Recent studies have emphasized the importance of dopamine projections to the prefrontal cortex (PFC) for working memory (WM) function, although this system has rarely been studied in humans in vivo. However, dopamine and PFC activity can be directly measured with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), respectively. In this study, we examined WM capacity, dopamine, and PFC function in healthy older participants in order to test the hypothesis that there is a relationship between these 3 factors. We used the PET tracer 6-[18F]fluoro-L-tyrosine to measure dopamine synthesis capacity in the striatum (caudate, putamen), and event-related fMRI to measure brain activation during different epochs (cue, delay, probe) of a WM task. Caudate (but not putamen) dopamine correlated positively with WM capacity, whereas putamen (but not caudate) dopamine correlated positively with motor speed. In addition, delay-related fMRI activation in a left inferior prefrontal region was related to both caudate dopamine and task accuracy, suggesting that this may be a critical site for the integration of WM maintenance processes. These results provide new evidence that striatal dopaminergic function is related to PFC-dependent functions, particularly brain activation and behavioral performance during WM tasks.

Keywords: aging, caudate, fMRI, maintenance, PET, putamen

Introduction

Working memory (WM) is the set of cognitive and neural processes involved in holding information in mind for later use (Baddeley 1992), and it is critical for carrying out many everyday tasks. A substantial body of evidence supports roles for both prefrontal cortex (PFC) and dopaminergic neurotransmission in normal WM function (Cools and Robbins 2004). During the delay epoch of WM tasks, maintenance processes make it possible to hold information in mind in the absence of external stimuli. This period, in particular, appears to engage the dopamine system in the PFC (Williams and Goldman-Rakic 1995; Floresco and Phillips 2001) through a cyclic adenosine monophosphate and D1 receptor mediated process in which low levels of dopamine improve spatial tuning of PFC neurons, whereas high levels of dopamine impair tuning (Vijayraghavan et al. 2007). A variety of factors related to variability in dopamine function may thus underlie behavioral performance on WM tasks. It has been hypothesized that WM capacity, in particular, is associated with dopaminergic variability (Salthouse et al. 1991; Kimberg et al. 1997; Kimberg et al. 2001). Although the mesocortical circuit is the source of direct dopaminergic input to the PFC, influencing neural function and behavior, it has also been proposed that nondopaminergic inputs to the PFC from the caudate (via basal ganglia-thalamocortical loops) (Alexander et al. 1986) may be critically involved as well, a theory supported by the involvement of the caudate in WM tasks (Lewis et al. 2004) as well as studies of WM in patients with Parkinson’s disease (PD; Owen et al. 1998).

The hypothesized associations between dopamine function and WM capacity (Kimberg et al. 2001) are based on inferences, rather than direct measurements, of endogenous dopamine markers. However, direct measurement of dopamine (DA) function in humans is possible with positron emission tomography (PET) and a number of different ligands for presynaptic DA synthesis capacity, DA transporters, vesicular transporters and dopamine receptors. In this study, we utilized the tracer 6-[18F]fluoro-L-tyrosine (FMT) which is a good substrate for aromatic amino acid decarboxylase (AADC) thus providing a method of assaying the synthesis capacity of DA neurons in the densely DA-innervated striatum (DeJesus et al. 1997; Jordan et al. 1997).

In this study, our goal was to relate DA synthesis capacity (measured with FMT-PET) to event-related brain activation (measured with functional magnetic resonance imaging [fMRI]) during performance of a WM task as an index of brain activation. We were specifically interested in evaluating relationships between dopaminergic function, WM capacity, and load-related activation in the PFC, based on the known neural circuits (Alexander and Crutcher 1990; Middleton and Strick 2000) and the substantial evidence linking caudate activation, dopamine, and WM (Volkow et al. 1998; Kimberg et al. 2001; Carbon et al. 2004; Chang et al. 2007; Cools et al. 2008). We were also interested in examining possible differences in caudate and putamen dopamine, based on the hypothesis that the putamen is disproportionately involved in motor processing, whereas the caudate is primarily involved in cognitive function (Bhatia and Marsden 1994; Rinne et al. 2000). Finally, we studied healthy older individuals because normal aging is associated with increased individual differences in WM performance, brain activation (Reuter-Lorenz and Lustig 2005), and dopamine function (Backman et al. 2000; Erixon-Lindroth et al. 2005), so this group was likely to provide sufficient variability to identify correlational relationships between these factors.

Materials and Methods

Participants

23 healthy older right-handed participants (5 males; mean age = 67.1 ± 7.4; mean years of education = 17.9 ± 3.3) were recruited from the Berkeley Aging Cohort, a database of healthy older participants living in Berkeley and the surrounding community. Inclusion criteria for participation were 1) age between 55 and 85 years, 2) Mini-Mental State Examination (MMSE) score ≥ 26, 3) normal cognitive function as...
Methods). Accuracy scores were highly positively skewed (mean percent trials and accuracy for low load trials (2 letters), and high-load trials this test.

Our WM capacity was the total number of words recalled across all 7 levels of final word from each sentence in the correct order. Our WM capacity questions they read simultaneously, then turn the page and write the sets of consecutive unrelated sentences (e.g., "After dinner, the chef..."

Salthouse and Babcock Listening Span task (Salthouse et al. 1991). That WM performance (but not global cognitive ability) was related to questions they read simultaneously, then turn the page and write the sets of consecutive unrelated sentences (e.g., "After dinner, the chef..."

Behavioral Testing and Analysis

A neuropsychological battery was given during an initial session within 2 months of the fMRI and PET scans in order to obtain measures of 1) global cognitive ability, to ensure normal cognitive function, 2) WM function, 3) motor speed. Correlations (Pearson’s R) were conducted between these neuropsychological test measures and the PET region of interest (ROI) measures (see PET methods below) at P < 0.05.

Tests of global cognitive ability included the MMSE (Folstein et al. 1975) and several subsets of the Wechsler Adult Intelligence Scale—Revised (Wechsler 1987).

Two WM performance measures were used to test our hypothesis that WM performance (but not global cognitive ability) was related to dopamine function. First, WM capacity was measured using the Salthouse and Babcock Listening Span task (Salthouse et al. 1991).

Briefly, this test requires participants to listen to the experimenter read sets of consecutive unrelated sentences (e.g., "After dinner, the chef prepared dessert for her guests") that increase in number from 1 to 7. There are 3 trials at each the 7 levels, for a total score of 84 possible correct words. During each trial, the participant is asked to listen to the sentences while checking boxes in response to comprehension questions they read simultaneously, then turn the page and write the final word from each sentence in the correct order. Our WM capacity measure was the total number of words recalled across all 7 levels of this test.

The second WM measure was mean reaction times (RTs) for correct trials and accuracy for low load trials (2 letters), and high-load trials (6 letters) of the Sternberg delayed recognition task (Sternberg 1966), performed during the fMRI scanning session (see fMRI Behavioral Methods). Accuracy scores were highly positively skewed (mean percent trials correct = 93.2 ± 9.9%) and were corrected using an arcsine transformation ($x = \arcsin(\sqrt{p})$). Finally, motor speed was measured with the simple RT (zero load) condition of the Sternberg task. Planned linear regressions between dopamine ROI $K_i$ and behavioral measures were carried out at $P < 0.05$, 2 tailed.

PET Methods

The tracer FMT is a substrate for AADC and thus reflects the capacity of AAAD to produce 6-[18F]fluorometatyramine (FMA). FMA is rapidly cleared (half-life approximately 10 min) and is quickly eliminated in the urine (Salthouse et al. 1991).

PET Voxelwise Correlational Analyses

To prepare voxelwise $K_i$ volumes in a common space across subjects, each voxelwise $K_i$ volume in native space was spatially normalized to a custom template that was created using the minimum deformation method of Kochunov et al. (2001) that was implemented using SPM2, and spatial normalization. Briefly, this template was created as follows: First, $K_i$ volumes were coregistered to each subject’s high-resolution MR volume; second, an arbitrary MR volume was coregistered to Montreal Neurological Institute (MNI) template space; third, the other MR volumes were coregistered to this arbitrary MR volume; third, the $K_i$ volume that minimized deformations for all other $K_i$ volumes was identified and mean deformations were applied to it. This interpolated...
volume served as the final template. All MR volumes were normalized to the template, and the normalization parameters were applied to each subject’s Ki volume.

Voxelwise linear regressions were carried out with these Ki volumes and subjects’ test scores for the neuropsychological measures listed in Table 1 (Listening Span Test, Vocabulary, Arithmetic, motor speed) at $P < 0.001$ (2 tailed), uncorrected. A 15 voxel extent threshold was used rather than the clusterwise correction applied to the fMRI data because we anticipated finding relatively small clusters within the striatum, the predominant site of FMT uptake.

### fMRI Imaging Methods

fMRI experiments were performed at the Henry H. Wheeler, Jr. Brain Imaging Center with a Varian Unity-Inova whole body 4.0T scanner (Palo Alto, CA; www.varianinc.com) with a transverse electromagnetic send-and-receive head coil (MR Instruments, Minneapolis, MN; www.mrinstruments.com).

The imaging session lasted approximately 70 min, and consisted of acquisition of anatomical and functional images. Two Ti-weighted anatomical scans were acquired. The first was coplanar with the echoplanar imaging (EPI) data and was collected using a gradient-echo multislice sequence (time repetition [TR] = 200 ms, time echo [TE] = 5 ms, field of view [FOV] = 22.4 cm$^2$, matrix size = 256 x 256, in-plane resolution $= 0.875 \times 0.875$). The second was a high-resolution anatomical scan for use in ROI drawing, intersubject coregistration, and normalization to the MNI reference brain. This scan was acquired with an MP-FLASH 3D sequence (TR = 9 ms, TE = 5 ms, FOV = 22.4 x 22.4 x 19.8 cm, matrix size = 256 x 256 x 128, resolution = 0.875 x 0.875 x 1.54 mm).

Functional imaging consisted of 2-shot gradient-echo EPI images acquired for 18 axial slices with a FOV of 22.4 cm, flip angle of 20°, 3.5 mm x 3.5 mm x 5 mm in-plane voxel size with 5-mm slice thickness and a 1-mm gap for full brain coverage, and a 64 x 64 matrix. Functional scans were conducted with TR = 2000 ms and TE = 28 ms.

Letter stimuli for the delayed recognition task were presented using E-Prime (Psychology Software Tools, Pittsburgh, PA) during continuous scanning. Participants viewed stimuli in the scanner via back-projection onto a custom designed nonmagnetic screen mounted at the participant’s chest level, which was viewed using an angled mirror placed inside the head coil. Participants responded to stimuli presented on the screen by making yes/no key-presses on a nonmagnetic response box designed for use in the scanner. Prior to scanning, participants with poor visual acuity were fitted with nonmagnetic corrective lenses.

### fMRI Behavioral Methods

Subjects performed a version of the Sternberg delayed recognition task using letter stimuli (Sternberg 1966; Rypma et al. 2002; Gibbs and D’Esposito 2005) during the fMRI scanning session. Prior to scanning, participants completed a practice run of 15 trials on a computer in order to familiarize them with the task.

Each trial of the Sternberg delayed recognition task consisted of cue (4 s), delay (12 s), and probe (2 s) epochs. During the cue, 2, 4, or 6 block capital letters were presented, followed by an unfilled delay. Following the delay, a single lowercase probe letter appeared, and participants were instructed to indicate whether the probe letter was a part of the set presented during the cue with a manual button-press (right = yes left = no). A lowercase letter was used for the probe in order to prevent retrieval from the encoding set based on perceptual features alone. The probe was followed by a jittered intertrial interval lasting between 8 and 12 s. Five trials of each of the 3 types were presented per 7-min run. There were 6 runs, for a total of 90 trials per scanning session. The 3 memory loads were counterbalanced across each scanning run and across the session.

At the end of the scanning session, when the high-resolution image was being acquired (but no functional data), subjects performed 15 trials of a “zero load” condition of the delayed recognition task in order to measure RT under conditions when WM load did not contribute to RT. These trials were identical to the 2, 4, and 6 load conditions, except that the letter stimuli were replaced with 4 Xs during the cue and with a single “X” during the probe, and only behavioral data was acquired in order to measure simple motor speed. Subjects were instructed to press both right and left buttons when they saw the single “X” presented during the probe epoch.

### fMRI Statistical Analyses

Functional images acquired from the scanner were reconstructed offline from k-space. Image volumes were corrected for slice timing skew using temporal sync-interpolation and corrected for movement using rigid-body transformation parameters. Image preprocessing and statistical analyses were performed using SPM2 (www.filion.uc.ac.uk/spm). Images were smoothed with a 7-mm FWHM Gaussian kernel. A high-pass filter was used to remove frequencies below 0.01 Hz from the data.

Data were analyzed using the general linear model (GLM) (Worsley and Friston 1995). For each subject, the blood oxygen level-dependent (BOLD) signal for each task epoch (cue, delay, and probe) and for each trial type (low load, 2 letters; medium load, 4 letters; high load, 6 letters) were modeled as impulses of neural activity convolved with the SPM canonical hemodynamic response function relative to the fixation epoch. Covariates were entered into the GLM according to the following structure: the first covariate was at the onset of the cue epoch (first TR, 0 s), modeling encoding processes during the cue epoch. A second covariate at the third TR (+ 4 s) modeled late cue-related activity. Because late encoding processes may continue into the delay, this late cue covariate was modeled to reduce noise in the estimate of the baseline, but was not included in contrasts used to define ROIs (Zarahn et al. 1999). The early and late phases of the delay epoch were modeled with covariates at the fifth and seventh TRs, respectively (8 and 12 s), associated with maintenance processing. The delay effects reported here represent the sum of the 2 delay covariates. The probe epoch was modeled with a covariate at the onset of the probe (ninth TR, 16 s), associated with memory retrieval.

In order to restrict our analyses to activation related to accurate performance (correct trials only), we modeled incorrect trials using a separate covariate which was not included in the subsequent contrasts outlined below. In order to examine brain activation related to increased WM demand, rather than primary sensory or motor processing, individual contrast maps of regions with greater activation at higher WM loads were then generated with the contrast [1, 0, +1] (low load, 2 letters; medium load, 4 letters; high load, 6 letters) for each task epoch (cue, delay, probe).

Finally, each participant’s brain was normalized to the MNI reference brain using SPM2. Spatial normalization was then performed as a 2-step procedure: first, the high-resolution MP-FLASH anatomical structural image was coregistered to the structural image in-plane with the EPI images using SPM2. Second, the MP-FLASH image was spatially normalized using SPM2. The resulting transformation was used to spatially normalize the individual contrast maps.

### Table 1

Caudate and putamen dopamine function correlate with distinct behavioral indices

<table>
<thead>
<tr>
<th>Dopamine synthesis</th>
<th>Caudate</th>
<th></th>
<th>Putamen</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R$</td>
<td>$p$</td>
<td>$R$</td>
<td>$p$</td>
<td></td>
</tr>
<tr>
<td>Neuropsychological measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Listening span</td>
<td>0.45</td>
<td>0.04</td>
<td>0.34</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Vocabulary</td>
<td>-0.10</td>
<td>0.97</td>
<td>0.06</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>Arithmetic</td>
<td>-0.06</td>
<td>0.81</td>
<td>0.18</td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td>Sternberg task performance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT—zero load/simple RT only</td>
<td>-0.12</td>
<td>0.60</td>
<td>-0.45</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>RT—low load trials</td>
<td>0.13</td>
<td>0.57</td>
<td>0.01</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>RT—high load trials</td>
<td>0.30</td>
<td>0.18</td>
<td>0.20</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>Accuracy—low-load trials</td>
<td>0.13</td>
<td>0.56</td>
<td>0.22</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>Accuracy—high-load trials</td>
<td>0.39</td>
<td>0.08</td>
<td>0.29</td>
<td>0.19</td>
<td></td>
</tr>
</tbody>
</table>

Note: Pearson’s correlation coefficients ($R$) are shown for relationships between behavioral data (neuropsychological test measures, behavioral measures from the Sternberg task performed during fMRI scanning) and $K_i$ values reflecting dopamine synthesis capacity in caudate and putamen. Sternberg delayed recognition task performance measures include mean accuracy and RT for low (2 letters) high (6 letters) WM loads.
ROI measures (caudate and putamen activation at each trial epoch (cue, delay probe) correlated with PET uncorrected, in order to identify regions where load-sensitive dopamine synthesis correlates with WM capacity across individuals (see Fig. 1). There were no significant voxels that resulted from correlations with vocabulary and arithmetic scores. PET Voxelwise Analysis Linear regression was conducted on the voxelwise PET volumes using the neuropsychological measures listed in Table 1 as covariates. This analysis revealed that in bilateral regions in the dorsomedial portion of the caudate was related to WM capacity across individuals (see Fig. 1). There were no significant voxels that resulted from correlations with vocabulary or arithmetic scores. PET ROI Analysis Across individuals, caudate ROI \( K_i \) values ranged from 0.0162 to 0.0240 (mean = 0.0201 ± 0.0025). Putamen \( K_i \) values were higher than caudate \( K_i \) values (\( P < 0.001, \) 2 tailed).

Regression analyses between behavioral measures (neuropsychological test and Sternberg task data) and caudate and putamen ROI \( K_i \) values are listed in Table 1. With respect to the neuropsychological measures, Caudate \( K_i \) values showed a positive correlation with WM capacity (Listening Span Test) (\( R = 0.45, P = 0.04 \)) and a marginal correlation with Sternberg task accuracy for high-load (but not low load) trials (\( R = 0.39, P = 0.08 \)). Putamen \( K_i \) values did not correlate with any of the cognitive neuropsychological measures, but putamen did correlate negatively with simple RT (zero load trials on the Sternberg task; \( R = -0.45, P = 0.05 \), 2 tailed; Table 1), indicating that faster motor speed was associated with higher putamen dopamine function. Caudate \( K_i \) values showed no relationship to motor speed.

Finally, age did not correlate with caudate or putamen \( K_i \) values. Age did correlate negatively with Listening Span test performance (\( R = -0.43, P = 0.04 \)), but effects of age were not significant for other neuropsychological measures (\( P > 0.10 \)). Because of the correlation between age and Listening Span test performance, we performed a follow-up analysis, partialling out the effect of age in the significant relationship between Listening Span test performance and caudate ROI \( K_i \) (shown in Table 1). The positive correlation between Listening Span test performance and caudate ROI \( K_i \) remained significant (\( R = 0.54, P = 0.01 \)) after accounting for age.

Load-Sensitive Brain Activation The fMRI random-effects analysis identified a number of brain regions showing significantly greater activation with increased WM load during performance of the delayed recognition task (see Fig. 2 and Table 2). Overall, we observed load-related activation across a bilateral network of prefrontal, premotor, motor, parietal, and visual regions during the cue and delay epochs, but only one region (in the left middle frontal gyrus) during the probe.

During the cue epoch, there was increased load-sensitive activation in bilateral middle frontal gyri, inferior frontal gyri, precentral gyri, supplementary motor area, superior and inferior parietal lobules, occipital cortex, caudate, putamen,
and thalamus. During delay, load-sensitive regions included bilateral premotor gyri, middle and inferior frontal gyri, and left superior parietal lobule. During the presentation of the probe, there was only one load-sensitive region, located in left middle frontal gyrus.

**fMRI Voxelwise Analysis**

Voxelwise regressions on load-sensitive voxels during all 3 trial epochs revealed that there were no significant voxels during the cue or probe epochs that correlated with either caudate or putamen ROI $K_i$. During the delay period, however, we identified a correlation between putamen $K_i$ and delay activation located in the right supramarginal gyrus (maximum; 45, −38, 46 mm) (not shown).

Also during the delay period, we identified a significant correlation between caudate $K_i$ and activation in a region at the border of the left middle frontal gyrus and precentral gyrus (maximum; −38, 4, 36 mm). The correlation between caudate $K_i$
and mean parameter estimates in this region for each individual is shown in Figure 3. This region overlaps with the inferior frontal junction (IFJ), which lies posterior to the mid-dorsolateral PFC at the intersection of inferior frontal sulcus and the inferior precentral sulcus (Brass et al. 2005). A follow-up analysis also showed that the mean parameter estimates for this region correlated positively with mean task accuracy ($R = 0.64, P < 0.05$).

**Discussion**

This study reports that variability in striatal dopamine function is linked to both WM capacity and brain activation during WM maintenance in older individuals. In particular, ROI and voxelwise analyses of PET data revealed that caudate dopamine function is correlated with WM capacity. Putamen dopamine, in contrast, correlated with motor speed but not WM performance. With respect to our fMRI results, we observed significant relationships between brain activation and dopamine function only during the delay epoch of the WM task, and not the cue or probe. Specifically, we found that activation related to increased WM load in a left IFJ region correlated with caudate dopamine ROI $K_v$ and Sternberg task accuracy. Also during the delay, activation in a right supramarginal gyrus region correlated with putamen dopamine.

Taken together, the relationships between all 3 factors (striatal dopamine, WM performance, and brain activation related to WM maintenance) suggest that caudate dopamine function plays a unique role in mediating WM capacity and load-dependent PFC activation.

The association between caudate dopamine and WM capacity is congruent with our fMRI results, which show that caudate dopamine was associated with activation in the inferior frontal gyrus during WM maintenance. The maintenance processes and motor preparation processes required during the delay epoch of WM tasks are thought to be more dependent on dopamine function than other WM processes (Goldman-Rakic 1996). Maintenance processing under high-load demand is also likely a key component of the complex set skills required for the Listening Span Test, which would explain why caudate dopamine correlated with both maintenance-related activation and performance on this task.

Our findings are consistent with previous studies that have reported correlations between dopamine function and measures of cognitive and motor performance in healthy aging (Volkow et al. 1998; Errixon-Lindroth et al. 2005) and young subjects (Kimberg et al. 1997, 2001), along with recent data.
supporting a relationship between WM capacity and dopamine synthesis capacity in young adults (Cools et al. 2008). Our behavioral results are also in agreement with previous studies and existing conceptualizations of separate roles for caudate and putamen in motor and cognitive functions, respectively. Our finding that WM capacity (and, marginally, recognition accuracy) is related to caudate $K_c$ whereas motor speed is related only to putamen $K_p$ agrees with data from studies of PD patients (Rubin 1999; Rinne et al. 2000; Bruck et al. 2001), patients with striatal lesions (Bhatia and Marsden 1994), and fMRI studies of activation in healthy subjects as well (Lewis et al. 2004). In addition, this pattern is consistent with the functional organization of basal ganglia-thalamocortical loops in which pathways are segregated into motor and dorsolateral PFC or “cognitive” circuits involving putamen and caudate, respectively (Alexander et al. 1986). Our data also show that caudate dopamine is related with some topographic specificity to delay-period activation in PFC, in the left IFJ, to which it is reciprocally linked (Lehericy et al. 2004) (Fig. 3).

Putamen dopamine, on the other hand, correlated with maintenance-related activation in the supramarginal gyrus, just posterior to the postcentral gyrus. Based on our behavioral results, we predicted that putamen dopamine would correlate primarily with activation in regions that participate in motor or motor preparation. However, the right supramarginal gyrus activation we observed is posterior to these regions, in the inferior parietal lobule, a multimodal region that is involved in the integration of visual and sensorimotor information, and is frequently coactivated with PFC during WM paradigms (Wager and Smith 2003).

The neuroimaging data thus do not support a strict dissociation for the roles of caudate and putamen with cognitive and motor functions, respectively, but instead provide evidence that both caudate and putamen dopamine contribute to cognitive aspects of the task. Thus dopaminergic neurotransmission within caudate and putamen nigrostriatal circuits may jointly influence WM function because of some degree of functional integration (Haber 2003). Through the integration of these nigrostriatal circuits, dopaminergic changes that influence the PFC will also lead to changes in parietal regions as well. Supporting this idea are recent FDG PET studies which report that inferior and posterior parietal regions are part of a network including the PFC that shows reduced glucose metabolism that parallels disease progression (Huang, Tang, et al. 2007) and executive function deficits (Huang, Mattis, et al. 2007) in Parkinson’s disease patients. This concept of the joint influence of caudate and putamen dopamine on WM is also consistent with the nonsignificant correlation trend we found between WM capacity and putamen dopamine ($P = 0.12$, see Table 1) and with the findings of Chang et al. (2007), who reported bilateral dorsal putamen load-related BOLD activation during the encoding and maintenance phases of a very similar task (Chang et al. 2007). Finally, another explanation that is compatible with these ideas is that because the maintenance period involves motor preparation as well as WM maintenance, the supramarginal gyrus activation that correlates with putamen dopamine may reflect engagement of attentional processes required specifically for the motor preparation of the upcoming response.

Although the mesocortical dopamine system has previously been thought to support WM function through innervation of the PFC, our results support a specific role for the nigrostriatal dopaminergic system in this cognitive process. This role is consistent with results obtained in PD patients (Owen et al. 1998; Mattay et al. 2002; Lewis et al. 2003; Monchi et al. 2004) and normal subjects (Owen et al. 1996; Chang et al. 2007). In a recent study that also used the Sternberg task and an event-related fMRI design (Chang et al. 2007), load-related patterns of both basal ganglia and cortical activation were similar to those reported here. Interestingly, this study also employed a connectivity analysis to show associations between striatal and cortical activity during the maintenance phase of this task, supporting a role for basal ganglia–PFC interactions during WM maintenance. Both our study and Chang et al. reported bilateral load-related activation of the striatum during performance of this task, which supports the idea that putamen, as well as caudate, contributes to the cognitive aspects of the task. We observed this load-related activation during the encoding period, as opposed to the delay period as also observed by Chang et al. which we would have predicted because we observed the correlations with dopamine variability. The fact that we did not observe striatal activity during the delay may be due to differences in statistical thresholding used in our study compared with that of Chang et al. Nonetheless, these findings provide support for the idea that dopamine release is associated with increased BOLD signal (Knutson and Gibbs 2007). Our data extend these findings by providing support for a relationship between striatal dopaminergic function, behavior, and PFC activity that is most pronounced during the delay period of this task. We report here that improved cognition is associated with greater dopaminergic function and more cortical activation, findings that support the idea of increased activation in healthy aging that provides a compensatory role and underlies successful performance (Cabeza 2002; Cabeza et al. 2002).

The anatomy and physiology of the basal ganglia-thalamocortical circuits provide a mechanism that may account for these findings. Through its inhibitory action via the “direct” pathway (Parent and Lavoie 1993), striatal dopamine should reduce inhibitory pallidal outflow to the thalamus and thereby excite cortex. This idea has been supported by observations of altered pallidal outflow in PD patients (Owen et al. 1992) and increased brain activation in motor cortex with dopaminergic treatment of PD patients (Jenkins et al. 1992; Rascol et al. 1994; Sabatini et al. 2000; Mattay et al. 2002). Electrophysiological studies in primates demonstrate increased firing rates in both caudate (Hikosaka et al. 1989) and thalamus (Fuster and Alexander 1973) during the delay period of a delayed-response task, and decreased firing rates in globus pallidus (Mushiake and Strick 1995). These data have prompted computational models of WM in which the striatum plays an active role in maintenance through pallido-thalamocortical projections that sustain activity in PFC (Monchi et al. 2000; Frank et al. 2001; Ashby et al. 2005; Gruber et al. 2006). Our data thus support a model in which striatal dopamine plays a key role in WM maintenance and cortical excitation.

Although striatal dopamine function appears to play an important role in this WM task, the PFC is critically involved as well. The left PFC, in particular, appears to play several roles that are relevant to the interpretation of our results. Load-related fMRI activation in the left inferior frontal gyrus has been observed previously for this task (Awh et al. 1996; Altamura et al. 2007) and may be related to subvocal rehearsal. There is a great deal of evidence that PFC activation increases when WM
demand is high (Hester and Garavan 2004). This data, in conjunction with studies reporting changes in PFC activation that are associated with responses to dopaminergic medication (Gibbs and D’Esposito 2005), provide support for our findings that the influence of dopamine on PFC function is most apparent under high-load conditions.

The IFJ is a region receiving recent attention for its role in cognitive control (Brass et al. 2005), a process that is also strongly associated with dopamine function and the PFC (Braver and Cohen 2000a). The IFJ is located just posterior to the ventral PFC, at the junction of premotor, language, and WM domains, and is known to be activated in tasks that require the unification of these domains (Brass et al. 2005). In particular, the peak coordinates of a region found to increase activation in parallel with increased WM load during a task similar to ours were very close to the region we report here (Hester and Garavan 2004). Furthermore, a recent meta-analysis identified the IFJ as a critical region for a number of tasks whose common theme was updating abstract task representations following a cue (Derrfuss et al. 2005). This is entirely consistent with our observation of activation in this region, in that both WM maintenance and high-load conditions are situations requiring updating of abstract task representations.

A critical feature of the IFJ region we identified was that it correlated with caudate dopamine function and task accuracy (Fig. 3), suggesting that it is a candidate site for the integration of to-be-remembered information with preparation of the motor response. Dopaminergic transmission may be particularly important during WM maintenance because it is during this period that subjects maintain the cue stimulus in WM and prepare for the appearance of the probe stimulus and the subsequent motor response. This period requires both stimulus maintenance and motor preparation, the integration of which is associated with activation the IFJ. Thus our data provides evidence that this integrative role of the IFJ may, in addition, depend on dopamine function in the caudate.

Several additional points related to the interpretation of these findings also deserve comment. First, an important distinction between our 2 neuroimaging measures was that our PET data represent a static measure of dopamine synthesis occurring over long times, whereas our fMRI data represent a dynamic measure of brain activation.

Second, it is important to note that the associations we observed between striatal dopamine and PFC function do not indicate which factor plays the causal role. Although the most obvious explanation is that variability in dopamine levels influences PFC function via the nigrostriatal circuit as described above, the effects we observed could also be explained by increased input from frontal regions to the striatum. Within the nigrostriatal circuit, there is glutamatergic feedback frontal regions to the anterior caudate and putamen (Pycock et al. 1980; Parent and Hazrati 1995), and this pathway has been shown to induce dopamine release in the striatum using repetitive transcranial magnetic stimulation of the dorsolateral PFC (Strafella et al. 2001). Finally, our study does not compare young and old subjects and therefore does not address possible differences in dopamine function or PFC activity across the lifespan. Although we found no evidence for an effect of age on dopamine synthesis, it is possible that age-related processes contributed to the variability in both dopamine and brain activation. The tracer FMT is an index of AADC activity, which appears to remain stable or show only slight decreases with age (Kish et al. 1992) that are disproportionate to the marked decreases in dopamine transporters (Volkow et al. 1996; Erixon-Lindroth et al. 2005) and receptors (Volkow et al. 2000) in normal aging. These findings, in conjunction with studies in rodents which have reported increases in AADC activity following treatments that decrease dopaminergic transmission (Zhu et al. 1992; Young et al. 1993) suggest that successful WM processing in aging may involve preservation or upregulation of the dopamine-mediated nigrostriatal pathway, although this idea is not proven (Haycock et al. 2003).

Although these data provide support for the role of striatal dopamine in WM capacity and maintenance, many questions about the specific role of these structures as well as the pharmacology of the effect require exploration. For example, it is unclear exactly how the striatum is involved in maintenance, and whether its function is also related to the proposed role that this structure may play in both gating and updating representations. Our data suggest that a major role may be to integrate maintenance and motor preparation. As we have examined dopamine synthesis capacity, the relative contribution of D1 and D2 receptor families is also unknown. Finally, the considerable evidence implicating PFC dopamine in WM function suggests that the mesocortical and nigrostriatal dopamine systems must work together in carrying out this cognitive task although the nature of this interaction is unknown.

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**References**


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