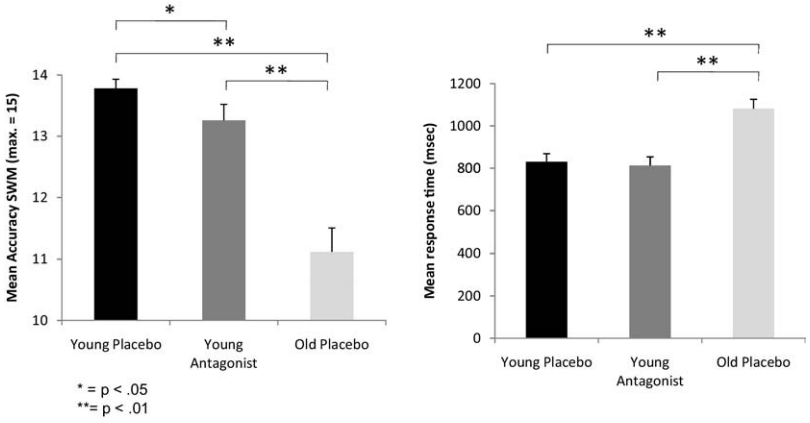

Figure 2. Accuracy and response latencies collapsed across the working memory– high and working memory–low conditions for the young placebo, young antagonist, and older subjects groups. SWM, spatial working memory. *$p < .05$; **$p < .01$.

Table 1. Brain Areas Showing Activity Increases as a Function of Load in Young Participants Under Placebo

Region of Activation	Peak-Coordinates
R Parietal Lobe	46, −30, 44
L Parietal Lobe	−48, −40, 44
R Frontal Lobe	34, 48, 26
	32, 5, 48
	4, 30, 36
L Frontal Lobe	−54, 14, 32
	−34, 2, 54
	−48, 30, 24
	−06, 30, 38
	−02, 14, 48
L Cingulate Gyrus	−20, −20, 42

Spatial coordinates (Montreal Neurological Institute) are for a peak activation of suprathreshold voxels.

voxel size of 2 × 2 × 2 mm. The striatum was delineated on all sagittal slices. The DLPFC included the medial inferior and lateral part of the superior frontal gyrus delineated in all coronal planes anterior to the corpus callosum. The cerebellum was delineated on the six central slices. The MRI-defined regions of interest were displayed on the corresponding PET images. To obtain time–activity curves, regional radioactivity was pooled between the hemispheres, calculated for each frame, corrected for decay, and plotted against time. The BP for [^{11}C]SCH23390 was calculated according to the Simplified Reference Tissue model (30). The cerebellum, where DA D1 receptor density is negligible, served as the reference region. The D1 receptor occupancy was calculated for the striatum according to the expression: $(BP_{rest} - BP_{antagonist})/BP_{rest}$.

The PET analysis demonstrated an average BP reduction of 47% in the striatum and of 50% in the DLPFC during the pharmacological challenge. These data confirm the expected 50% blockade of D1 receptors by the antagonist (26).

Results

Behavioral Data

The behavioral data are shown in Figure 2. For both accuracy and response latency, younger adults outperformed older adults, but there was no significant effect of load. Under the influence of the antagonist, the younger adults performance level dropped by approximately .6 items, and they were somewhat slower. These findings indicate that the antagonist had a detrimental effect on performance. This impression was substantiated by ANOVAs. For accuracy, there was a significant effect of age group [YP > older subjects; $F(1,36) = 36.33$, $p < .001$] but no significant effect of load [$F(1,36) < 1$] and no age group × load interaction ($F < 1$). There was also a significant effect of drug [YP > YA; $F(1,17) = 6.11$, $p = .02$] but no significant effect of load ($F < 1$) or drug × load interaction ($F < 1$).

For response latency, we also found a significant effect of age group [$F(1,36) = 18.10$, $p < .001$] but no significant effect of load ($F < 1$) and no age group × load interaction ($F < 1$). Finally, there was no significant effect of drug ($F < 1$) or load [$F(1,36) = 1.50$, $p = .23$] and no drug × load interaction ($F < 1$) for latency.

To control for order of administration (i.e., placebo first vs. antagonist first), this variable was entered as a between-subjects factor in the repeated-measures ANOVA. Results showed no significant effects of order either for accuracy ($F < 1$) or latency [$F(1,16) = 1.14$, $p = .30$].

fMRI Data

As expected, the comparison of the WM/high and WM/low conditions in the YP group revealed a network of fronto-parietal regions (Table 1). In these regions, a significant effect of group was seen in left inferior frontal gyrus (Brodmann area [BA] 9) and left inferior parietal lobule (BA 40) (Figure 3, Table 2). Follow-up *t* tests demonstrated significant differences in the frontal area between YP and older subjects ($p = .0007$) and YP and YA ($p = .002$) but not between YA and older subjects ($p = .79$). For the parietal area, there were significant differences between YP and older subjects ($p = .002$) and trends toward significance between YP and YA ($p = .10$) and between YA and older subjects ($p = .09$).

In regions outside the load-sensitive network (Table 1), the ANOVA revealed two significant effects of group. These regions were in left temporo-parietal junction (BA 39; Montreal Neurological Institute coordinates x = −54, y = −64, z = 18; $F = 11.9$) and left posterior cingulate gyrus (BA 23; x = −4, y = −60, z = 20; $F = 13.2$). In both these regions, the YP group showed a negative load-dependent response, whereas older adults and the YA group showed a positive response. Follow-up tests revealed significant differences in the temporal area between YP and older subjects ($p = .0005$) and between YP and YA ($p = .001$) but not between YA and older subjects ($p = .74$). For the posterior cingulate, the difference was again significant between YP and older subjects ($p = .0007$) and between YP and YA ($p = .002$) but not between YA and older subjects ($p = .71$).

Finally, in control analyses we defined load-sensitive regions on the basis of the data from all three groups (not only the YP group as in the preceding text). This resulted in highly similar patterns compared with the previous analysis regarding left frontal (BA 9, peak voxel −54,10,32) and parietal (BA 40, peak voxel −48,−40,44) regions. The only difference was that an additional region was revealed, located in extrastriate cortex (BA 18, peak voxel −12,−76,14). Further analysis of the response in this occipital region showed a reversed pattern compared with the activations in fronto-parietal cortex, such that load-depen-

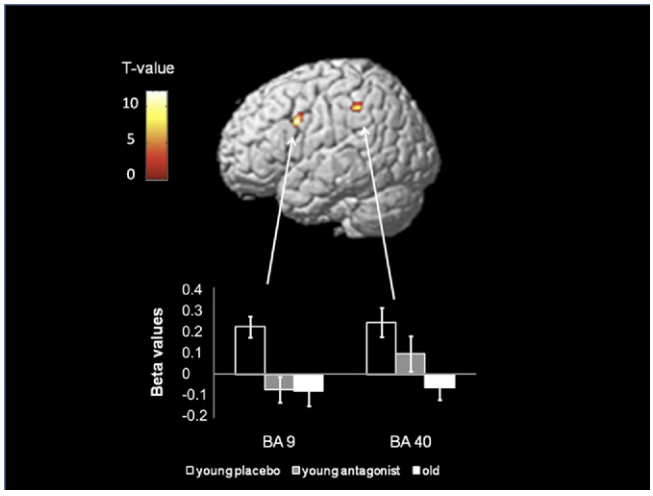

Figure 3. Brain regions showing load-dependent parametric blood oxygen level dependent effects (working memory–high > working memory–low) in young placebo, young antagonist, and older subjects groups during spatial working memory in left frontal (Brodmann area [BA] 9; −52,16,32) and parietal (BA 40; −48,−40,44) cortices.

Table 2. Parametric Differences in Brain Activation Between Younger Adults with and without D1 Antagonist and Older Adults During Spatial WM

Brain Area	Hemisphere	Brodmann Area	x	y	z	*F*	*p*
Frontal Cortex	L	9	−52	16	32	12.09	.001
Parietal Cortex	L	40	−48	−40	44	11.04	.002

Spatial coordinates (Montreal Neurological Institute) are for a peak activation of suprathreshold voxels. WM, working memory.

dent occipital activity was most pronounced in the older subjects group (mean = .18, SD = .23), intermediate in the YA group (mean = .08, SD = .25), and lowest in the YP group (mean = −.07, SD = .19). Because our focus was on examining whether a weaker load-dependent BOLD response in old age (and in younger adults under the influence of the dopaminergic antagonist) results from an altered DA system, we did not consider the occipital response further.

Discussion

The present finding of a load-dependent working memory effect in fronto-parietal regions along with age-related reductions within the same network is consistent with several previous observations (23–25). A novel observation is that younger adults under the influence of the DA-D1 receptor antagonist SCH23390 showed reduced accuracy in the SWM task accompanied by reduced load-dependent BOLD activity in the same fronto-parietal regions, with the strongest effect seen in frontal cortex. Thus, our findings show that challenge of the DA system by means of the D1 antagonist hampered both cognitive performance and functional brain activity. This impression is further supported by the PET findings, which on average showed a 50% blockade of D1 receptors after administration of the antagonist. It is notable that the load-dependent modulation of the BOLD signal in the younger subjects under placebo conditions occurred in the absence of behavioral load effects. Thus, although the performance levels were similar, increased working memory demands modulated neural activity in the placebo condition for the younger subjects. This pattern is consistent with past research indicating that neurobiological effects can co-occur with no behavioral differences (31–33).

Several previous studies implicate the dopaminergic systems in working memory (e.g., 34,35), and in a related study we demonstrated that D1 binding measured by PET accounted for much of the age-related variance in fronto-parietal BOLD data (36). The apparent positive relationship between DA and BOLD activity is also consistent with a number of recent studies (25,37,38). However, our findings add to prior research in suggesting a more direct link among: 1) altered DA neurotransmission, 2) age-related cognitive deficits, and 3) associated reductions in functional brain activity. As such, they support and extend correlational data that have related age-related cognitive deficits to a dysfunctional dopaminergic system (for review, see 6). The present findings also support predictions from computational models that altered dopaminergic neurotransmission in aging leads to less distinct cortical representations and resulting cognitive deficits (39,40). Thus, together with previous findings, the present data suggest that reduced dopaminergic neurotransmission results in lowered neural efficiency (weaker task-related modulation), possibly by decreasing the signal-to-noise ratio in relevant neuronal networks (41,42).

In two regions located outside the load-dependent network (left temporo-parietal cortex and posterior cingulate gyrus), group differences were also seen. In both these regions, younger adults under placebo conditions showed a negative load-dependent response, whereas older adults and younger adults under the antagonist showed a positive response. This pattern mimics previous findings of an aging-related attenuation of deactivation patterns seen in younger adults (43) and most critically constitutes additional evidence that dopaminergic depletion will make younger adults look more similar to elderly adults with regard to functional activation patterns.

Some study limitations should be noted. The first concerns the single- rather than double-blind nature of the study. The fact that the administering physician was not blind to the drug condition might have contributed to the effects observed. Another limitation is that the older group was not tested in a placebo condition, resulting in an unbalanced design. Finally, to demonstrate discriminant validity, future research should extend the current study, targeting other neurotransmitter systems as well as other pharmacological agents affecting dopaminergic neurotransmission (e.g., D2 antagonists).

In conclusion, the current findings point in the direction of a causative link of age-related reductions in D1 neurotransmission to lowered cognitive performance and associated brain activity. Dopamine is a key transmitter for many higher-order cognitive functions (for reviews, see 6,44), but other transmitters are most certainly also of relevance. An interesting task for future studies is therefore to extend this line of work to other neuromodulatory systems.

This research was supported by grants from the Swedish Research Council to LB and HF and from Swedish Brain Power to LB. The author LB was also supported by an Alexander von Humboldt Research Award. The author LN was supported by grants from the Swedish Research Council and the Joint Committee for Nordic Research Councils for the Humanities and the Social Sciences. The author SK was supported by a postdoctoral fellowship from the Swedish Research Council, and SM was supported by a Scholar Award from the Michael Smith Foundation for Health Research.

The authors reported no biomedical financial interests or potential conflicts of interest.

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