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Review

# Linking cognitive aging to alterations in dopamine neurotransmitter functioning: Recent data and future avenues

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ABSTRACT

Molecular-imaging studies of dopaminergic neurotransmission measure biomarkers of dopamine (DA), such as the DA transporter and $D_1$ and $D_2$ receptor densities in the living brain. These studies indicate that individual differences in DA functions are linked to cognitive performance irrespective of age, and serve as powerful mediators of age-related decline in executive functioning, episodic memory, and perceptual speed. This focused review targets several recent findings pertaining to these relationships. Specifically, we discuss novel evidence concerning (a) the role of DA in within-person cognitive variability; (b) age-related differences in DA release during cognitive processing; (c) DA release following cognitive training in younger and older adults; and (d) the relationship between DA and task-induced functional brain activity. Based on these lines of empirical inquiry, we outline a series of avenues for future research on aging, DA, and cognition.



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Few informed observers would disagree with the following propositions: (a) human aging is associated with deficits in several cognitive abilities, including executive functions, episodic memory, and perceptual speed (e.g., Bäckman et al., 2001; Craik and Salthouse, 2007); (b) dopamine (DA) is strongly implicated in higher-order cognitive functioning (e.g., Bäckman et al., 1997; Glickstein et al., 2005; Luciana and Collins, 1997); and (c) there is a loss of striatal and extrastriatal DA biomarkers from early through late adulthood (e.g., Kaasinen et al., 2000; Wang et al., 1998). As to the latter, although most studies have found a negative linear relationship between adult age and DA (see Reeves et al., 2002, for a review), some research indicates a curvilinear trajectory, with accelerated losses from young-old to very-old age (Rinne et al., 1990; Antonini et al., 1993; Bannon and Whitty, 1997; Ma et al., 1999).

These relationships have spurred interest in what has come to be known as the correlative triad among aging, DA, and cognition (Bäckman and Farde, 2005; Bäckman et al., 2006). In examining this triad, a key issue is the extent to which age-related deficits in cognitive performance can be accounted for by age-related DA losses, as assessed using molecular-imaging techniques such as PET and SPECT.

To date, relatively few studies have addressed this issue, but the empirical pattern is remarkably consistent: age-related differences in postsynaptic markers such as $D_1$ (Wang et al., 1998) and $D_2$ (Bäckman et al., 2000; Volkow et al., 1998) receptor densities as well as presynaptic markers such as binding potential for the DA transporter (Erixon-Lindroth et al., 2005; Mozley et al., 2001)

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statistically account for sizable portions of the age-related variation in executive functioning, episodic memory, and speed. These findings are in line with the hypothesis that DA decline in aging causes cognitive decline.

Note, however, that research demonstrating such mediation has used adult-life span samples with rectangular age distributions or contrasted younger and older adults. Two recent studies examined the DA-cognition link in samples ranging from young-old to very-old age. Interestingly, in these studies no age-related losses in $D_2$ binding potential (Reeves et al., 2005) or DA transporter availability (Van Dyck et al., 2008) were observed, although the DA markers were related to spatial planning and reaction time, respectively. The reason for the apparent lack of age-related DA losses in these studies remains unclear. The findings may reflect sample selectivity (i.e., individuals in the oldest ages may have had very high DA levels earlier in life), or represent a true leveling-off of the age-DA trajectory in late senescence. However, given the documented role of DA in higher-order cognition (for reviews, see Bäckman et al., 2006; Cropley et al., 2006; Li et al., 2009), the latter possibility is difficult to reconcile with behavioral findings indicating accelerated cognitive decline from the 70 s and onwards (e.g., Lindenberger and Ghisletta, 2009; Rönnlund et al., 2005; Schaie, 1996). Further, the age invariance in DA markers reported by Reeves et al. and van Dyck et al. runs counter to earlier observations of exacerbated DA losses in late life (Rinne et al., 1990; Antonini et al., 1993; Bannon and Whitty, 1997; Ma et al., 1999). Future research, preferably with a longitudinal design, is needed to characterize in more detail the mapping of age-related losses in DA and cognition.

Relationships between imaging markers of DA functions and cognition have also been documented in age-homogenous samples. Most of these studies have involved clinical populations such as patients with schizophrenia (McGowan et al., 2004; Okubo et al., 1997; but see Abi-Dargham et al., 2002), Parkinson's disease (Bruck et al., 2005; Nagano-Saito et al., 2004), and Huntington's disease (Bäckman et al., 1997; Lawrence et al., 1998). However, similarly strong DA-cognition associations are observed in normal samples of adults using striatal as well as extrastriatal DA markers (Landau et al., 2009; Mozley et al., 2001; Takahashi et al., 2007, 2008). Thus, in addition to being a solid biomarker of cognitive aging, DA appears to be critically implicated in cognitive functioning irrespective of adult age.

In a recent review published in this journal (Bäckman et al., 2006), we identified several hot topics in research on DA and cognition, some of which involve age-group comparisons. Evidence has now accumulated that speaks to a few of these issues. In the remainder of this article, we discuss novel findings in this area of research focusing largely on work from our own laboratories. The review is structured into four different themes: (a) DA and within-person cognitive variability; (b) age-related differences in DA release during cognitive processing; (c) DA release following cognitive training in younger and older adults; and (d) the relationship between DA and task-induced functional brain activity. In addition to discussing new data on these topics, we outline several lines of inquiry where further empirical investigation is warranted. For general reviews of the role of DA in cognitive aging as well as in cognition irrespective of age, the reader is referred to Bäckman et al. (2006), Cropley et al. (2006), Egelton et al. (2009), and Li et al. (2009).

## 1. DA and within-person cognitive variability

Empirical evidence indicates that increased within-person performance fluctuations reflect suboptimal neuronal information processing (see MacDonald et al., 2006, for review), in line with propositions derived from computational models (e.g., Servan-Schreiber et al., 1990; Li et al., 2001). Higher levels of within-person behavioral variability in sensorimotor, perceptual, and cognitive tasks are often accompanied by lower mean levels of performance associated with various conditions (see Table 1 for examples). It is critical to note that between-group differences in within-person fluctuations are not simply an artifact of mean-level differences, for these are routinely partialed out in the analysis of within-person variability. At a cognitive level, performance fluctuations are generally thought to reflect momentary lapses of attention – a failure to exert executive control (West et al., 2002). Consequently, it has been argued that the frontal lobes are particularly crucial for maintaining cognitive stability, hence minimizing performance fluctuations (e.g., Picton et al., 2007; Stuss et al., 2003). The fact that patients with frontotemporal dementia show greater performance fluctuations than Alzheimer patients at the same severity level (Murtha et al., 2002) supports this contention. Furthermore, longitudinal data demonstrate that older adults who exhibited higher within-person fluctuations declined more in executive functioning over several years than their more stable counterparts (Lövdèn et al., 2007).

**Table 1**
Conditions associated with increased within-person cognitive variability. Adapted from MacDonald et al. (2006).

| Condition | Source |
|---|---|
| Childhood | Li et al. (2004) |
| Older adult age | Anstey (1999) |
| Cognitive decline | Lövdèn et al. (2007) |
| Impending death | Shipley et al. (2006) |
| ADHD | Castellanos and Tannock (2002) |
| Traumatic brain injury | Stuss et al. (1994) |
| Schizophrenia | Winterer et al. (2004) |
| Parkinson's disease | Burton et al. (2006) |
| Frontotemporal dementia | Murtha et al. (2002) |

Of special interest here is the potential link between dopaminergic modulation and processing fluctuations. Animal studies have shown that DA receptor reductions, as observed during aging, not only slow down performance, but also increase performance variability (MacRae et al., 1988; Schultz et al., 1989). Toward this end, MacDonald et al. (2006) made the point that many groups of individuals who exhibit large performance fluctuations are characterized by alterations in DA neurotransmission (e.g., older adults, Parkinson patients, schizophrenics, children with ADHD). Indeed, neurocomputational work on DA, aging, and cognition suggests that reduced DA activity increases neuronal noise (Li et al., 2001). The lowered signal-to-noise ratio of neural information processing in the aged brain could have various functional consequences. These include less distinctive neuronal representations of perceptual stimuli and memory items, increased interference between different functional networks (Li and Sikström, 2002), and altered interactions between intrinsic neuronal noise and perceptual noise (Li et al., 2006). In turn, these effects could lead to increased performance fluctuations and impaired cognitive performance at the behavioral level

In the first attempt to directly link DA functions to processing fluctuations, MacDonald et al. (2009) measured $D_2$ binding in striatum, anterior cingulate cortex, frontal cortex, and hippocampus in a middle-aged group. Processing fluctuations were assessed in terms of within-person variability in reaction time during episodic memory retrieval and concept formation. Because the sample was relatively age-homogeneous, between-person differences in $D_2$ binding and processing fluctuations were relatively small. There was no relationship between striatal $D_2$ binding and processing fluctuations. However, there were systematic negative correlations between $D_2$ binding and processing fluctuations across all three extrastriatal brain regions examined (*rs* ranging

from −.30 to −.45). Thus, these data indicate that, even within normal ranges, reduced availability of DA may result in more fluctuating behavior.

The initial findings of MacDonald et al. (2009) need to be replicated and extended. In particular, it is necessary to extend these data to tasks that (a) are typically employed in research on within-person variability (e.g., reaction-time tasks); and (b) involve more trials than what was available in MacDonald et al., resulting in more reliable estimates of variability. In addition, the association between intraindividual variability at behavioral and neuronal levels of analysis in relation to age changes in DA levels needs to be delineated. Computational simulations suggest that this relation may be non-linear, such that less neuronal variability, or adaptability, may at times be related to greater behavioral variability (Faisal et al., 2008; Li et al., 2006; McIntosh et al., 2008; Stein et al., 2005). Finally, given that aging is associated with both DA losses (e.g., Bäckman et al., 2000; Kaasinen et al., 2000; Volkow et al., 1998; Wang et al., 1998) and increased processing fluctuations (e.g., Anstey, 1999; Hultsch et al., 2002; Li et al., 2004; Nesselroade and Salthouse, 2004; Rabbitt et al., 2001), another interesting avenue for future research is to examine the extent to which age-related increases in within-person cognitive variability are mediated by individual differences in DA.

## 2. Age-related differences in DA release during cognitive processing

Cognitive performance in molecular-imaging studies is typically assessed outside the scanner; thus, the biomarker (e.g., receptor densities) is related to off-line cognitive markers (see Bäckman et al., 2006; Cropley et al., 2006, for reviews). There is, however, emerging evidence for in vivo mapping of actual release of DA, as assessed during cognitive activity. A paradigm used to address this issue involves contrasting DA binding in two conditions varying in cognitive load. DA release is inferred if the binding potential is lower under the high-load condition compared with the low-load condition. This is so because binding of the ligand is supposed to compete more fiercely with binding of endogenous DA to receptors when conditions are more cognitively challenging.

An early study showed that striatal D2 receptor binding was reduced when individuals played a video game that required goal-directed motor activities compared to a baseline condition (Koepp et al., 1998). More recently, a range of studies using similar paradigms also found reduced DA receptor binding during cognitive activities. Specifically, in young adults there is evidence for DA release in frontal cortex and hippocampus during working-memory performance (Aalto et al., 2005), and evidence for striatal DA release during card-sorting (Monchi et al., 2006) and sequential learning (Badgaiyan et al., 2007). A recent PET $D_2$ receptor imaging study also showed that caudate binding potential was sensitive to the demands of cognitive control (Sawamoto et al., 2008), suggesting endogenous DA release due to increased executive requirements. However, this task-induced alteration of $D_2$ binding was not observed in Parkinson patients, likely reflecting deficient striatal DA modulation in this disease.

The demonstration of DA release in young adults during cognitive activity in conjunction with deficient modulation in Parkinson's disease (Aalto et al., 2005; Badgaiyan et al., 2007; Monchi et al., 2006; Sawamoto et al., 2008) opens up for interesting age-comparative work on this topic. We know that age-related cognitive deficits are especially pronounced in tasks that require active (executive) stimulus processing (e.g., Bäckman et al., 2001; Craik and Salthouse, 2007). We also know that DA markers are strongly related to performance in executively demanding tasks (Bäckman et al., 2000; Erixon-Lindroth et al., 2005; Volkow et al., 1998). Given these observations, we might hypothesize that age differences observed in executively demanding tasks partly reflect the fact that such tasks require greater DA release to be successfully performed (Mattay et al., 2003). As a result, age-related DA losses may be particularly detrimental in more demanding relative to less demanding tasks. This would be consistent with the general observation that negative adult age differences in cognitive performance tend to increase with increasing task difficulty (Salthouse, 1992).

Karlsson et al. (2009) examined this hypothesis by measuring $D_1$ receptor binding in young and old adults while they performed the Multi-Source Interference Task (MSIT; Bush et al., 2003) and while they were at rest. The MSIT assesses the ability to inhibit prepotent responses. $D_1$ receptors are strongly implicated in higher-order cognition such as executive functioning and working memory (e.g., Sawaguchi and Goldman-Rakic, 1991; Vijayraghavan et al., 2007), and changes in parietal and frontal $D_1$ receptor density were observed following 5 weeks of executively demanding cognitive training (McNab et al., 2009). Although age-group differences in performance were relatively small in the Karlsson et al. study, the young outperformed the old with regard to both accuracy and latency, especially under conflict conditions. The striatum was compartmentalized into sensorimotor, associative, and limbic (ventral) compartments (Cervenka et al., 2008; Martinez et al., 2003). In line with corresponding work on $D_2$ receptors (Aalto et al., 2005; Monchi et al., 2006), the young showed less binding of the ligand to $D_1$ receptors in all three striatal compartments during the cognitive task compared with baseline (Fig. 1). This difference likely reflects displacement because of competition with endogenous DA as a function of the cognitive challenge (Laruelle, 2000). The functional role of the

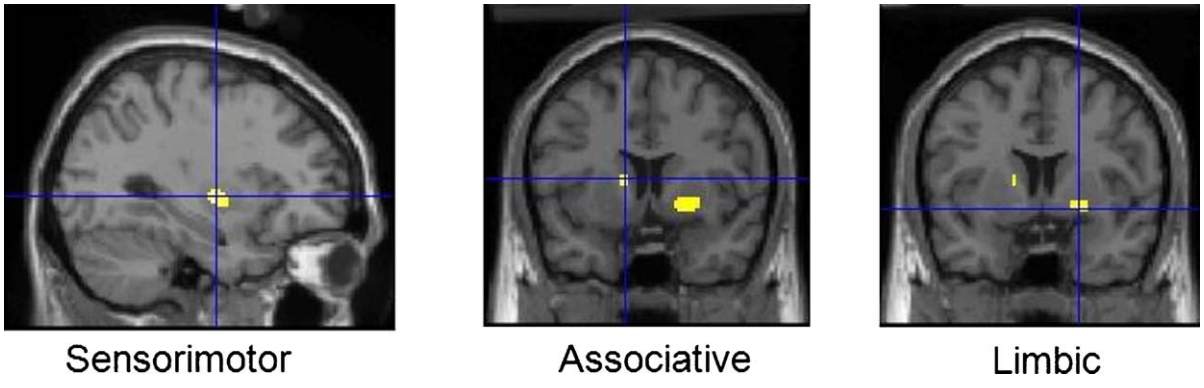


**Fig. 1.** Map of *t*-values showing voxels with decreases of D1 binding potential in sensorimotor, associative, and limbic striatum in younger persons during the MSIT ($p < .005$, $\geq$10 voxels). Adapted from Karlsson et al. (2009).

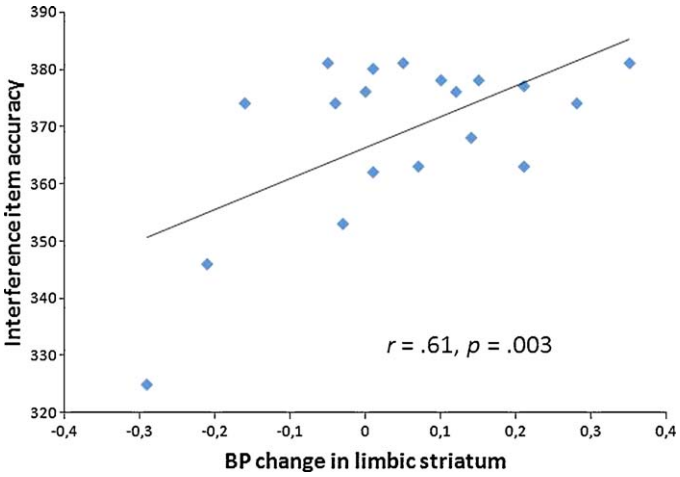


**Fig. 2.** Relationship between change in D1 binding potential (rest minus MSIT) in limbic striatum and interference item accuracy for younger persons. Adapted from Karlsson et al. (2009).

reduced $D_1$ binding potential during cognitive activity in the young was evidenced by the fact that the degree of binding reduction in limbic striatum was positively related to accuracy in the MSIT (Fig. 2).

However, the pattern of data was radically different for the old sample, which showed no difference in $D_1$ receptor binding between the two conditions in any striatal subregion (Fig. 3). This null effect suggests unaltered DA release in response to increasing executive task demands in old adults – that is, a less responsive neurotransmitter system in face of a cognitive challenge. Although the data pattern observed by Karlsson et al. (2009) is intriguing, a word of caution is warranted. As is true with related research inferring DA release during cognitive processing, there is a potential for experimental bias that may have several origins, including head movement or blood flow changes during task performance (see Egelton et al., 2009, for review).

Whether the negative results for the old reported by Karlsson et al. (2009) generalize to other types of executive or memory challenges and to other DA biomarkers remain unknown. In cognitive training research, a common finding is that, although younger adults benefit more from various training regimens than older adults (e.g., Brehmer et al., 2007; Kliegl et al., 1989; Nyberg et al., 2003), the old nevertheless show sizable performance gains post-training. The fact that aging is associated with a certain degree of cognitive plasticity suggests that the apparent lack of neurochemical plasticity in the old observed by Karlsson et al.

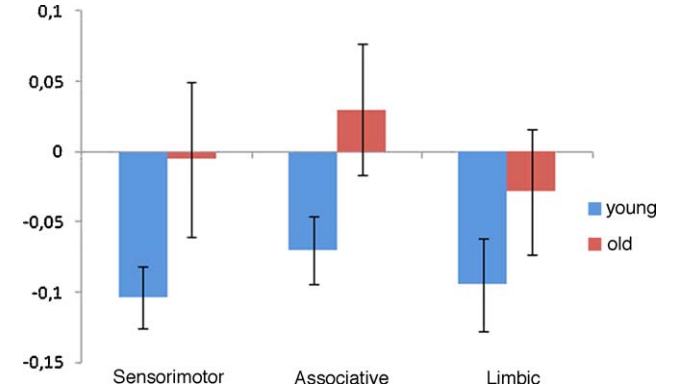


**Fig. 3.** Reductions in $D_1$ binding potential in younger, but not older, persons during the MSIT in sensorimotor, associative, and limbic striatum. Data are extracted from SPM-based analyses. Error bars indicate standard errors around the means. Adapted from Karlsson et al. (2009).

might be modifiable. Delineating boundary conditions for the under-responsive older DA system constitutes an intriguing line of future research.

## 3. DA release following cognitive training in younger and older adults

Until relatively recently, adult cognitive intervention research was largely focused on training of strategies to boost episodic memory performance (for reviews, see Hill et al., 2000; Verhaeghen and Marcoen, 1996). A common assumption was that "hardware-based" cognitive functions such as working memory are less amenable to training and practice.

In recent years, however, several studies have demonstrated that extended practice may enhance performance in executively demanding situations such as dual-task performance (Kramer et al., 1999), verbal working memory (Jaeggi et al., 2008), and spatial working memory (McNab and Klingberg, 2004). Although most of this research involves young adults only, there is evidence of executive plasticity also in older adults (Basak et al., 2008; Buschkuehl et al., 2008; Li et al., 2008). However, as is true with episodic memory training (e.g., Kliegl et al., 1989; Hill et al., 2000; Jones et al., 2006), the magnitude of gains and transfer to non-trained tasks are typically larger for younger compared to older adults (e.g., Li et al., 2008).

In an attempt to delineate neural correlates of gains and transfer from working-memory training, Dahlin et al. (2008b) used fMRI to examine younger and older adults before and after five weeks of training of updating information in working memory. Conforming to the patterns described above, both younger and older adults showed clear performance increments on a letter-memory criterion task (Miyake et al., 2000) following training. However, as shown in Fig. 4a, the posttest minus pretest difference score was larger in the young, indicating attenuated executive plasticity in old age.

In addition, both younger and older trained subjects exhibited increased blood flow in associative striatum during letter-memory performance. The degree of training-related striatal increases of neural activity was greater in the young, hence mimicking the patterns in the behavioral data (Fig. 4b). The training-related increase of striatal blood flow is interesting to view in light of the fact that neurocomputational models assume that striatal neurons serve an important gating function for updating information in working memory (O'Reilly, 2006).

Dahlin et al. (2008b) also administered two transfer tasks in the scanner before and after training, a numerical *n*-back task and Stroop. For Stroop, there were no transfer effects in either age group. By contrast, in the *n*-back task the trained young, but not the trained old, showed transfer of learning. Letter memory and *n*-back share common demands on updating operations, which may be a key determinant of the transfer effects observed. However, these two tasks also differed on several dimensions, including memorial content, set size, presentation rate, response format, and patterns of functional brain activation before training. These differences are critical, given that previous research has indicated that quite subtle procedural variations can affect the degree of transfer (Derwinger et al., 2003; Verhaeghen and Marcoen, 1996). Thus, these data suggest that the *n*-back improvement seen in the young trained group reflects a change at the skill level rather than task-specific stimulus-response facilitation. Further support for this assertion comes from the observation that the transfer effects observed after 5 weeks were maintained 1.5 years later (Dahlin et al., 2008a).

Of chief interest, an overlapping region in the associative striatum was activated during both letter memory and *n*-back prior to training in the young, but not in the old. Further, the young only showed similar increases of activity in the very same region

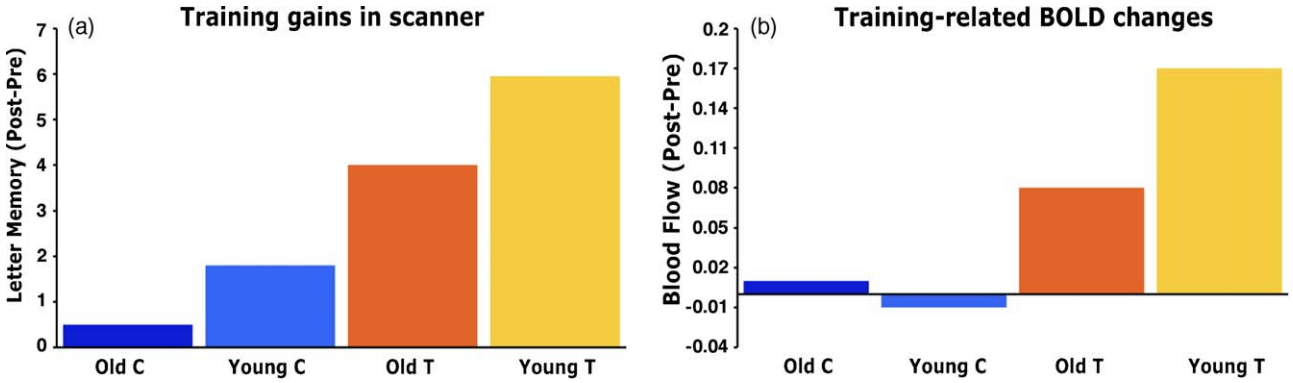


**Fig. 4.** (a) Gains in letter-memory performance (posttest minus pretest) in old controls (C), young C, old trained (T), and young T subjects during fMRI assessment. (b) Training-related increases of blood flow (posttest minus pretest) in associative striatum during letter-memory performance in old C, young C, old T, and young T subjects. Adapted from Dahlin et al. (2008b).

for both the criterion and transfer tasks as a function of training. These findings suggest that a neural prerequisite for transfer of learning is that the criterion and transfer tasks engage similar brain regions, and that the response to training in these regions is similar for trained and untrained tasks. Further, age-related alterations in striatal functioning (e.g., DA losses) may constrain the room for transfer of working-memory training in late life. Note that the overlap in activated brain regions seems to be quite specific, as overlapping fronto-parietal activation patters among letter memory, *n*-back, and Stroop in the young was not sufficient for transfer. Thus, transfer seems to depend on a highly specific pattern of overlap regarding the key processes involved and the corresponding brain systems.

Knutson and Gibbs (2007) suggested that the striatal BOLD signal may be driven by DA agonism. Given this possibility, it is tempting to speculate that the increased striatal BOLD response after training observed by Dahlin et al. (2008b) reflects training-related increases in DA release during task performance. This issue could be addressed by examining individuals under the same experimental conditions as used by Dahlin et al. (2008b). However, rather than assessing blood flow with fMRI, PET could be employed to determine, for example, striatal $D_2$ binding before and after cognitive training (cf. Monchi et al., 2006). If the above reasoning is valid, we would expect training-related reductions of ligand binding to striatal DA receptors during task performance, reflecting increased release of DA.

## 4. The relationship between DA and task-induced functional brain activity

For some time, we have argued for the importance of linking DA activity, blood flow, and behavior, thereby elucidating the chain that progresses from neuromodulation through functional activation to cognitive performance (e.g., Nyberg and Bäckman, 2004). The approach outlined in the preceding subsection on training, striatal BOLD response, and DA binding constitutes one step in that direction.

However, a direct way of addressing this issue is to collect PET-derived DA data and fMRI data on the same individuals. A few recent studies have adopted this design. In a group of younger adults, Schott et al. (2008) used PET imaging of $D_2$ receptors and fMRI to examine the relationship between DA release in ventral striatum and reward-related functional brain activity in the same brain region. In agreement with the view that DA agonism affects the BOLD signal (Knutson and Gibbs, 2007), Schott et al. observed a strong positive relationship between a measure of striatal DA release and the magnitude of the BOLD response during reward-related learning.

Given the abundant dopaminergic influx to neocortical areas via the striato-thalamo-cortical pathway (e.g., Alexander et al., 1986; Sánchez-González et al., 2005), more distant DA-BOLD relationships could also be expected. Consistent with this possibility, Landau et al. (2009) found that a PET marker of DA synthesis capacity was associated with delay-dependent activation in left inferior frontal cortex during a working-memory task in a group of middle-aged adults. This finding corroborates the point that dopaminergic neurotransmission is linked to PFC-related functions. Extending the DA-BOLD relationship to the domain of episodic memory, Nyberg et al. (2009a) showed a positive association between striatal $D_2$ binding and BOLD activation in left lateral prefrontal cortex during a long-term memory updating task in another sample of middle-aged adults (Fig. 5).

Mapping the relationship between indicators of DA activity and functional brain activation across the life course constitutes a key question for future research. Of particular interest in this context is the fact that older adults typically show reduced activation in fronto-parietal regions during working-memory performance, especially under executively demanding conditions (e.g., Mattay et al., 2006; Nagel et al., in press; Nyberg et al., 2009b; Rypma and D'Esposito, 2000). Given the (a) positive DA-BOLD associations

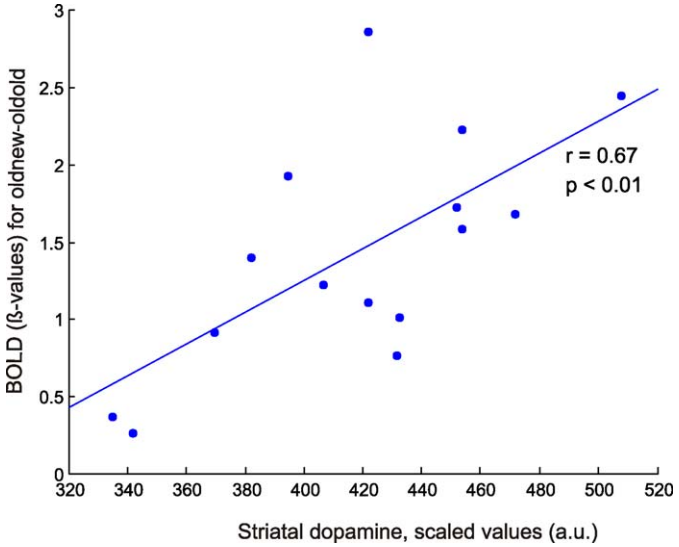


**Fig. 5.** Relationship between striatal dopamine $D_2$ binding and left prefrontal BOLD activity related to updating of long-term memory (LTM) representations. The critical old–new minus old–old contrast in the fMRI analysis compares two conditions that vary with regard to demands on LTM updating. a.u. = arbitrary unit (whole-brain mean = 100) for $D_2$ binding. Adapted from Nyberg et al. (2009a).

described above (Landau et al., 2009; Nyberg et al., 2009a; Schott et al., 2008); and (b) well-known decline of pre- and postsynaptic DA markers in aging (Bäckman et al., 2006), it is conceivable that DA losses contribute to under-recruitment of task-relevant brain regions during cognitive processing in late life.

Initial evidence from a study exploring this new correlative triad (adult age-DA functions-BOLD signal) provides support for this hypothesis (Bäckman et al., 2009). In this combined fMRI and PET study, younger adults showed load-dependent modulation of the BOLD response (higher load > lower load) in distinct prefrontal and parietal regions during a spatial working-memory task. By contrast, older adults did not modulate their fronto-parietal BOLD responses as a function of load. Further, there were marked age-related losses in $D_1$ binding potential in both caudate and dorsolateral prefrontal cortex (DLPFC). Critically, statistically controlling for caudate and DLPFC $D_1$ binding attenuated markedly the age differences in modulation of the BOLD signal. These findings suggest that age-related alterations in dopaminergic neurotransmission may contribute to under-recruitment of task-relevant brain regions during working-memory performance in old age.

## 5. Concluding comments

We have reviewed new evidence on aging, DA, and cognition dealing with distinct, albeit interrelated, phenomena. These include the role of DA in processing fluctuations; age-related differences in DA release in response to cognitive activity and training; and the relationship between DA and the BOLD signal during cognitive activity. The novel findings emanating from these research themes solidify the assertion that DA is implicated in cognitive aging as well as in cognitive functioning irrespective of age. Emerging evidence suggests that age-related DA losses lower the signal-to-noise ratio in relevant neural networks. Among the many consequences of these alterations are increased within-person variability in cognitive processing, as well as under-recruitment of task-relevant brain regions and non-selective recruitment of other regions during cognitive performance in advanced age.

By combining new methodologies (e.g., multimodal imaging) with intelligent task selection, future research will strengthen the integration of DA modulation of aging and cognition at various analytical levels, broadening the phenomena investigated. As a result, the perspectives for future research on the role of DA in aging and cognition will be both deepened and widened. How aging-related DA losses alter the relation between behavioral and neuronal variability will be among the research topics of primary interest.

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