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Relationship of dopamine D1 receptor binding in striatal and extrastriatal regions to cognitive functioning in healthy humans

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ABSTRACT

Dopamine (DA) availability in both striatal and extrastriatal brain regions has been implicated in cognitive performance. Given that different brain regions are neuroanatomically and functionally different, DA receptor binding in different brain regions may be selectively important to specific cognitive functions. Using PET and the radioligand SCH23390, we measured D1 receptor binding potential (BP_{ND}) in dorsolateral prefrontal cortex (DLPFC), hippocampus (HC), as well as in sensorimotor (SMST), associative (AST), and limbic (LST) striatum in 20 healthy younger persons. Subjects completed tasks assessing executive functioning, episodic memory, speed, and general knowledge. Unlike previous reports, we found no linear or curvilinear relationships between D1 receptor binding in DLPFC and performance in any cognitive task. However, BP_{ND} in HC was positively linked to executive performance as well as to speed and knowledge. With regard to the striatal subregions, D1 BP_{ND} in SMST was more strongly related to speed compared to the other striatal subregions, whereas D1 BP_{ND} in AST was more strongly linked to general knowledge. These findings provide support for the notion that D1 receptors in separate brain regions are differentially related to performance in tasks tapping various cognitive domains.

Introduction

There is pervasive evidence for the role of dopamine (DA) in cognitive functioning (see Bäckman et al., 2006, 2010; Cropley et al., 2006, for reviews). In studies relating DA receptor binding potential (BP_{ND}) to cognitive performance in healthy adults, relationships have been observed to executive functions/working memory (Lumme et al., 2007; Reeves et al., 2005; Takahashi et al., 2007, 2008), episodic memory (Bäckman et al., 2000; Chen et al., 2005; Takahashi et al., 2007, 2008), speed (Bäckman et al., 2000; Volkow et al., 1998; Wang et al., 1998), and general knowledge (Cerevenka et al., 2008). Relationships between DA binding within the striatum and cognition are often observed (Bäckman et al., 2000; Cervenka et al., 2008; Chen et al., 2005; Karlsson et al., 2009; Reeves et al., 2005; Volkow et al., 1998; Wang et al., 1998), but DA-cognition links have also been demonstrated in extrastriatal regions such as in hippocampus (HC; Takahashi et al., 2007, 2008), dorsolateral prefrontal cortex (DLPFC; Takahashi et al., 2008), and anterior cingulate cortex (ACC; Lumme et al., 2007; Takahashi et al., 2007). These patterns indicate a rather global influence of DA on cognitive functioning. However, given that DA has projections throughout the brain via different pathways (see Lewis and Sesack, 1997, for review), DA receptor binding in different brain regions may be selectively important to performance in tasks tapping different cognitive domains.

Most studies linking DA to cognitive performance have examined the relationship between D2 binding and cognitive performance; only a few investigations have addressed the D1–cognition link in healthy samples (Karlsson et al., 2009; Takahashi et al., 2008; Wang et al., 1998). This is so despite the fact that D1 receptors in PFC may be particularly important to higher-order cognitive functions (Floresco and Magyar, 2006). Much of this work has involved administering D1 receptor agonists or antagonists to both non-human primates (Sawaguchi and Goldman-Rakic, 1994; Wang et al., 2004; Williams and Goldman-Rakic, 1995) and humans (Kimberg and D'Esposito, 2003; Müller et al., 1998). The findings from these studies suggest that the relationship between D1 receptors and executive performance is curvilinear, with too little or too much DA being detrimental to performance. In line with this hypothesis, a recent study showed that D1 receptor binding in the DLPFC was curvilinearly related to working memory, whereas D2 binding in the HC was related to episodic memory (Takahashi et al., 2008).

The striatum, a subcortical structure in which DA receptors are particularly abundant, can be divided into limbic (LST), associative (AST), and sensorimotor (SMST) subregions based on their afferent and efferent connections (Cervenka et al., 2008; Martinez, et al., 2003). The

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limbic striatum (LST) is innervated by the ventral tegmental area (VTA) via the mesolimbic pathway. The associative (AST) and sensorimotor (SMST) parts of the striatum are innervated by the substantia nigra via the nigrostriatal pathway. Whereas the AST has connections to associative regions of the neocortex, the SMST has connections to premotor cortex. Thus also within the striatum different subregions may be differentially related to cognition. In recent work, D2 BP_{ND} in the three striatal subregions was differentially related to cognitive performance (Cervenka et al., 2008; Rieckmann et al., in press): D2 binding in LST was more strongly related to episodic memory, whereas D2 binding in AST and SMST was more strongly linked to general knowledge. Although D1 receptor binding in the striatum has been linked to cognition (Wang et al., 1998; Karlsson et al., 2009), D1 binding within the striatal subdivisions has not previously been related to performance in tasks tapping different cognitive domains.

Given the relative scarcity of studies relating D1 BP_{ND} to cognitive performance, the aim of the present study was to investigate this relationship further. Hence, D1 BP_{ND} in DLPFC, HC, and the three subregions of the striatum was related to performance in different cognitive tasks in order to elucidate potential differential relationships. The cognitive tasks selected have all previously been related to DA functions. Perseverative errors in the WCST have been related to D1 binding in DLPFC (Takahashi et al., 2008), whereas speed, episodic memory, and general knowledge have been linked to D2 binding in the striatum (Cervenka et al., 2008). Episodic memory has also been related to D2 binding in the HC (Takahashi et al., 2007). Specifically, we wanted to test the hypotheses that (1) D1 binding in DLPFC is related to executive functioning, and (2) D1 binding in the different subregions of the striatum (SMST, AST, and LST) is differentially related to speed, episodic memory, and general intelligence. The radioligand SCH23390 and PET were used to quantify D1 receptor binding.

Materials and methods

Participants

Twenty healthy younger participants were included (mean age = 25.2 years, range = 22–30; 10 male, 10 female). Mean years of education was 14.67 (SD = 1.97). Participants were recruited through a newspaper advertisement. Exclusion criteria were history of a mental disorder, brain damage, other significant medical conditions, actual or previous drug or alcohol abuse, nicotine use, and hormone therapy. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden, and the Radiation Safety Committee of the Karolinska Hospital, Stockholm, Sweden. Written informed consent was obtained from all subjects, who were paid 5000 SEK for their participation.

Cognitive assessment

Cognitive performance was assessed 0–39 days (M = 11.71, SD = 21.94) before the PET assessment. Four cognitive variables were included. Perseverative errors from a computerized version of the Wisconsin Card Sorting Test or WCST (Heaton et al., 1993) were used as a measure of executive functioning. One male subject had missing data on the WCST. Free recall and recognition of words were used to assess episodic memory. There was very limited variability among the participants in recognition and thus the recognition data were dropped from further analyses. In free recall, participants were asked to remember as many items as possible from a list of 16 consecutively presented unrelated words. The Digit symbol substitution test from the Wechsler Adult Intelligence Scale (WAIS-R; Wechsler, 1981) was used as a measure of processing speed, and the Information subtest from the WAIS-R assessed general knowledge. Summary statistics for the cognitive measures are presented in Table 1.

Positron emission tomography (PET)

All PET measurements were performed in the afternoon. The PET measurements were obtained with an ECAT Exact HR 47 system (CTI/Siemens, Knoxville, TN) run in 3D 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 radially at 20 cm from the center. Prior to each emission measurement, a transmission measurement of 10 min was performed using three rotating 68Ge–68Ga sources. This information was used for attenuation correction. The radioligand [^{11}C] SCH23390 was prepared as previously described (Halldin et al., 1986) and injected into the left antecubital vein as a rapid bolus injection (<2 s). The specific radioactivity was high so there was no mass effect on radioligand binding (range 3043–14064 Ci/mmol). 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 BP_{ND}.

Magnetic resonance imaging (MRI)

Whole-brain imaging data were acquired on a 1.5 T GE Signa Echospeed MR scanner (GE Medical Systems, USA), using a standard circular one-channel head coil. T1 weighted 3-D-SPGR images (TR = 24 ms, TE = 6 ms, flip angle = 35°) were acquired for anatomical co-registration in 124 contiguous 1.5 mm coronal slices (image resolution = 256 × 256 × 186 mm, voxel size = 0.9 × 0.9 × 1.5 mm).

Quantification of PET data

The T1-weighted MRI images were spatially normalized and re-sliced to 1 mm isometric voxels using the SPM2 software (Wellcome Department of Cognitive Neurology, UK). The line defined by the anterior and posterior commissures was parallel to the horizontal plane, and the inter-hemispheric plane was parallel to the sagittal plane. Regions of interest (ROIs) were manually delineated for DLPFC, HC, SMST, AST, and LST, and cerebellum was delineated on each individual MR image using the Human Brain Atlas software (Roland et al., 1994). The DLPFC was defined as the medial-inferior and lateral parts of the superior frontal gyrus delineated in coronal planes anterior to the corpus callosum. The HC was delineated in all sagittal slices and included the anterior part (head), the medial part, and the posterior part (tail). The three striatal compartments were delineated as previously described (Martinez et al., 2003; Cervenka et al., 2008; Fig. 1). Briefly, the SMST corresponds to the postcommissural part of the dorsal putamen, the AST was defined as the precommissural putamen and dorsal caudate nucleus, and the LST includes the ventral portion of the

Table 1
Means, standard deviations, and ranges for cognitive performance and D1 binding potential.

Measure	Mean	SD	Range
Cognitive performance			
WCST, perseverative errors	8.00	3.70	4–19
Free recall	11.90	2.31	7–16
Digit symbol	35.75	13.90	16–63
Information	23.20	2.28	18–26
Binding potential			
DLPFC	.49	.10	.25–.65
HC	.19	.10	.01–.36
SMST	1.65	.30	1.15–2.49
AST	1.61	.26	1.12–2.23
LST	1.20	.27	.80–1.71

Note. WCST = Wisconsin Card Sorting Test, DLPFC = dorsolateral prefrontal cortex, HC = hippocampus, SMST = sensorimotor striatum, AST = associative striatum, LST = limbic striatum.

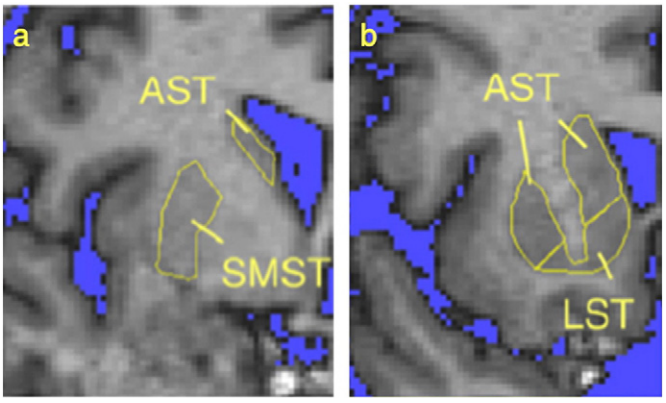

Fig. 1. Coronal MRI sections depicting manually drawn ROIs for striatum in one subject; posterior (a) and anterior (b) to the anterior commissure. Right hemisphere is shown. LST = limbic striatum; AST = associative striatum; SMST = sensorimotor striatum (adapted from Cervenka et al., 2008 with permission, Copyright Elsevier Science 2008).

striatal complex. The cerebellum, where dopamine D1 receptor density is negligible, was delineated on six central slices and served as reference region (Hall et al., 1998). All ROIs were manually delineated on the MR images and then segmented into white and gray matter. PET images were coregistered with the MRI images and re-sliced to a voxel size of 2×2×2 mm.

To obtain time–activity curves, regional radioactivity was calculated for each frame, corrected for decay, and plotted versus time. BP_{ND}, which represents the product of receptor density (B_{max}), apparent affinity ($1/K_d$), and the free fraction of free and non-specific bound ligand (f2; Mintun et al., 1984) for [^{11}C] SCH23390 binding to D1 receptors was calculated according to the Simplified Reference Tissue model (Gunn et al., 1997). BP_{ND} was calculated separately for both hemispheres of each gray matter ROI, but because the BP_{ND} values were highly correlated for DLPFC ($r=.95$, $p<.001$), SMST ($r=.88$, $p=.001$), AST ($r=.83$, $p<.001$), and LST ($r=.67$, $p=.001$), these were pooled across hemispheres. Because of the small ROI volumes, the left and right BP_{ND} values of the HC were pooled, although they were not significantly correlated ($r=.26$, $p=.28$). Thus, interhemispheric ROIs for all regions were used in the correlational analyses. BP_{ND} data across the five ROIs are shown in Table 1.

Data analysis

Partial product-moment correlations, controlling for education and sex, were calculated between BP_{ND}s for each ROI and cognitive test performance. Education was controlled for in all analyses, because performance on two cognitive tests was significantly related to education (Digit symbol: $r=.46$, $p<.05$; Information: $r=.51$, $p<.05$). Sex was also controlled for, because several studies have suggested that both DA availability and the DA–cognition relationship may be different in men and women (Mozley et al., 2001; Kaasinen et al., 2001). The significance level was set at $p<.05$, two-tailed.

Results

The D1 BP_{ND} values for each region (Table 1) are comparable to what has previously been reported by Ito et al. (2008). As expected, BP_{ND}s in the striatal regions were much higher than those in DLPFC and HC. Also, the rank order within the striatum was as expected, with SMST yielding the highest BP_{ND}, followed by AST, and LST, in descending order (Cervenka et al., 2008; Ito et al., 2008).

Relationships between D1 receptor binding and cognition

Correlations between D1 BP_{ND} in the five selected ROIs and performance in the four cognitive tests are provided in Table 2. We hypothesized that BP_{ND} in DLPFC would be related to WCST performance; however, the results did not confirm this hypothesis: There was no linear ($p>.35$) or curvilinear ($p>.20$) relationship between BP_{ND} for DLPFC and perseverative errors in the WCST. However, D1 binding in the HC was linearly related to the WCST measure (see also Fig. 2). In addition, HC BP_{ND} was reliably related to performance in the tests of speed and knowledge.

With regard to our second hypothesis, BP_{ND} in SMST was related to Digit symbol performance, whereas BP_{ND} in all striatal regions was related to general knowledge, but not to episodic memory performance. It should be noted that BP_{ND} in the three striatal compartments was strongly correlated (SMST–AST, $r=.85$; SMST–LST, $r=.74$; AST–LST, $r=.93$). The correlation between BP_{ND} in SMST and Digit symbol ($r=.62$, $p=.006$; Fig. 3) was stronger than for BP_{ND} in the other striatal ROIs (AST: $r=.46$, $p=.052$; LS: $r=.42$, $p=.080$), but the differences in correlational strength were significant only at trend level ($p=.07$; $p=.08$, respectively) when conducting a direct inferential comparison (Meng et al., 1992). In contrast, for general knowledge stronger correlations were obtained for BP_{ND} in AST ($r=.68$, $p=002$; Fig. 4) and LST ($r=.67$, $p=.002$) than for SMST ($r=.51$, $p=.031$). In this case, comparisons yielded a significant difference between BP_{ND} in AST and BP_{ND} in SMST ($p=.04$), although the difference in correlations between BP_{ND} in SMST and BP_{ND} in LS for general knowledge was not significant ($p=.12$).

A final point to note is that D1 BP_{ND} across all five ROIs was unrelated to episodic memory performance ($ps>.35$).

Discussion

The aim of this study was to investigate differential relationships between D1 binding in separate brain regions and performance on tasks tapping various cognitive domains. The first hypothesis was that D1 binding in DLPFC is related to executive functioning, as indexed by perseverative errors in the WCST. However, unlike Takahashi et al. (2008), we found no significant relationship between these two variables, neither linear nor curvilinear. This is an unexpected finding, given that human pharmacological studies as well as an abundant animal literature have demonstrated the importance of D1 receptors in executive tasks (Floresco and Magyar, 2006; Sawaguchi and Goldman-Rakic, 1994; Müller et al., 1998; see Bäckman et al., 2006, 2010, for reviews). The discrepant findings between the current data and those of Takahashi and colleagues may reflect differences in methodology, particularly regarding how the DLPFC ROI was delineated. We delineated a DLPFC ROI, which includes BA 9, 10, and 46, whereas Takahashi et al. used only 3 axial slices approximately corresponding to BA 46. A larger ROI is less specific, and thus, it may be more difficult to observe associations between DA binding

Table 2
Relationships between D1 binding potential and cognitive performance.

	WCST	Free recall	Digit symbol	Information
DLPFC	−.14	.22	.12	.41
HC	−.52*	.11	.51*	.62**
SMST	−.22	−.01	.62*	.51*
AST	−.20	−.03	.46	.68**
LST	−.30	−.23	.42	.67**

Note. DLPFC = dorsolateral prefrontal cortex, HC = hippocampus, SMST = sensorimotor striatum, AST = associative striatum, LST = limbic striatum, WCST = Wisconsin Card Sorting Test, perseverative errors.
* $p<.05$.
** $p<.01$.

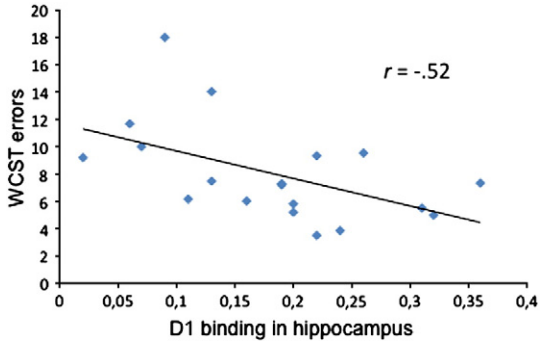

Fig. 2. Relationship between D1 receptor binding in hippocampus and perseverative errors in the Wisconsin Card Sorting Test (WCST) adjusted for years of education and sex.

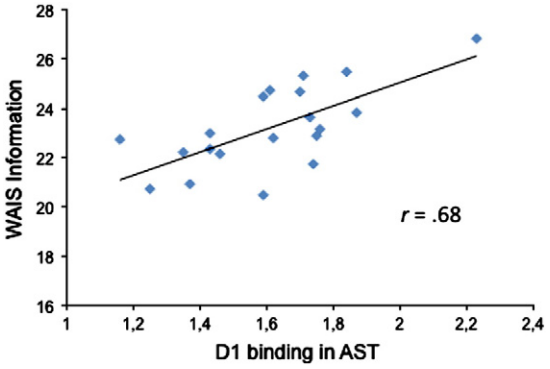

Fig. 4. Relationship between D1 receptor binding in associative striatum (AST) and WAIS Information adjusted for years of education and sex.

and cognitive performance compared to a more restricted ROI. In addition, discrepant findings between studies relating DA binding and cognition are common. For example, whereas Takahashi et al. (2008) found a correlation between D2 receptor binding in HC and episodic memory, Lumme et al. (2010) found no such relationship for HC or any other brain region. Differences in results across studies may be due to variations in PET imaging methods, sample composition, task selection, or a combination among these factors.

D1 binding in HC showed the most consistent relationship to performance across the cognitive domains assessed in this study; it was related to perseverative errors in WCST, Digit symbol, and general knowledge. D2 BP_{ND} in HC has previously been related to executive functions, episodic memory, reasoning, and verbal fluency (Takahashi et al., 2007, 2008). However, the same group did not find any relationships between D1 BP_{ND} in HC and any measure of cognition (Takahashi et al., 2008). On balance, then, despite some irregularities for the two main receptor subtypes, both D1 and D2 BP_{ND}s in HC seem to be important to performance in various cognitive tasks. This is noteworthy, given that D1 and D2 BP_{ND}s in the HC are very low in comparison to other brain regions (Ito et al., 2008; Table 1). One reason for the predictive relationships to various cognitive tasks may be the HC–PFC interaction. HC is unidirectionally connected to the PFC. Within this pathway, plasticity at the synapses seems to be differentially related to performance in different cognitive domains, such that long-term potentiation is related to episodic memory, whereas long-term depression is related to working memory (Laroche et al., 2000). Although the exact functional mechanisms are not entirely clear, the HC–PFC interaction appears to be important to different aspects of cognitive processing and modulated by DA (Seamans et al., 1998). Thus, DA in the HC may be important even to performance in tasks that are not directly dependent on this structure.

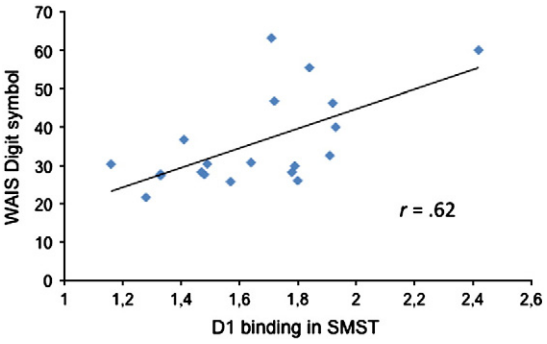

Fig. 3. Relationship between D1 receptor binding in sensorimotor striatum (SMST) and WAIS Digit symbol adjusted for years of education and sex.

With regard to our second hypothesis, there was some support for the notion that striatal subregions are differentially related to cognitive performance. D1 BP_{ND} in SMST was related to perceptual speed, whereas D1 BP_{ND} in all three subregions was related to general knowledge. Further, DA binding in SMST was more strongly related to perceptual speed as compared to the other striatal regions, whereas binding in AST was more strongly related to general knowledge as compared to SMST. This pattern is in line with the notion that the SMST, which has projections to primary motor and premotor cortex as well as to the supplementary motor area, is primarily involved in motor functions. However, the AST, which has projections to associative regions in the cortex including the DLPFC, is more involved in higher-order cognitive processing (Cervenka et al., 2008; Martinez et al., 2003). LST has connections with medial prefrontal, orbitofrontal, and anterior cingulated cortex, and is supposed to mostly be involved in drive and motivation, but a relationship between D2 binding in the LST and episodic memory has been reported (Cervenka et al., 2008). In this study, neither episodic memory nor executive performance was related to D1 receptor binding in any of the striatal ROIs. A lack of D1-episodic memory association was seen also for DLPFC and HC. This is an interesting observation in view of the fact that D2 BP_{ND} in HC (Takahashi et al., 2007, 2008) as well as in striatum (Bäckman et al., 2000; Cervenka et al., 2008; Chen et al., 2005) has been linked to performance in various episodic memory tasks.

D1 and D2 receptors differ in terms of distribution in the brain. D1 receptors are expressed in higher concentrations in the neocortex than D2 receptors (Hall et al., 1994). Moreover, D1 receptors are mainly expressed in the "direct" nigrostriatal feedback pathway, whereas D2 receptors are more abundant in the "indirect" pathways (Gerfen, et al., 1995; Hersch et al., 1995). Comparing the present data on the D1–cognition link to past studies on the association between D1 and D2 receptor binding and cognition, a pattern emerges that suggests both similarities and differences across receptor subtypes. As to similarities, in agreement with the current data both D1 and D2 BP_{ND}s in the striatum have been associated with speed (Cervenka et al., 2008; Wang, 1998; Volkow et al., 1998) and striatal D2 BP_{ND} has been related to general knowledge (Cervenka et al., 2008). For both receptor subtypes, BP_{ND} in HC has been related to executive functions and to several other cognitive domains (Takahashi et al., 2007, 2008). Additionally, both D1 and D2 BP_{ND}s in the striatum have been related to executive functioning (Cropley et al., 2008; Reeves et al., 2005; Volkow et al., 1998). However, this relationship was not observed in the present study. One apparent difference between receptor subtypes is that only D2 BP_{ND} has been related to episodic memory (Bäckman et al., 2000; Cervenka, 2008; Chen et al., 2005; Takahashi et al., 2007, 2008). In line with this observation, a recent study showed increased episodic memory performance as well as enhanced

functional brain activation patterns when younger and older adults were given a D2 receptor agonist, whereas a D2 receptor antagonist had the opposite effect. Thus, a direct relationship of D2 receptor functions to both behavioral and functional indices of episodic memory was observed (Morcom et al., 2010).

Regarding the patterns discussed above, it should be underscored that very few studies have investigated the link between D1 BP_{ND} and cognition in healthy samples. Additionally, in the present study only free recall of episodic memory was assessed, whereas several previous studies show relationships between D2 binding and recognition (Bäckman et al., 2000; Cervenka et al., 2008). That said, the observed patterns open up for the possibility that D2 receptors may be more critically implicated in episodic memory than D1 receptors. In line with this assertion, the two-state model of DA function proposed by Seamans et al. (2001) poses that D2 receptors facilitate the formation of new representations and switching between multiple network representations, whereas D1 receptors are more important for stable cognitive representations over time. A key feature of episodic memory is the formation of new associations. Thus D2 receptors may be more important than D1 receptors for this type of memory.

A possible confounder in this work concerns serotonin receptors (5-HT2A) that have shown a significant contribution to [^{11}C] SCH23390 binding signal in the neocortex (e.g. Ekelund et al., 2007). Thus, if we would have observed associations between SCH23390 binding and cognition in cortical regions these may partly have been due to serotonin receptors. However, striatum and hippocampus have very low densities of serotonin receptors in humans (Ito et al., 1998; Hall et al., 2000). Thus, confounding effects of 5-HT2A are unlikely with regard to the positive correlations that were observed for SCH23390 binding in the hippocampus and the striatal subdivisions to various cognitive functions.

An important point to note with regard to investigations of the DA–cognition link in healthy samples is that subjects perform at relatively high levels and are likely to have more optimal levels of DA binding compared to different patient groups (e.g., schizophrenia or Parkinson's disease). Therefore, there is relatively little variation in both the DA and the cognitive parameters in normal populations. As a consequence, the risk of false negatives increases. DA–cognition associations may be more easily detected in samples with more variation in DA functions and cognitive scores. To illustrate, studies including patients with schizophrenia have found strong relationships of D1 binding in the PFC to executive functioning and working memory (Okubo et al., 1997; Abi-Dargham et al., 2002).

In conclusion, this study provides support for a link between D1 receptor binding and cognition in healthy adults. The results also indicate that D1 binding in different brain regions may be differentially related to cognition, both in the striatum and extrastriatally. In addition, a comparison between the current findings and past research suggests differences between D1 and D2 receptors with regard to the DA–cognition link. In order to obtain a more comprehensive picture of how different DA markers relate to cognitive functioning, a systematic, quantitative review is called for.

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