

Dopamine D2 receptor availability is linked to hippocampal–caudate functional connectivity and episodic memory

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D1 and D2 dopamine receptors (D1DRs and D2DRs) may contribute differently to various aspects of memory and cognition. The D1DR system has been linked to functions supported by the prefrontal cortex. By contrast, the role of the D2DR system is less clear, although it has been hypothesized that D2DRs make a specific contribution to hippocampus-based cognitive functions. Here we present results from 181 healthy adults between 64 and 68 y of age who underwent comprehensive assessment of episodic memory, working memory, and processing speed, along with MRI and D2DR assessment with [¹¹C]raclopride and PET. Caudate D2DR availability was positively associated with episodic memory but not with working memory or speed. Whole-brain analyses further revealed a relation between hippocampal D2DR availability and episodic memory. Hippocampal and caudate D2DR availability were interrelated, and functional MRI-based resting-state functional connectivity between the ventral caudate and medial temporal cortex increased as a function of caudate D2DR availability. Collectively, these findings indicate that D2DRs make a specific contribution to hippocampus-based cognition by influencing striatal and hippocampal regions, and their interactions.

dopamine | memory | hippocampus

Dopamine (DA) plays a key role in several cognitive processes (1–4). Reductions of D1 and D2 DA receptors (D1DRs and D2DRs) in aging (5–7) have been linked to age-related cognitive deficits (8, 9). The D1DR system has been related to functions supported by the prefrontal cortex (PFC), such as working memory and executive functions (10–12), which may reflect the relatively high density of D1DRs in the PFC (13). However, the role of D2DRs is far less clear. D2DRs are present in the PFC at very low densities (13), and evidence supporting a role for the D2DR system in working memory and executive functions is elusive (10). Pharmacological (14, 15) and PET studies assessing striatal D2DR availability (or binding potential to nondisplaceable tissue uptake; BP_{ND}) with [¹¹C]raclopride (16, 17) have yielded mixed findings in relation to cognition. It has been hypothesized that D2DRs make a specific contribution to hippocampus-based cognitive functions (10, 18, 19). Supporting these claims, positive links between D2DR BP_{ND} and episodic memory are commonly observed (20–23). PET imaging of hippocampal D2DR BP_{ND} also provides support for this hypothesis, although some studies indicate that hippocampal D2DRs may be related to both episodic memory and PFC-based executive functions (22, 23), including verbal working memory (24). Medial temporal lobe regions have been implicated in working memory (25, 26), and D2DR-mediated modulation may be exerted via hippocampal–cortical pathways (27). In addition, a [¹¹C]raclopride task-activation PET study demonstrated contributions of striatal D2DRs to a verbal working-memory task (11).

Taken together, the specific role of the D2DR system in cognition remains unclear, likely due to the fact that past studies included small and age-heterogeneous samples and lacked comprehensive test batteries that allowed systematic comparison of the role of D2DRs in different cognitive functions. Here we present results from the Cognition, Brain, and Aging (COBRA) study that include assessment of episodic memory, working memory, and processing speed, in combination with [¹¹C]raclopride PET and MRI of 181 healthy adults between 64 and 68 y of age (28). The main analyses concerned caudate D2DR–cognition associations, as this striatal region has been implicated in cognitive functioning (11, 12, 29, 30). Subsequently, whole-brain analyses were conducted to examine extra-striatal (especially hippocampal) D2DRs in relation to cognition. Finally, resting-state functional connectivity patterns were analyzed in relation to D2DR BP_{ND}, with special focus on interactions between the ventral caudate (31) and medial temporal cortex regions (32, 33).

Results

Caudate D2DR Availability and Cognitive Performance. We observed a significant positive relation between caudate D2DR BP_{ND} and episodic memory ($r = 0.19$, $P = 0.012$; Fig. 1A) but not for working memory or perceptual speed ($r = -0.09$, $P > 0.05$ for both). Performing the same analyses while controlling for caudate volume, correlations of similar magnitudes between D2DR BP_{ND} and performance were obtained ($r = 0.20$, $P = 0.010$ for episodic memory; $r = -0.08$, $P > 0.05$ for both working memory and speed). Thus,

Significance

Cognitive functioning depends in part on dopamine neurotransmission in the brain. Research implicates the dopamine D1 receptor family in cognitive functions linked to the prefrontal cortex, such as working memory. The dopamine D2 receptor family has also been linked to cognition, but it remains unclear to which cognitive functions it is specifically related. We examined the relation of D2 receptors to episodic memory, working memory, and speed of processing. D2 receptors in the caudate and hippocampus were related to episodic memory and modulated caudate–hippocampal functional connections. These findings link the dopamine D2 system to hippocampus-based cognitive functions.

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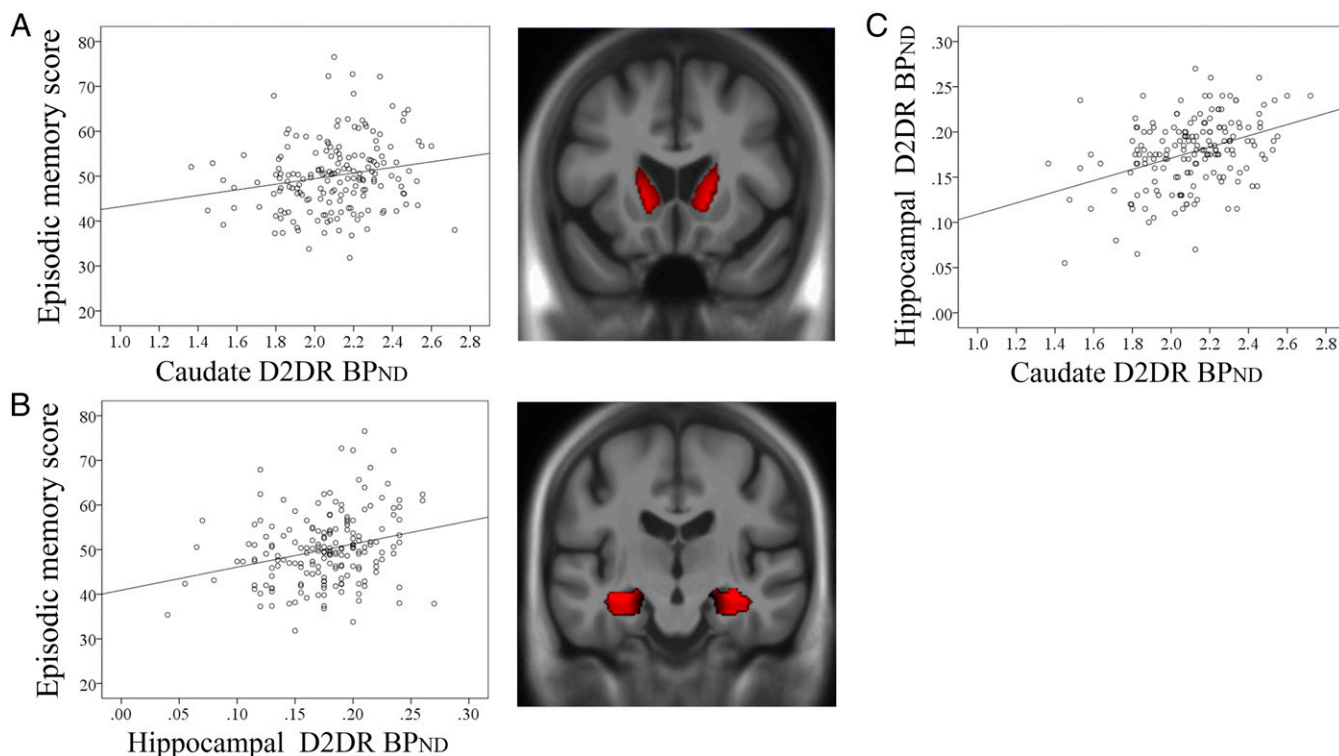


Fig. 1. Mean caudate (A) and hippocampal (B) D2DR BP_{ND} correlated with episodic-memory performance, and (C) caudate D2DR BP_{ND} was related to hippocampal D2DR BP_{ND}.

partial-volume effects on the D2DR BP_{ND} measures were negligible (caudate D2DR BP_{ND} versus volume: $r = -0.08$, $P > 0.05$). A supplementary analysis of D2DR BP_{ND} in the inferior ventral caudate (*Materials and Methods*) and episodic memory confirmed a significant association ($r = 0.15$, $P = 0.05$). No correlations were found between putamen D2DR BP_{ND} and cognition (all $r \leq 0.1$, $P > 0.05$), even though caudate and putamen D2DR BP_{ND} were significantly interrelated ($r = 0.68$, $P < 0.001$).

Correlations between caudate D2DR BP_{ND} and performance were compared with Z tests (34) for differences between cognitive abilities. The correlation between D2DR BP_{ND} and episodic memory was significantly different from those for working memory ($Z = 3.23$, $P < 0.001$) and perceptual speed ($Z = 2.89$, $P = 0.002$). The corresponding correlations for working memory or perceptual speed did not differ ($Z = 0.02$, $P > 0.05$). There was no indication of quadratic associations for any of the cognitive domains ($P > 0.05$ for all domains).

Whole-Brain Voxelwise Analyses of D2DR–Cognition Associations. To assess D2DR BP_{ND}–cognition associations across the whole brain, cognitive-composite scores were regressed onto whole-brain D2DR BP_{ND} values. The result for episodic memory revealed a significant cluster ($P < 0.05$, small-volume correction; SVC) in the left hippocampal complex ($x, y, z = -18, -10, -18$). A plot for this region revealed a positive linear association ($r = 0.30$). No significant relation was observed in the caudate, but in line with the analyses reported above, an association with episodic memory was seen in the left caudate ($x, y, z = -28, 8, 4$) at a more liberal threshold ($P < 0.01$, uncorrected). The corresponding whole-brain analyses for working memory and speed revealed no significant effects at the corrected threshold.

In view of the hippocampus finding in the whole-brain analysis, we further probed this finding with a region-of-interest (ROI) analysis, which also allowed us to consider the influence of hippocampal volume on the observed relation. Hippocampal D2DR BP_{ND} values (mean 0.18; SD 0.04) were normally distributed (skewness -0.52 ; kurtosis 0.59) and the signal was significantly

higher than in the cerebellum [$t(180) = 67.25$, $P < 0.001$]. Critically, findings from the whole hippocampus (left and right) revealed a significant correlation with episodic memory, when controlling for hippocampal volume ($r = 0.28$, $P < 0.001$; Fig. 1B). A direct test of the caudate–hippocampal D2DR BP_{ND} link revealed a significant positive correlation ($r = 0.38$, $P < 0.001$; Fig. 1C). Thus, individuals with higher caudate D2DR BP_{ND} had higher hippocampal D2DR BP_{ND} and higher episodic memory.

Caudate D2DR Availability in Relation to Volume and Perfusion. Caudate D2DR BP_{ND} did not correlate with hippocampal, caudate, or putamen gray-matter volumes (corrected for intracranial volume; $r < 0.06$, $P > 0.05$). However, hippocampal volumes were positively correlated with episodic-memory performance ($r = 0.15$, $P = 0.04$). Furthermore, gray-matter volumes were interrelated (caudate–putamen: $r = 0.41$; caudate–hippocampus: $r = 0.24$; hippocampus–putamen: $r = 0.21$; $P < 0.01$ for all). Thus, in addition to having high D2DR BP_{ND}, individuals who were high-performing for episodic memory were characterized by larger hippocampal volumes. No association was found between hippocampal perfusion and D2DR BP_{ND} ($r < 0.05$, $P > 0.05$).

D2DR Availability and Functional Connectivity. In light of the observed relationships of episodic memory to D2DR BP_{ND} in caudate and hippocampal regions, MRI resting-state functional-connectivity data were analyzed. The functional-connectivity pattern for the inferior ventral caudate seed (VCI; *Materials and Methods*) included the bilateral hippocampus (left hippocampus: $x, y, z = -22, -20, -16$, $t = 8.93$; right hippocampus: $x, y, z = 26, -38, -2$, $t = 9.67$; Fig. 2A). Analyses of the relation between caudate D2DR BP_{ND} and the functional connectivity map of the VCI revealed a significant positive relation in the left hippocampus/parahippocampal gyrus ($x, y, z = -22, -26, -12$; $r = 0.29$, $P = 0.05$, SVC-corrected; Fig. 2B) and in the left anterior medial temporal lobe (MTL; $x, y, z = -14, 2, -18$, $P = 0.005$, uncorrected). When episodic-memory performance was linked to the connectivity map of the VCI, a significant cluster was also found in an adjacent MTL region ($x, y, z = -16, 0, -10$,

$P = 0.005$, uncorrected). Given the proximity of these two MTL regions, and at the request of one reviewer, we performed a path analysis and found that the link between caudate D2DR BP_{ND} and episodic memory was mediated through connectivity of the VCI and MTL (Fig. 2C). We note that this result must be interpreted with caution given the nonexperimental and cross-sectional nature of the data.

Discussion

The primary goal of this study was to examine D2DR BP_{ND} -cognition associations based on [^{11}C]raclopride-PET data from a large age-homogeneous cohort of healthy adults in their mid-60s. In ROI-based analyses, we observed a positive relation of caudate and hippocampal D2DR BP_{ND} to episodic memory. No associations were found between D2DR BP_{ND} and working memory or perceptual speed. Thus, D2DRs appear crucial for hippocampus-based cognitive functions. Indeed, high-performing individuals were characterized by increased functional connectivity between these structures, which was positively associated with caudate D2DR BP_{ND} as well as high caudate and hippocampal D2DR BP_{ND} and larger hippocampal volumes.

The selective nature of the observed association for episodic memory is in line with the hypothesis that the D2DR system makes a specific contribution to hippocampus-based cognitive functions (10). This assertion is substantiated by experimental rodent work involving both genetic and pharmacological manipulations, which demonstrated that hippocampal D2DRs modulate long-term potentiation, long-term depression, as well as learning and memory (35). Further support for this hypothesis was obtained from the current whole-brain analysis. Here, an association between caudate D2DR BP_{ND} and episodic memory was seen, although the strongest effects were located extrastrially, in the hippocampal complex. This finding is consistent with observations in previous PET-imaging studies with a high-affinity D2 ligand (22, 23). Although extrastriatal D2DR availability has been detected previously with [^{11}C]raclopride (36, 37) and with relatively high reliability (38), this low-affinity ligand is not optimal for imaging of extrastriatal BP_{ND} . However, the reported D2DR BP_{ND} values for the hippocampus were in the expected range [5–10% of caudate levels (13)], and the signal was positive and significantly higher compared with the receptor-free cerebellar region. [^{11}C]Raclopride binding can be influenced by blood flow (39), and individual differences in episodic memory have been related to blood-flow differences in the hippocampal region (40). Importantly, however, hippocampal perfusion was unrelated to memory performance and D2DR BP_{ND} .

MRI analyses of functional connectivity at rest revealed that individuals with high caudate D2DR BP_{ND} and high episodic-memory scores had stronger functional interactions between the

ventral caudate and hippocampus. Previous studies showed that several striatal subregions (especially caudate) and the hippocampus interact during episodic memory (41–46), and considerable overlap has been observed in the pattern of functional connectivity for hippocampal and caudate seeds (47). This suggests that these regions are part of a shared functional network. This view is further supported by meta-analytic findings of a relation between functional connectivity in the ventral caudate and hippocampus, which guided our choice of seed region (31). Animal studies have demonstrated pathways interconnecting the hippocampus and ventral striatum (48), and increased striatal DA release upon hippocampal hyperactivity (49). Past research has linked striatal DA to functional brain activity in specific brain regions in both rodents (50, 51) and humans (52–54). The present data extend these observations to the level of functional connectivity.

The results of the path analysis indicated that the association between D2DR BP_{ND} and episodic memory was mediated through functional connectivity between the VCI and MTL. That is, the direct link between D2DR BP_{ND} and episodic memory observed at the zero-order level was no longer reliably different from zero when the indirect link through VCI-MTL connectivity was included in the model. Given the cross-sectional, nonexperimental nature of the data, the statistical assumptions of causal mediation, such as sequential ignorability, are unlikely to be met. Hence, the mediating role of functional VCI-MTL connectivity awaits validation by longitudinal data, and the reported path coefficient must not be interpreted causally. Nevertheless, the fact that caudate D2DR BP_{ND} was associated with VCI-MTL connectivity, which, in turn, had a bearing on episodic memory, extends past observations of a link among dopamine activity, functional brain activity, and memory performance (52–55) to VCI-MTL connectivity. The ventral striatum has been assigned a role in episodic memory by integrating inputs from several areas, including MTL regions (56). MTL input to the ventral striatum can affect dopaminergic activity in the ventral tegmental area (VTA). This leaves open the possibility that the observed DA-episodic memory relation is driven by stronger functional MTL input to the caudate for some individuals. On this view, MTL-VCI functional connectivity could be seen as a predictor of individual differences in episodic memory, which is in line with recent evidence that resting-state connectivity is a relatively stable individual-difference variable (57). The current findings suggest that D2DR neurotransmission contributes to this link.

Another interesting finding was that D2DR BP_{ND} in the caudate and hippocampus was not only related to episodic memory but also positively interrelated. Because the caudate and hippocampus are target areas for DA projections originating from different nuclei (substantia nigra and VTA, respectively), it is in keeping with the

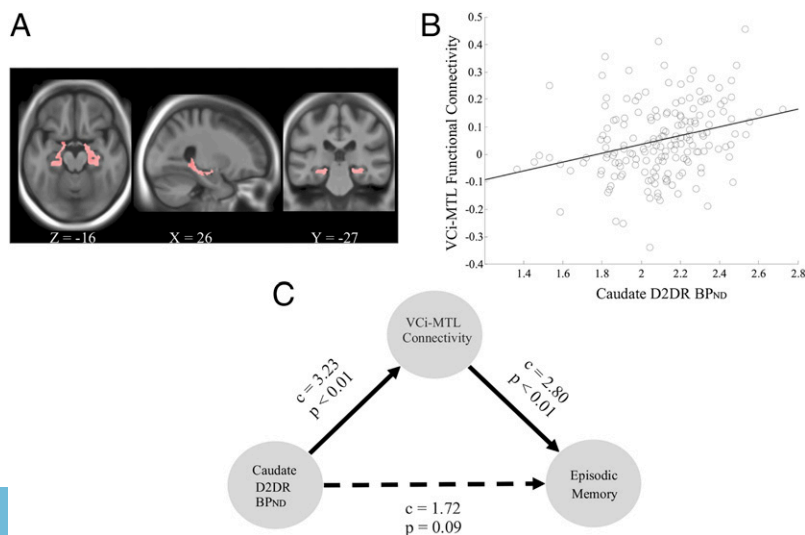


Fig. 2. (A) Horizontal, sagittal, and coronal slices showing that the functional connectivity pattern of the inferior ventral caudate included the bilateral hippocampus ($P < 0.05$, familywise error-corrected). (B) The degree of functional connectivity between the VCI and MTL was positively associated with caudate D2DR BP_{ND} . (C) Path analysis showing that the link between caudate D2DR BP_{ND} and episodic memory was mediated through functional connectivity between the VCI and MTL. c , coefficient. Both the total and indirect effects were significant ($P < 0.05$), whereas the direct effect (dashed line) was not.

notion that there is crosstalk between different DA pathways (58, 59) and resembles findings on D1DR BP_{ND} across the major dopaminergic pathways (60). DA integrity and hippocampal volume may both be indicators of brain maintenance in aging (61, 62), a role that seems to persist when resources move toward the lower end of the distribution, as illustrated in a study of Parkinson's disease (63). D2DRs may exert protective effects against aging-related processes, such as neuroinflammation (64) and excitotoxicity in hippocampal neurons (65–70). Excitotoxicity is particularly detrimental for hippocampal neurons, possibly due to the high density of glutamatergic synapses (71–73). Relatedly, hippocampal/temporal lobe D2DRs are reduced in pathological conditions such as Alzheimer's disease, and are correlated with cognitive deficits in these patients (74–76).

The analyses of caudate D2DR–cognition associations revealed no reliable link to working memory or speed. The lack of a significant association between striatal D2DRs and working memory is noteworthy. Although this negative finding does not rule out a role of D2DRs in phasic working-memory processes (77, 78) that may require PET activation study designs to be detected (11), it suggests that basal levels of striatal D2DR do not account for between-person differences in working memory. Instead, integrity of the D1DR system (especially tonic processes therein) may be critical to performance when maintenance of information in working memory is required (27, 79, 80). Although speed of processing has been linked to DA in past theoretical (81) and empirical (20) work, reasons for the lack of association in our study could be the age homogeneity of the current sample, or that the comparison tasks we used may have taxed motor processing to a lesser degree than in previous studies.

In conclusion, our PET and functional (f)MRI findings indicate that D2DRs make a specific contribution to hippocampus-based cognition by influencing caudate and hippocampal regions and their interactions. Some of the reported effects were modest, but they were observed in a highly controlled situation with atypical age homogeneity. Thus, the current results could serve as a lower bound for robust effects in the general population. More generally, these findings support and extend previous arguments (18, 19) for a relation between DA and episodic memory.

Materials and Methods

We have previously reported the COBRA design, recruitment procedure, imaging protocols, and details of the cognitive and lifestyle battery (28). Here we restrict the presentation to methodological details directly relevant to the present results. The study was approved by the local Ethical and Radiation Safety Committee of Umeå, Sweden, and all participants provided signed written informed consent prior to initiation of any testing. Written consent was also acquired for storage of blood samples at the Department of Biobank Research at Norrland's University Hospital.

Participants. The initial sample included 181 healthy older individuals (64–68 y; mean 66.2; SD 1.2; 81 women) who were randomly selected from the population register of Umeå, in northern Sweden. Individuals with pathological deviations in brain and cognitive functions or circumstances that could bias task performance or obstruct imaging sessions (e.g., metal implants) were excluded. The resulting sample had a lower prevalence of hypertension than nationwide reports [33% in COBRA, ~50% nationwide (82)] and normal or slightly increased body-mass index (>30 in 14.4% of the sample), and 17.7% consumed nicotine. Caudate and putamen D2DR BP data were excluded for 7 individuals; these concerned cases with imperfect segmentation of MR images and PET/MR image coregistration ($n = 4$) and statistical outliers ($n = 3$). In addition, fMRI data were missing for 1 individual. Thus, the effective sample included 174 individuals.

Image Acquisition.

Structural MRI. A 3D fast spoiled gradient-echo sequence was used to achieve high-resolution anatomical T1-weighted images. These were collected as 176 slices, with thickness 1 mm, repetition time (TR) 8.2 ms, echo time (TE) 3.2 ms, flip angle 12°, and field of view 25 × 25 cm.

Functional MRI at resting state. Resting-state blood oxygen level-dependent scans were acquired using a T2*-weighted single-shot gradient echo-planar imaging sequence. Imaging parameters were 37 transaxial slices, slice thickness 3.4 mm, spacing 0.5 mm, TE/TR 30/2,000 ms, flip angle 80°, field of view 25 × 25 cm, and a 96 × 96 acquisition matrix. A total of 170 volumes were collected. Before data collection, 10 dummy scans were performed to allow steady-state imaging.

Perfusion. Whole-brain perfusion measurements were made with 3D pseudocontinuous arterial spin labeling acquired with background suppression and a spiral acquisition scheme. Labeling time 1.5 s, postlabeling delay time 1.5 s, field of view 24 cm, slice thickness 4 mm, and acquisition resolution eight arms by 512 data points, with three signal averages. Perfusion maps were calculated to obtain cerebral blood flow in ml·100 g⁻¹·min⁻¹.

PET image acquisition. All participants underwent a PET scan (Discovery PET/CT 690; GE Healthcare) performed during resting-state conditions following an i.v. bolus injection of 250 MBq [¹¹C]raclopride. Preceding the injection, a 5-min low-dose helical CT scan (20 mA, 120 kV, 0.8 s per revolution) was obtained for the purpose of PET attenuation correction. Following the bolus injection, a 55-min 18-frame dynamic scan was acquired. Attenuation- and decay-corrected PET images (47 slices, field of view 25 cm, 256 × 256-pixel transaxial images, voxel size 0.977 × 0.977 × 3.27 mm³) were reconstructed with the iterative algorithm VUE Point HD-SharpIR [GE Healthcare (83); 6 iterations, 24 subsets, 3.0 mm postfiltering], yielding a full width at half maximum of 3.2 mm (84). Head movements during the imaging sessions were minimized with an individually fitted thermoplastic mask that was attached to the bed surface.

Cognitive Testing. Each cognitive ability (i.e., episodic memory, working memory, and perceptual speed) was evaluated with three separate tasks (verbal, numerical, and figural). Episodic memory was tested with word recall, number-word recall, and object-position recall; working memory was tested with letter-string updating, numerical 3-back, and spatial updating; and speed was tested with letter comparison, number comparison, and figure comparison (28). For each task, summary scores were computed across the total number of blocks or trials. These summary scores were standardized to form composites for each task (T score: mean 50; SD 10). Finally, the three T-scored measures per ability were averaged to create one summary score for each cognitive domain. Thus, episodic memory, working memory, and perceptual speed are each represented by one score. In the case of missing data (<1.2% for all variables), an average of the available observed scores was imputed into these ability measures so that these variables do not have any missing values.

Image Analyses.

Volumetric MRI analyses. Weighted MRI templates were used to delineate and segregate brain structures. Automatic segmentation was performed with FreeSurfer 5.3 software [surfer.nmr.mgh.harvard.edu (85–87)]. Voxel edit mode in Freeview was used to correct striatal volumes manually, when deemed necessary. The number of voxels within the delineated structures defined gray-matter volumes.

PET data analyses. For determining D2DR BP_{ND} (88–90), T1-weighted MRI images and PET emission scans were merged. ROIs included the caudate, putamen, hippocampus, and cerebellum, which were delineated with FreeSurfer 5.3 segmentation software (85–87). In brief, the PET emission scan format was converted from DICOM to NIfTI, corrected for head movements, and then coregistered to the corresponding MRI image using Statistical Parametric Mapping software [SPM8 (91)]. Time–activity curves for striatal and hippocampal regions and the cerebellum were used to calculate BP_{ND} using the analysis in Logan et al. (90). The cerebellum was used as a reference region due to its negligible D2DR expression (92–94).

Voxelwise analyses. PET and perfusion images were nonlinearly normalized to a sample-specific group template using diffeomorphic anatomical registration using exponentiated lie algebra [DARTEL (95)]. T1-weighted images as implemented in SPM8 were affine-aligned into stereotactic space of the Montreal Neurological Institute and smoothed using an 8.0-mm full width at half maximum Gaussian filter. To assess D2DR BP_{ND}–cognition associations, composite cognitive scores were regressed onto whole-brain D2DR BP_{ND} values. Perfusion maps were used to examine potential confounding effects in the hippocampus.

Functional connectivity. fMRI preprocessing steps were carried out using the Data Processing Assistant for Resting-State fMRI (DPARSF), which is based upon the SPM software package (96). fMRI data were first corrected for acquisition time differences between slices within each volume and then motion-corrected. A within-subject rigid registration was carried out to align functional and structural T1-weighted images. Next, the effect of physiological noise was removed by regressing out Friston's 24 parameters of a motion model (97), as well as nuisance variables such as global signal, white matter, and cerebrospinal fluid signal, along with both linear and quadratic trends. In addition, nuisance-corrected data were band pass-filtered (pass-band 0.01–0.1 Hz). Finally, by means of DARTEL (95), the nuisance-corrected realigned fMRI images were nonlinearly normalized to the sample-specific group template, affine-aligned into stereotactic space of the Montreal Neurological Institute, and smoothed using an 8.0-mm full width at half maximum Gaussian filter.

Previous findings have demonstrated functional coupling between striatal regions and the MTL (31, 98). To obtain a finer parcellation, the caudate was divided into subregions. To do so, Di Martino and colleagues (98) first distinguished the ventral caudate and dorsal caudate based on the Z coordinates following ref. 31. Second, the ventral caudate was further subdivided into inferior and superior regions (VCi and VCs) (99). Note that the VCi also encompasses the nucleus accumbens. Di Martino et al. showed that the VCi (relative to VCs) is more connected functionally to several regions of the limbic system, including the hippocampus and parahippocampal gyrus. As such, we followed Di Martino and colleagues' placement of a seed in the bilateral VCi ($x, y, z = \pm 9, +9, -8$). Then, we generated a 4-mm-diameter sphere centered on the aforementioned coordinates, and the mean time series was computed by averaging across voxels of the seed in each hemisphere.

Multiple regression analyses were carried out for each hemisphere and subject on the time series of each seed, yielding subject-specific functional connectivity maps. The functional connectivity map for each subject was taken to a second-level multiple regression analysis to delineate regions that are functionally connected to the seed. Local maxima with $P < 0.05$ (familywise error-corrected), with an extent threshold of 10 continuous voxels ($K > 10$; $2 \times 2 \times 2$ mm per voxel), were considered to be statistically significant.

Statistical Evaluation of Associations Between Brain and Cognitive Measures.

Linear and quadratic correlational analyses were carried out between the caudate and putamen (mean of left + right) D2DR BP_{ND} and the cognitive ability scores. Differences between correlations were compared with Z tests. Next, performance for episodic memory, speed, and working memory were used as covariates of interest in separate voxelwise whole-brain analyses of D2DR BP_{ND}-cognition relations. In a subsequent step, results concerning the hippocampus were controlled for by hippocampal perfusion. Furthermore, linear associations were tested among caudate, putamen, and hippocampal gray-matter volumes, D2DR BP_{ND}, and cognitive performance. For within-person estimates of partial-volume effects, uncorrected gray-matter volumes and BP_{ND}

were compared; otherwise, corrected regional volumes were used, from which the intracranial volume factor had been regressed out (100, 101).

The functional connectivity map of the VCi and D2DR BP_{ND} was analyzed, and within the resulting map the association between caudate-hippocampal connectivity and caudate D2DR BP_{ND} was quantified.

The alpha level was set to $P = 0.05$ for the correlational analyses (Bonferroni-corrected for three cognitive domains; $P < 0.017$). In the whole-brain SPM analyses, an SVC was applied for the caudate and hippocampus, respectively, at a threshold of $P < 0.05$.

Mediational Analysis of the Role of Striato-Hippocampal Connectivity in the Caudate D2DR BP_{ND}-Episodic Memory Link.

To specifically assess the potentially mediating role of functional connectivity between the VCi and MTL in the association between caudate D2DR BP_{ND} and episodic memory, we conducted a path analysis. In this analysis, caudate D2DR BP_{ND} served as the independent variable, VCi-MTL connectivity as the mediating variable, and the composite episodic-memory score as the dependent variable. Of chief interest was whether the link between caudate D2DR BP_{ND} and episodic memory would be attenuated or eliminated once the connectivity variable was entered into the model. This analysis was conducted using the Mediation toolbox (wagerlab.colorado.edu/wiki/doku.php/help/mediation/m3_mediation_fmri_toolbox). For limitations of causal mediation analysis applied to cross-sectional, nonexperimental data, see refs. 102 and 103.

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