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Age-related variability in decision-making: Insights from neurochemistry

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Abstract

Despite dopamine's significant role in models of value-based decision-making and findings demonstrating loss of dopamine function in aging, evidence of systematic changes in decision-making over the life span remains elusive. Previous studies attempting to resolve the neural basis of age-related alteration in decision-making have typically focused on physical age, which can be a poor proxy for age-related effects on neural systems. There is growing appreciation that aging has heterogeneous effects on distinct components of the dopamine system within subject in addition to substantial variability between subjects. We propose that some of the conflicting findings in age-related effects on decision-making may be reconciled if we can observe the underlying dopamine components within individuals. This can be achieved by incorporating in vivo imaging techniques including positron emission tomography (PET) and neuromelanin-sensitive MR. Further, we discuss how affective factors may contribute to individual differences in decision-making performance among older adults. Specifically, we propose that age-related shifts in affective attention ("positivity effect") can, in some cases, counteract the impact of altered dopamine function on specific decision-making processes, contributing to variability in findings. In an effort to provide clarity to the field and advance productive hypothesis testing, we propose ways in which in vivo dopamine imaging can be leveraged to disambiguate dopaminergic influences on decision-making, and suggest strategies for assessing individual differences in the contribution of affective attentional focus.

Keywords

decision-making; dopamine; aging; positivity effect; PET

As life expectancies increase, there is a growing need to understand how aging affects cognitive functions critical to activities of daily living. One target domain is decision-making. Older adults show impairment in some aspects of everyday decision-making. Relevant to financial behavior, older adults are more likely to borrow at higher interest rates (Agarwal, Driscoll, Gabaix, & Laibson, 2009), and despite greater experience than their

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younger counterparts, demonstrate lower investment skill leading to an estimated loss of up to 5% in annual returns (Korniotis & Kumar, 2010). Older adults, however, do not appear to show general deficits in discounting the value of returns over time (Seaman, Brooks, et al., 2018). Identifying the contexts in which older adults are likely to make suboptimal decisions, and defining the neural mechanisms underlying this susceptibility will be essential for designing interventions that support the maintenance of successful independence in aging.

The dopamine system has been implicated in multiple aspects of value-based learning and decision-making. For example, lines of research that unite behavioral neuroscience with computational modeling approaches suggest a role of phasic dopamine in generating reward prediction errors (RPEs), which are central to models of reinforcement learning (Kim et al., 2012; Schultz, Dayan, & Montague, 1997; Steinberg et al., 2013). RPEs may support value-based reinforcement learning by reporting the discrepancy between expected and received reward. In humans, productive lines of research have combined computational reinforcement learning models with task-based fMRI to reveal signatures of striatal activation that mimic dopaminergic RPEs observed in animal models (McClure, Berns, & Montague, 2003; O'Doherty et al., 2004; O'Doherty, Dayan, Friston, Critchley, & Dolan, 2003). Though there is a paucity of human research linking endogenous measures of dopamine function with reinforcement learning, dopaminergic drugs modulate RPE-like fMRI signals (Chowdhury, Guitart-Masip, Lambert, Dayan, et al., 2013; Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006; Rutledge et al., 2009). Beyond reinforcement learning, dopamine has been linked to a multitude of cognitive processes thought to support complex, goal-directed decision-making such as episodic memory (Shohamy & Adcock, 2010), working memory (Puig, Rose, Schmidt, & Freund, 2014), flexibility (Floresco, 2013), and valuation (Schelp et al., 2017). Therefore, it would be reasonable to expect that deficits in dopamine function would negatively impact decision-making, and possibly through multiple paths.

Aging is accompanied by alterations in multiple components of the dopamine system, including loss of dopamine-producing neurons in the substantia nigra (Fearnley & Lees, 1991), and losses in dopamine receptors and transporters (Karrer, Josef, Mata, Morris, & Samanez-Larkin, 2017). However, there is accumulating evidence from in vivo PET imaging in humans indicating that dopamine changes in aging are more heterogenous than previously thought. In this review, we focus on three aspects of intra and interindividual variability and consider how they may obscure evidence of systematic changes in decision-making with age. First, declines in the dopamine system vary substantially across individuals (e.g., Dang et al., 2017). Second, pre and post synaptic components of the dopamine system may decline at different rates and in different directions (e.g., Karrer et al., 2017). Third, declines in the dopamine system may be spatially heterogeneous (e.g., Rieckmann et al., 2011; Seaman, Juarez, et al., 2018). We provide examples for how these factors may affect decision-making processes relying on reinforcement learning (sometimes called "model-free" learning) as well as goal-directed processes thought to rely on working memory (sometimes called "model-based" learning; Daw, Niv, & Dayan, 2005; Dickinson & Balleine, 2002; Dolan & Dayan, 2013; Doya 1999). We posit that incorporating in vivo imaging to account for intraindividual and interindividual variability in dopamine function may explain some of the null or conflicting age effects in the decision sciences.

Perhaps reflecting the complex relationship between dopamine function and aging, there is surprisingly little consensus on the nature of age-related changes in value-based decision-making using laboratory-based tasks. For example, studies in animal models strongly implicate dopamine in risk-taking (reviewed in Orsini, Moorman, Young, Setlow, & Floresco, 2015). However, meta-analyses of tasks assessing risk-taking in young and older adults found no effect of age (Mata, Josef, Samanez-Larkin, & Hertwig, 2011), or small effects indicating greater risk aversion in older adults when potential financial gains are at stake (Best & Charness, 2015; see Mamerow, Frey, & Mata, 2016, for evidence of reduced self-reported risk taking in aging). Previous discussions of the mixed effects in the decision-making literature have emphasized how variability in task framing and difficulty have profound effects on performance in older adults and can potentially alter the direction of observed age differences (Mamerow et al., 2016; Mata et al., 2011; Mather, 2006; Mienaltowski, 2011; Strough, Karns, & Schlosnagle, 2011; Westbrook, Kester, & Braver, 2013). For example, a recent meta-analysis of the Iowa gambling task suggests risk aversion in aging may develop progressively over the course of a single experimental session (Pasion et al., 2017). Therefore, older adults may appear more risk seeking or more risk averse depending on a given task's demands on learning. While previous discussions have brought to light the importance of between-study task differences in interpreting inconsistencies in the direction of reported age-group differences, here we emphasize the ways in which interindividual variability in older adults preclude the identification of systematic age-group differences within a single study.

One limitation of previous studies is the absence of in vivo assessment of dopamine function using methods such as PET. PET imaging has been critical for clarifying essential questions in cognitive aging. For example, relevant to the field of Alzheimer's disease research, PET imaging is being used to resolve conflicting accounts of the pathological mechanisms affecting memory. Recent PET findings have demonstrated preferential relationships between the accumulation of tau (but not amyloid-β) and memory (e.g., Maass et al., 2018). Similarly, dopamine PET imaging has been central for resolving controversies regarding the neural basis of cognitive training gains and mechanisms of transfer. Backman and colleagues have demonstrated 5 weeks of working memory training increases striatal dopamine release during performance of the training task (Bäckman et al., 2011; Bäckman et al., 2017) as well during performance on untrained working memory tasks (Bäckman et al., 2017). Incorporation of neurochemical and neuropathological quantitation allows for unique insights into the mechanisms underlying cognitive decline or enhancement in humans that are not possible using fMRI, electroencephalography, or structural imaging alone.

Here, we discuss how the addition of in vivo dopamine measures (PET, neuromelanin-sensitive MR) to behavioral and structural and functional imaging studies will be useful for organizing the range of age effects reported in the decision sciences. We first provide background on in vivo dopamine imaging, and describe the strengths and limitations of these methods. We next identify three sources of interindividual and intraindividual variability in age-related changes in brain dopamine, which have been revealed through PET imaging. Using specific examples to illustrate how these sources of variability can produce inconsistent age group effects, we propose ways in which in vivo imaging can clarify the neural basis for these findings. Finally, we address the possibility that changes in dopamine

function join with age-related alterations in affective attention to increase interindividual variability in decision-making performance. We suggest that age-related changes in affective attention (i.e., positivity effect) influence decision-making, and may, at times, oppose the effects of altered dopamine function on performance. We propose that accounting for interactions between dopamine and affective attention will be useful for explaining apparent noise in decision-making performance between individuals and between tasks.

In vivo dopamine imaging: strengths and weaknesses

In this section, we briefly review methods for in vivo dopamine imaging in humans, which we hope provides useful background information for our discussion of how these methods can bolster our understanding of decision-making in aging. PET imaging allows for the assessment of multiple components of dopamine function in vivo in animal models and humans. Here, we focus our review on PET imaging methods, though similar principles apply to SPECT imaging.

Radiotracers have been developed that target dopamine receptors, transporters, and enzymes involved in dopamine synthesis (see. Fig. 1a). Commonly, PET imaging is conducted while subjects are not cognitively engaged in a specific task, but are in baseline resting conditions. Examples of how dopamine PET is paired with simultaneous cognitive task performance is described below. In a typical experiment, a subject is injected with a single bolus of the radiotracer and undergoes imaging over the course of 60–90 minutes. Kinetic modeling is applied to the data to provide a single whole-brain image (for review of modeling, see Morris et al., 2004). This image provides a static snapshot of the occupancy of specific dopamine receptors or transporters, or enzymatic function underlying dopamine synthesis capacity within an individual (see Fig. 1b). Similarly, neuromelanin-sensitive MR approaches provide a static snapshot of the health of the nigral dopamine system (see Fig. 1c), though relationships between MR and PET measures have not yet been established (discussed below). Region of interest analyses can test how these measures vary across individuals and correlate with specific behaviors or other neural measures.

For imaging receptors and transporters, radiotracers that act as competitive agonists or antagonists are used. It is worth noting that while most tracers give good quantitation in the striatum where the concentration of dopamine targets is high, fewer tracers allow for measurement in regions such as thalamus, amygdala, hippocampus, and cortex, where concentrations may be 10-fold less. Therefore, higher affinity tracers for D1 (e.g., SCH23390) and D2/3 (e.g., fallypride) receptors must be used for research aimed at delineating contributions of cortical dopamine in decision-making. Tracers targeting receptors and transporters are characterized as “reversible,” meaning they bind to their target but can also dissociate until they reach a steady state during which the flux of tracer tissue binding equals the flux of dissociation back into blood. Calculations of nondisplaceable binding potential (BP_{ND}) are common for assessing individual difference in the availability of dopamine receptors and transporters (Hume et al., 1992). In a given region of interest, BP_{ND} reflects the density and affinity of the targeted receptor or transporter. However, as the tracer is in competition with endogenous dopamine to bind to its target, BP_{ND} is also sensitive to individual differences in the concentration of endogenous dopamine. Therefore,

BP_{ND} comprises both the density/affinity of the receptor/transporter of interest as well as the concentration of competing dopamine particularly for lower affinity tracers. Thus, there is no "pure" PET measure of dopamine receptor density or transporter density.

There are established PET methods for assessing dopamine release within individual subjects, which capitalize on the competitive displacement of radiotracers by endogenous dopamine (Endres et al., 1997; see Fig. 1d). Specifically, decreases in receptor BP_{ND} accompany increases in extracellular dopamine concentration, which has been validated by simultaneous microdialysis (Laruelle et al., 1997). Due to slow tracer kinetics, current PET imaging methods do not allow for event-related measurement of dopamine release for single trials. Therefore, direct comparison with phasic dopamine release afforded by fast scan cyclic voltammetry in animal models is untenable. In humans, PET measures of dopamine release reflect changes in extracellular dopamine across 10–60 minutes, depending on study design. One approach is to collect two PET scans per subject and compare baseline BP_{ND} (Scan 1) with BP_{ND} during task performance (e.g., Koepp et al., 1998), or following administration of a drug that increases synaptic dopamine concentration by blocking dopamine reuptake or stimulating release (Scan 2; see Fig. 1d). A second approach is to measure alteration in dopamine release across a single session. These protocols are somewhat more onerous and usually require constant infusion of the radiotracer, but have demonstrated increases in dopamine release associated with cognitive task performance (Jonasson et al., 2014).

In addition to PET imaging, it is possible to assess dopaminergic function in vivo using neuromelanin-sensitive MR. This approach enables the visualization of monoaminergic nuclei in the substantia nigra pars compacta (dopamine) and locus ceruleus (norepinephrine/dopamine; Sasaki et al., 2008). Neuromelanin is produced by the oxidation of dopamine and norepinephrine (Muñoz, Huenchuguala, Paris, & Segura-Aguilar, 2012; Wakamatsu et al., 2015) and is stored in lysosomes (reviewed in Sulzer et al., 2008). Neuromelanin's binding to iron and copper (Enochs et al., 1989; Trujillo et al., 2017) facilitates the visualization of neuromelanin-rich regions in using MR approaches (see Fig. 1c). Its sequestration of heavy metals is likely neuroprotective, though after neuronal death, the release of toxins into extracellular space may be detrimental (reviewed in Zucca et al., 2017).

Supporting the validity of this measure for assessing individual differences in the integrity of substantia nigra dopaminergic function, there is evidence that neuromelanin MR signal is reduced in Parkinson's disease (Sasaki et al., 2006) and distinguishes healthy controls from people with schizophrenia and depression (Shibata et al., 2008). Consistent with PET dopamine synthesis findings, healthy aging is associated with elevation of neuromelanin (Zecca et al., 2002; Zecca et al., 2001; Zucca et al., 2006). Individual differences in neuromelanin MR signal in healthy aging have been linked to variability in reward learning (Chowdhury, Guitart-Masip, Lambert, Dolan, & Düzel, 2013), memory performance (Hämmerer et al., 2018), and fMRI activation during encoding (Clewett, Huang, Velasco, Lee, & Mather, 2018). To date, there has been little investigation characterizing relationships between neuromelanin MR signal and dopamine PET measures within subject in young or older adults. One study reported a positive relationship between neuromelanin signal and D2/3 BP_{ND} in VTA/substantia nigra, but failed to find a relationship with dopamine

synthesis capacity (Ito et al., 2017). However, this study may have been underpowered (n = 11), and used L-[β−^{11}C]DOPA to measure dopamine synthesis capacity, which complicates data analysis compared to the fluoro-l-mtyrosine PET measure of dopamine synthesis capacity (see Berry, Shah, Furman, et al., 2018, for discussion). While the neuromelanin MR imaging approach is still under active development (Betts, Cardenas-Blanco, Kanowski, Jessen, & Düzel, 2017), it represents a low-cost and easily implemented way to approximate individual differences in the integrity of neurochemical systems relevant to cognition.

Nonuniform changes in the dopamine system in aging

In vivo imaging has the advantage of providing a within-subject, continuous measure of dopamine function that can be used to assess individual differences and offers a perspective of which brain regions may be preferentially associated with specific aspects of cognitive performance. What has emerged in the study of aging is the observation that changes are not monotonic. Different components of the dopamine system appear to change at different rates, in different directions, or not at all. Further, age-related changes in dopamine receptors may be spatially nonuniform. Below, we summarize these findings, which together speak to the limitations of experimental approaches that do not seek to account for such heterogeneity in the effects of aging on the neural systems supporting decision-making.

A recent meta-analysis examining age-related changes in dopamine PET measures found consistent evidence that D1 and D2/3 BP_{ND} decline with aging (Karrer et al., 2017). Though the studies examined in this meta-analysis were cross-sectional rather than longitudinal, the magnitude of age-related reductions was illustrated by the estimation of the percent reduction per decade of life. D1 receptors declined at a rate of ~14% per decade while D2/3 receptors and the dopamine transporter declined at a rate of 8%–9% per decade. These estimations derived from human PET imaging studies are generally consistent with, though in some cases are slightly higher than quantitation from postmortem human tissue (Hemby, Trojanowski, & Ginsberg, 2003; Rinne, Lönnberg, & Marjamäki, 1990; Ma et al., 1999) and nonhuman animal studies (Hoekzema et al., 2010; Ingram et al., 2001; Madras et al., 1998). While receptor BP_{ND} is lower in older adults relative to young, studies consistently reveal substantial inter-individual variability in D1 and D2/3 BP_{ND} in older adults. For example, D2/3 BP_{ND} is relatively preserved in people who are more physically active (Dang et al., 2017). Such interindividual variability appears to be relevant to cognition, as it correlated with differences in psychomotor function (Wang et al., 1998), executive function (MacDonald, Karlsson, Rieckmann, Nyberg, & Backman, 2012; Volkow et al., 1998), and memory (Bäckman et al., 2000; Nyberg et al., 2016; Rieckmann, Johnson, Sperling, Buckner, & Hedden, 2018) in older adults.

While dopamine receptor BP_{ND} declines in aging, there is accumulating evidence that dopamine synthesis capacity is elevated in older adults (Berry et al., 2016; Braskie et al., 2008; Dejesus, Endres, Shelton, Nickles, & Holden, 2001). Higher synthesis coupled with reduced transporter activity (Karrer et al., 2017) may act to elevate synaptic dopamine concentrations in older adults, potentially reflecting compensatory mechanisms for counteracting losses in receptor density. However, research to date has not supported a clear role of elevated synthesis in benefiting cognition (Berry et al., 2016; Braskie et al., 2008;

Klostermann, Braskie, Landau, O'Neil, & Jagust, 2012; though see Berry, Shah, & Jagust, 2018, for evidence that elevated synthesis preserves relationships between functional connectivity and performance). Indeed, inverted-U-shaped relationships are observed for dopamine synthesis (Berry et al., 2016; Dreher, Meyer-Lindenberg, Kohn, & Berman, 2008), suggesting higher synthesis levels may, in some cases, be detrimental. Therefore, it may not be sufficient to consider aging as simply a hypodopaminergic state, but instead may be a dysregulated state characterized by a loss of balance between presynaptic and postsynaptic components of the system. Similar conceptualizations of dopamine dysregulation may be applied to psychological and psychiatric disorders including schizophrenia, ADHD, and addiction (Stone, Morrison, & Pilowsky, 2007; Volkow, Fowler, Wang, & Swanson, 2004; Wu, Xiao, Sun, Zou, & Zhu, 2012). This dysregulation may critically affect the precision of dopamine signaling, increasing the variability of its temporal dynamics and noise (Li, Lindenberger, & Sikström, 2001; MacDonald et al., 2012).

There is emerging evidence that regulation of dopamine receptors and age-related decline in receptor density is not spatially homogeneous (Rieckmann et al., 2011; Seaman, Juarez, et al., 2018; Zald et al., 2010). Rieckmann and colleagues report age-related reductions in interregional correlations in D1 BP_{ND} using [^{11}C]SCH23390. Their findings suggested that aging is associated with a dissociation in D1 receptor regulation between nigrostriatal and mesocortical/mesolimbic pathways. Seaman and colleagues evaluated regional differences in estimated rates of percentage of change in D2/3 BP_{ND} using [^{18}F]fallypride (Seaman, Juarez, et al., 2018). Their findings revealed tremendous heterogeneity across regions in the estimated rate of decline, which was variably linear or curvilinear. Even after correcting for differences in gray matter volume, they estimated the most extreme reductions in subgenual frontal cortex and superior temporal gyrus and less pronounced reductions in ventral striatum, pallidum and hippocampus (data available at http://13.58.222.229:3838/agebp/; https://osf.io/h67k4/?view_only=7f99796797894a1085d42b69c4d621c5).

Altogether, findings in aging indicate that changes in the dopamine system (1) vary across individuals, (2) vary across different presynaptic and postsynaptic components, and (3) vary spatially across the brain. In the following three sections, we highlight instances in which accounting for these three sources of variability may shed light on reported effects in value-based decision-making.

Interindividual variability of age effects on dopamine

Loss of dopamine has been linked with propensity to avoid punishment rather than approach reward. The probabilistic selection task (PST) is a well-known decision-making task that has been used to study these questions and has been applied to healthy adults and a variety of patient populations including those with Parkinson's disease (Frank, Seeberger, & O'Reilly, 2004) and schizophrenia (Ragland et al., 2012). It ostensibly taps into processes of model-free reinforcement learning, with some evidence suggesting it is preferentially associated with striatal rather than PFC dopamine function (Doll, Bath, Daw, & Frank, 2016). Despite links to dopamine, there have been largely null findings in previous studies examining consistent group-wise effects of age on performance. Here we provide background on the PST, and models of dopamine's role via the D1-mediated "direct" and D2-mediated

"indirect" pathways. We propose that any measure that captures individual differences in dopamine function (e.g., neuromelanin-sensitive MR) may useful in clarifying these null effects. Further, we discuss specific ways in which D1 and D2/3 receptor imaging can be leveraged to contribute to our basic understanding of the role of these pathways in human decision-making as well as individual differences in performance in aging.

The PST is composed of both a probabilistic learning phase and a choice phase. Its design aims to assess potential biases in choice action to approach reward versus choice action to avoid punishment. Briefly, three sets of Japanese hiragana characters (AB, CD, EF) are presented in randomized order and are associated with differing probabilities of reward or punishment (reward probabilities: 80/20, 70/30, 60/40). During the learning phase, participants learn to select the stimuli associated with reward. However, this learning could be driven by positive reinforcement from reward (A, C, E) or negative reinforcement from punishment (B, D, F). The choice phase of the PST is designed to dissociate these possibilities. The stimuli are presented in novel pairs to reveal underlying choice biases in incentive motivation to either approach reward (choose A) or avoid punishment (avoid B; see Fig. 2a).

The bias to avoid punishment was demonstrated in Parkinson's patients tested off medication, but was reversed when patients were tested on medication in presumably dopamine-replete states (see Fig. 2a; Frank et al., 2004). Since the original description of the PST task, there has been significant interest in understanding how age-related changes in dopamine function may affect biases in decision-making. A simple hypodopaminergic account of aging would predict that age effects mimic those observed in Parkinson's disease, but to a lesser degree given the relative sparing of dopaminergic function (though see Sojitra, Lerner, Petok, & Gluck, 2018, for discussion of dissociations between healthy aging and Parkinson's disease). Such biases, if they produce inoptimal choice behavior, would be a prime target for intervention in aging.

Behavioral evidence of age-related biases in choice selection is mixed, with greater individual differences reported for older adults. A bias to avoid punishment has been shown in an older subset (mean age = 77 years) of older adults, but not in a younger subset (mean age = 67 years; Frank & Kong, 2008). Some studies report greater individual differences in the balance between positively and negatively motivated choices in aging (see Fig. 2b; Simon, Howard, & Howard, 2010; Sojitra et al., 2018), or have shown selective reduction in positive learning but not negative learning (Eppinger, Schuck, Nystrom, & Cohen, 2013). Other aging studies have found no effects of valence (Lighthall, Gorlick, Schoeke, Frank, & Mather, 2013; Pietschmann, Endrass, Czerwon, & Kathmann, 2011). We posit that accounting for individual differences in the decline of dopamine function using specific dopamine targets in striatum or neuromelanin-sensitive MR will clarify these null and mixed results. Previous research using MR approaches for assessing midbrain dopaminergic nuclei suggest a benefit of greater structural integrity for reward learning (Chowdhury, Guitart-Masip, Lambert, Dolan, et al., 2013). We predict that the subgroup of older adults with a positive choice bias to approach reward will have greater midbrain neuromelanin MR signal than older adults with a negative choice bias (see Fig. 2c).

The proposed mechanisms of dopamine's involvement in approaching reward (choose A) versus avoiding punishment (avoid B) involve the weighting of two circuits, the direct pathway versus the indirect pathway, involving substantia nigra, striatum, globus pallidus, and thalamus. Activation of the direct "go" pathway leads to the disinhibition of thalamus, facilitating outputs to cortex. Conversely, activation of the indirect "no-go" pathway suppresses thalamic output to cortex. The direct pathway is associated with reward-based learning and approach, which may be mediated by stimulation of striatal D1 expressing medium spiny neurons (Kravitz, Tye, & Kreitzer, 2012; Tai, Lee, Benavidez, Bonci, & Wilbrecht, 2012). The indirect pathway is associated with aversion-based learning and avoidance, which may be mediated by stimulation of striatal D2 expressing medium spiny neurons (Kravitz et al., 2012; Tai et al., 2012). Frank and colleagues suggest that low tonic dopamine amplifies learning through D2 negative reinforcement mechanisms and accounts for biases to avoid punishment (rather than approach reward) in Parkinson's patients tested off medication (Frank & Kong, 2008; Frank et al., 2004). A recent PETstudy in healthy young adults (n = 28) directly probed relationships between individual differences in D1 and D2/3 BP_{ND} and propensity to approach reward versus avoid punishment in the PST (Cox et al., 2015). Individuals with higher D1 BP_{ND} (measured with SCH23390) showed greater propensity approach reward. However, higher D2/3 BP_{ND} (measured with raclopride) was not clearly related to a bias to avoid punishment in this young adult sample. It is currently not known whether D2/3 effects would emerge if these healthy subjects were tested in a dopamine depleted state (e.g., following acute phenylalanine and tyrosine depletion).

It is possible that individual differences in relative ratios of D1 and D2/3 receptor densities may underlie between-subject variability in PST performance in older adults, or variability in performance on other tasks, such as tasks involving risky gambles, which tap into approach versus avoidance mechanisms. There is some evidence, though limited, suggesting D1 and D2/3 receptor densities decline at different rates across the lifespan (see Fig. 2d). Estimated rates of decline are numerically greater for D1 receptors than D2/3 receptors for between-subject comparisons of PET data (Karrer et al., 2017) and within-subject analyses of postmortem tissue (Seeman et al., 1987; though see also Rinne et al., 1990, for null effects in a smaller sample). However, additional research is needed to establish whether there are asymmetric effects of aging on D1 versus D2/3 receptors. It is unclear what the underlying physiological mechanism might be for the relative vulnerability of D1 receptors or relative resilience of D2/3 receptors in aging. D1 and D2-expressing medium spiny neurons have distinct morphological and electrophysiological properties (Cepeda et al., 2008; Ma et al., 2012) which may confer unique susceptibilities. In culture, D2, rather than D1 receptors, may be more vulnerable to excitotoxic insults (Mesco, Joseph, & Roth, 1992). However, observations in early Parkinson's disease reveal (presumably compensatory) upregulation of D2/3 receptors, but not D1 receptors (Rinne, Laihinen, et al., 1990). This leaves open the possibility that differences in the capacity for receptor upregulation may underlie reductions of the ratio between D1 and D2/3 in healthy aging. Regardless of mechanism, the direction of these effects observed in aging is generally consistent with the view that aging shifts choice behavior toward a bias to avoid punishment rather than approach reward.

There is, however, significant interindividual variability in the trajectory of age-related changes in the dopamine system, which would warrant examination of within-subject ratios of D1 to D2/3 receptor densities and their relationship with performance. For the PST, evaluation of individual subject performance has revealed subgroups of older adults with a "positive" choice bias to approach reward and subgroups with a "negative" bias to avoid punishment (e.g., Simon et al., 2010; see Fig. 2b). Subjects with losses in D1 receptors but relative preservation of D2/3 receptors may show reduced choice behavior to approach reward (choose A), and greater choice behavior to avoid punishment (avoid B). Subjects with losses in D2/3 receptors but relative preservation of D1 receptors could be expected to show the opposite pattern of results (see Fig. 2e). In vivo PET imaging could resolve the underlying neural basis of these individual differences in positively and negatively motivated choices in aging. Further, complementary studies in animal models could test whether selective knock-down of D1 versus D2 receptors generates a similar pattern of results.

Heterogenous age effects on presynaptic and postsynaptic components

While the density of dopamine receptors declines with age, there is evidence for counteracting increases in dopamine synthesis (Berry et al., 2016; Braskie et al., 2008; Dejesus et al., 2001) and decreases in dopamine reuptake via reduced transporter BP_{ND} (Karrer et al., 2017; Rieckmann et al., 2018). If imbalance in the tuning of pre and postsynaptic components occurs in aging, this dysregulation may lead to reduced precision of RPEs implicated in value-based reinforcement learning (see Fig. 3a). Such dysregulation would be expected to result in slower model-free reinforcement learning. Behavioral evidence suggests that while older adults perform comparably to young adults when cue-reward contingencies are deterministic (Eppinger, Kray, Mock, & Mecklinger, 2008) older adults show impaired performance in situations in which outcomes are probabilistic or require learning from feedback (Eppinger, Schuck, et al., 2013; Mell, Heekeren, et al., 2005; Mell, Wartenburger, et al., 2009; Samanez-Larkin, Levens, Perry, Dougherty, & Knutson, 2012).

Though behavioral evidence indicates impaired reward-based learning in older adults, it is not clear that neural activity associated with reward anticipation or reward outcome is systematically altered in aging. Ventral striatum/nucleus accumbens activation in response to reward-predicting cues is the same in young and older adults (Samanez-Larkin et al., 2007; Wu, Samanez-Larkin, Katovich, & Knutson, 2014; though see also Schott et al., 2007). Further, responses to rewarding outcomes in ventral striatum and medial PFC have been shown to be similar in young and older adults (Cox, Aizenstein, & Fiez, 2008; Samanez-Larkin et al., 2007; Samanez-Larkin, Kuhnen, Yoo, & Knutson, 2010; Samanez-Larkin, Worthy, Mata, McClure, & Knutson, 2014; Schott et al., 2007; though see also Eppinger, Schuck, et al., 2013; Spaniol, Bowen, Wegier, & Grady, 2015). These measures of BOLD activation suggest there are no systematic differences in reward responsivity in aging. However, these measures typically rely on averages across many trials, and may not capture age-differences in trial-to-trial variability.

Fruitful lines of research in aging have linked reward-based learning with neurocomputational approaches to examine age differences in RPE-like BOLD signal that

rely on trial-based estimates. Together, these studies suggest that aging reduces correlations between RPEs derived from reward learning tasks and BOLD activation in ventral striatum/nucleus accumbens (Eppinger, Schuck, et al., 2013; Samanez-Larkin et al., 2014) and ventromedial PFC (Samanez-Larkin et al., 2014). Few studies have linked age-related reductions in these correlations with alteration in dopamine function in aging. In one notable exception, Chowdhury, Guitart-Masip, Lambert, Dayan, et al. (2013) pharmacologically manipulated dopamine to examine its effects on learning and RPEs. This study demonstrated that treatment of older adults with levodopa increased both RPE-like signals in ventral striatum and rates of learning. A recent study using the same task probed relationships between striatal D1 BP_{ND} and nucleus accumbens RPE's in young and older adults (de Boer et al., 2017). Surprisingly, they did not find striatal RPE-like responses in either young or older adults. D1 BP_{ND} was not correlated with performance for either group but was positively related to ventromedial PFC signal associated with reward anticipation.

Moving forward, it will be valuable to consider how dopamine changes in aging may fundamentally alter the reliability in dopamine signaling to affect reward-based learning. This can be achieved in studies in animal models that examine the effects of age on the amplitude and timing of phasic responses. In humans, foundational studies could investigate whether neuromelanin-sensitive MR measures of midbrain dopamine function are related to the strength of correlations between RPEs derived from reward learning tasks and striatal BOLD signal in older adults. Higher correlations may be predicted in older adults with higher midbrain neuromelanin MR contrast-to-noise ratios. Applying PET methods, future studies could consider relationships between presynaptic and postsynaptic components within subject. For example, individual differences in the ratio of dopamine transporter availability and D2/3 receptor availability within subject may correlate with rates of learning (see Fig. 3b). One may predict an inverted-U-shaped relationship between a presynaptic/postsynaptic composite measure and learning suggesting that an optimal balance in dopamine receptor binding and reuptake is associated with more precise RPEs and more efficient learning rates in aging.

There is precedent in the human cognitive neuroscience literature suggesting noisier representations in aging underlie performance decrements. Using fMRI, Samanez-Larkin et al. (2010) revealed that in older adults, greater temporal variability in nucleus accumbens BOLD response was directly related with suboptimal performance on a financial risk-taking task. Variability has been shown to be reproducible within subject across time and tasks (Arazi, Gonen-Yaacovi, & Dinstein, 2017), and has been linked to individual differences in dopamine (Bäckman, Lindenberger, Li, & Nyberg, 2010; Cohen & Servan-Schreiber, 1992; Li et al., 2001). In aging, declines in D1 receptors have been associated with increased intraindividual variability in reaction times during an executive function task (MacDonald et al., 2012). Generally, there is consensus that intraindividual variability in neural and behavioral responses is a valuable measure for understanding the underlying neural basis of impaired performance (Mohr & Nagel, 2010), though it is important to note that in some cases neural variability may be beneficial (Armbruster-Genç, Ueltzhöffer, & Fiebach, 2016). One central component of this line of research will be to distinguish between variability that is driven by imprecision in signaling versus variability that simply reflects a healthy dynamic range in neural responses that are not muted by, for example, disease processes

(Garrett et al., 2013). Important research by Garrett, Kovacevic, McIntosh, and Grady (2010, 2011) has demonstrated that, overall, older adults show less variability in BOLD signal than younger adults, and that this reduced variability is associated with poorer cognitive performance. Interestingly, they found subcortical structures including hippocampus and regions in the striatum that were more variable in older adults than young adults (Garrett et al., 2010, 2011). Together, these findings suggest variability in subcortical responses may be an important, age-sensitive measure in human imaging studies that warrants further investigation to establish possible relationships with dopamine. For example, future studies could test whether individuals with highly variable cortical responses also have highly variable subcortical response, or whether these are dissociable measures potentially reflecting different underlying sources.

Spatial variability in age-related changes in dopamine

PET imaging provides spatial information that allows for the assessment of regional differences in dopamine function. This provides unique opportunities to test hypotheses about the differential influence of region-specific measures of dopamine on discrete cognitive operations. For example, PET can be useful for specifying a role of PFC dopamine signaling in decision-making. Spatial information may be particularly relevant for studying dopaminergic mechanisms of decision-making in aging as there is growing evidence that dopamine receptor densities may decline at different rates across the brain (Rieckmann et al., 2011; Seaman, Juarez, et al., 2018). Here, we describe ways in which the spatial information afforded by PET imaging can be leveraged to probe the role of dopamine in age-related changes in reliance on striatal versus extrastriatal brain regions during decision-making.

Evolving research has developed our understanding of complementary learning mechanisms that may trade off or interact with model-free reinforcement learning processes to affect decision-making. These include, but are not limited to, processes for the building of deliberative internal models to guide choices (“model-based” evaluation; Daw et al., 2005; Dickinson & Balleine, 2002; Dolan & Dayan, 2013; Doya 1999), as well as processes for learning and planning that more heavily rely on prefrontal processes including working memory (Collins & Frank, 2012) or medial temporal lobe episodic memory (Gershman & Daw, 2017; Shohamy & Daw, 2015). The degree to which these processes interact, and the nature of these interactions is an area of active research (Collins & Frank, 2012; Eppinger, Walter, & Li, 2017; Russek, Momennejad, Botvinick, Gershman, & Daw, 2017; Shohamy & Daw, 2015). However, the multiprocess view of decision-making incorporates roles for multiple neural systems that include frontoparietal, medial temporal lobe, and limbic structures.

There is general agreement that most value-based decision-making tasks accommodate multiple strategies. In some cases, these strategies can be distinguished from one another using computational modeling approaches (Collins & Frank, 2012; Daw et al., 2005). These lines of research have revealed profound individual differences in the extent to which people adopt one strategy over another. Age differences in the adoption of task strategy has been identified as a critical factor in considering discrepant findings in the aging literature

(Eppinger, Hämmerer, & Li, 2011; Mather, 2006; Strough et al., 2011; Worthy, Gorlick, Pacheco, Schnyer, & Maddox, 2011). For example, older adults may show better or worse performance than young adults depending on whether a given task favors win-stay lose-shift strategies (Worthy & Maddox, 2012; for similar findings in aging rats, see Tomm et al., 2018). Research examining how reliance on specific strategies is affected by regional differences in dopamine function is only beginning, but holds promise for informing findings in aging.

Influential learning models have distinguished between model-free processes and model-based processes, which can be dissociated from one another computationally using the two-state Markov decision task (see Fig. 4a; Daw, Gershman, Seymour, Dayan, & Dolan, 2011). Briefly, this task involves two decision phases (in contrast to the single decision required in the PST learning phase). In the first step, participants choose between two stimuli, and this selection determines a second set of choices with differing reward probabilities. Similar to single phase tasks, learning can occur slowly and incrementally via model-free mechanisms. Task performance may also rely on goal-directed, model-based strategies, for which subjects develop an internal model of the task structure. At the first decision phase, subjects may prospectively consider future reward probabilities that would occur after the second phase. This strategy is more computationally demanding than model-free strategies, but supports rapid and flexible learning.

While links between model-free reinforcement learning and striatal dopamine have been long established, model-based strategies are also powerfully modulated by dopamine. Pharmacological manipulations provide general evidence that elevating dopamine tone increases reliance on model-based processes, though do not give information about the spatial specificity of dopamine's role. Enhancing dopamine (via levodopa) in young adults shifts bias in task strategy toward model-based processes (Wunderlich, Smittenaar, & Dolan, 2012). Consistent with this, Parkinson's disease patients tested off medication show selective impairment in model-based learning that is remediated by dopaminergic medication (Sharp, Foerde, Daw, & Shohamy, 2016). Complementing these findings in Parkinson's patients, model-based processing is reduced in people with disorders characterized by alteration in dopamine function such as addiction (Voon et al., 2015), obsessive compulsive disorder (Gillan, Kosinski, Whelan, Phelps, & Daw, 2016; Voon et al., 2015), and schizophrenia (Culbreth, Westbrook, Daw, Botvinick, & Barch, 2016). To date, there has been only limited investigation of the spatial specificity of dopamine's influence on model-based learning. Dopamine may modulate PFC via direct inputs from the ventral tegmental area or by indirect effects in striatum where dopamine affects PFC function via fronto-striato-thalamic loops (see Fig. 4b; Alexander, DeLong, & Strick, 1986). Pointing to a role of striatal dopamine, PET evidence in healthy young subjects demonstrated greater striatal dopamine synthesis capacity was associated with preferential reliance on model-based learning and was correlated with fMRI activation in PFC (Deserno et al., 2015). Pointing to a role of PFC dopamine, people with genetically inferred reductions in COMT enzymatic activity (putatively elevating PFC dopamine) show greater reliance on model-based processes (Doll et al., 2016). Additional research is needed to understand how direct dopamine signaling in PFC may influence model-based strategies.

Though model-based processing has been linked to striatal activity (Daw et al., 2011), it is also associated with increased reliance on prefrontal systems. Supporting this view, higher working memory capacity is associated with greater propensity to engage model-based strategies (Eppinger, Walter, Heekeren, & Li, 2013). Further, manipulations that increase cognitive load (Otto, Gershman, Markman, & Daw, 2013), stress (Otto, Raio, Chiang, Phelps, & Daw, 2013), or perturb PFC function via rTMS (Smittenaar, FitzGerald, Romei, Wright, & Dolan, 2013; see Wittkuhn et al., 2018, for rTMS manipulations of three-stage Markov decision task performance) reduce reliance on model-based processing, particularly in participants with low working memory capacity. In aging, there is evidence of reduced reliance on model-based processing (Eppinger, Walter, et al., 2013). These findings are generally consistent with age-related changes in PFC function (West, 1996) though, somewhat perplexingly, propensity to adopt model-based rather than model-free appears to be dissociated from working memory capacity (Eppinger, Walter, et al., 2013). Other studies have identified subgroups of older adults demonstrating an overreliance on model-free learning (Zhu, Walsh, & Hsu, 2012). However, the extent to which age-related shifts from model-based to model-free learning mechanisms are explained by alterations in PFC dopamine function is unknown.

Accounting for alteration in dopamine function in PFC and striatum may be valuable for understanding the neural basis of shifts away from model-based processes in aging. In aging, loss of PFC D2/3 dopamine receptors (particularly in subgenual frontal cortex) may outpace losses in ventral striatum (see Fig. 4b; Seaman, Juarez, et al., 2018). Further, rates of D1 receptor losses may differ between nigrostriatal pathways that innervate dorsal striatum versus mesocortical/mesolimbic pathways that innervate PFC and ventral aspects of striatum, respectively (Rieckmann et al., 2011). Together, such changes may alter the weighting of PFC versus striatal influences on task performance and the coherence of dorsal versus ventral striatal contributions to processes for learning, updating and integration that support value-based decision-making. Future studies pairing task performance with neurochemical PET measures could directly test how individual differences in receptor densities and dopamine release in PFC versus ventral striatum influence variability on the adoption of model-based versus model-free strategies in aging. Such studies may identify those subgroups of older adults most reliant on model-free processes (e.g., Zhu et al., 2012) are those with most marked reductions in PFC dopamine measures. Such lines of research are ripe for cross-species comparisons which could assess relationships between age and performance while providing critical information as to the temporal dynamics of dopamine signaling in PFC versus striatum using microdialysis techniques and voltammetry. Together, such studies hold promise for promoting our basic understanding of PFC dopamine's involvement in goal-directed decision-making while characterizing age differences in the recruitment of distinct dopamine pathways underlying specific task strategies.

Interactions between age-related changes in dopamine and affective attention

Models of complex decision-making support the view that multiple systems for learning, memory, and attention interact to shape our choices. We have argued that in vivo dopamine

imaging is a powerful tool for understanding the neural basis of individual differences in performance in aging. This line of research can illuminate the extent to which neurochemical traits affect decision-making. However, it is important to also consider how neurochemical influences on behavior interact with other attentional or state measures to affect decision-making. A recent study by Kircanski et al. (2018) illustrates the mutual influence of these factors on value-based choices. First, they modified the monetary incentive delay task (Samanez-Larkin et al., 2007) by including trials in which participants unexpectedly gained or lost relatively large amounts of money ($5 compared with $0.50; Kircanski et al., 2018). They found monetary loss and gain modifications (paired with salient auditory cues) induced negative and positive affective arousal respectively, which they assessed with self-report rating scales. Following the affective arousal manipulation, participants performed a separate decision-making task in which they chose whether or not to purchase items with misleading advertisements. They found deficits in choice performance following both arousal conditions relative to a neutral condition. Together, these findings demonstrate the capacity for financial reward and punishment manipulations to impact self-reported affective state, which in turn modulates the quality of subsequent value-based decisions. This study found no evidence for differences in the induction of arousal between young and older adults or in the detrimental effect of arousal on later choice performance. Other studies have shown differential age effects such that following positive affect induction (viewing emotion-rich videos), older adults, but not young adults, are more likely to make risky decisions than when in neutral states (Chou, Lee, & Ho, 2007). In the following section, we describe possible systematic changes in affective attention over the life span that may influence decision-making performance. We consider how these attentional changes may interact with influences of dopamine on performance, and suggest strategies for empirically examining these interactions.

There is longstanding appreciation that affective experience changes across the life span. Older adults report reduced levels of negative affective experience as they age, but preserved levels of positive experience (Mather & Carstensen, 2005). These observations have been linked specifically to memory and attention where older adults are more likely to remember positive events than young adults (Carstensen, 2006). It is possible that there are age-related changes in neurophysiology and neurochemistry that drive these effects, though there has been little direct investigation of this possibility (though see Kircanski et al., 2018, for discussion of the glutamate amplifies noradrenergic effects (GANE) model first described by Mather, Clewett, Sakaki, & Harley, 2016). Functionally, there appears to be relative preservation of the networks supporting emotional processing in aging (Nashiro, Sakaki, Braskie, & Mather, 2017), though in some cases the engagement of these networks by older adults may be more effortful (Martins, Florjanczyk, Jackson, Gatz, & Mather, 2018). The dominant interpretation is that at the end of life there is a shift in motivational goals derived from changes in the perception of time horizons (Reed & Carstensen, 2012). This view is supported by evidence that positivity effects have been reported in young people diagnosed with terminal illness, and people on death row, where systematic neurophysiologic and neurochemical changes mirroring those that occur in aging are unlikely (Goranson, Ritter, Waytz, Norton, & Gray, 2017; Hirschmüller & Egloff, 2015). Further, positivity can be

enhanced in young subjects experimentally in task scenarios in which they are encouraged to think about a limited future (Barber, Opitz, Martins, Sakaki, & Mather, 2016).

The positivity effect has been implicated in fMRI findings that responses associated with reward anticipation are intact in aging, but that responses associated with the anticipation of monetary losses in the insula are muted in older adults (Samanez-Larkin et al., 2007). Other studies have examined relationships between subjective ratings of emotional stimuli and fMRI responses in PFC and amygdala. Behaviorally, older adults report lower arousal for negative stimuli than young adults (Mather et al., 2004), report less unpleasantness for "low-arousal" negative stimuli, and greater pleasantness for "low-arousal" positive stimuli in a study that manipulated the levels of stimulus valence (Streubel & Kunzmann, 2011). These behavioral differences are accompanied by age-group differences in amygdala responsivity. Older adults consistently show greater enhancement of amygdala activation for positive relative to negative stimuli (Mather et al., 2004; for review, see Mather, 2016). Further, there is evidence that the relative suppression of amygdala activation for negatively valenced stimuli in aging is associated with greater recruitment of rostral anterior cingulate cortex when viewing unpleasant stimuli (Dolcos, Katsumi, & Dixon, 2014). Older adults with greatest engagement of rostral anterior cingulate, a prime regulator of amygdala activity (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006), self-reported less unpleasantness for low-arousal negative stimuli. Together, these findings provide insight into the neural basis of age-related changes in affective experience by which older adults preferentially enhance positive information, preferentially suppress negative information, or both. Given the recent reinvigoration of research establishing roles of the amygdala in reinforcement learning (Costa, Dal Monte, Lucas, Murray, & Averbeck, 2016) and decision-making (Gupta, Koscik, Bechara, & Tranel, 2011; Kim & Jung, 2018), future studies should pay specific attention to the amygdala as a possible hub where emotional affective processes and dopaminergic reward-based processes intersect.

The positivity effect may also influence decision-making through its modulation of medial temporal lobe memory systems. If positive information has privileged access to memory in aging (e.g., Carstensen, 2006), future choice behavior may be preferentially biased by positive experiences rather than negative experiences (for discussion of memory effects on choice behavior, see Wimmer & Shohamy, 2012). There is some evidence to suggest that in the context of reward-based learning paradigms, older adults show intact episodic memory performance for the visual cues that predicted reward (Eppinger, Herbert, & Kray, 2010). Intact subsequent memory for positive cues is particularly notable because it occurred despite reduced levels of reward-based probabilistic learning in the same subjects (putatively related to alterations in dopamine function). How the strength of episodic memory for reward-related information is related to individual differences in the positivity effect is an open question, but represents one mechanism by which age-related changes in affective attention may shape decision-making.

There are important boundary conditions that affect the occurrence and presentation of the positivity effect that are relevant for understanding how it may impact decision-making in aging. The positivity effect in aging is diminished in scenarios in which older adults are given explicit instructions on how to behave, and which stimuli to attend to (Reed, Chan, &

Mikels, 2014). Therefore, it is more likely to impact performance on tasks that permit multiple strategies. Supporting this view, in dynamic learning environments that support exploratory behavior, older adults preferentially bias decision-making on recent positive feedback (Glass & Osman, 2017). The positivity effect is also sensitive to cognitive load. Specifically, enhancement of attention and memory for positively valenced information is absent or reversed relative to young adults when cognitive load is increased (Gorlick et al., 2013; Knight et al., 2007; Mather & Knight, 2005). Therefore, the positivity effect is more likely to impact decision-making performance on tasks that support multiple strategies and are low in their computational requirements. To illustrate how the age-related positivity effect may influence decision-making performance, we use PST as an example.

The PST, which does not have explicit instructions guiding choice strategies and is relatively low on working memory demands, is potentially sensitive to the age-related positivity effect. For young adults in which the positivity effect is largely absent, performance may be primarily predicted from measures of dopamine function. For example, D1 BP_{ND} would be positively correlated with choice selection to approach reward (choose A; see Fig. 5a). For older adults in which the positivity effect is present, performance may be shifted from predictions based solely on measures of dopamine function (see Fig. 5b). Reduced D1 BP_{ND} in aging would predict a general reduction in choice selection to approach reward (choose A) relative to young participants. However, socioemotional selectivity accounts of PST performance in aging would predict greater choice selection driven by motivation to approach reward, especially if memory for the reward-predicting cue is particularly salient (Eppinger et al., 2010). Here, we suggest that the positivity effect can shift choice bias in directions that are opposite to what would be predicted based on dopamine effects alone. Such shifts may rely on the strength of the positivity effect within individuals, but nonetheless likely reflects a factor contributing to mixed and null effects in studies examining decision-making in aging.

Lines of future research should empirically test the possibility that dopaminergic decline and enhancement of positive affective processing counteract one another in laboratory-based decision-making tasks. Productive lines of research could aim to quantify individual differences in the positivity effect. This could be achieved by generating a normative measure of memory for positive, negative and neutral images in a large group of young adults from which to measure the magnitude of biases in individual older adults. Lang, Bradley, and Cuthbert (2008) have developed a catalogue of images with affective normative ratings, which could support these efforts (Lang et al., 2008). Assessment of the degree to which affective bias measures are related to variability in reward-based and punishment-based decision-making would be an important contribution. Future studies could also test the extent to which individual differences in amygdala reactivity and hippocampal engagement during learning positive versus negative associations are predicted by individual differences in the positivity effect.

Conclusions

There is an increasing number of innovative new studies examining the neural mechanisms underlying age-related changes in decision-making. The integration of in vivo imaging

measures such as PET and neuromelanin-sensitive MR with computational models is a promising avenue for resolving the basic neurochemical drivers of individual differences in performance. This approach will be essential for disentangling age effects of dopamine from age effects of affective attentional bias that contribute to biases in decision-making. This approach will also be useful for defining the nature of changes in reward processing in psychological and psychiatric disorders associated with altered dopamine function and dysregulated affective processing such as schizophrenia, addiction, and depression.

Critical steps for future research will be to determine the degree to which findings of laboratory-based assessments of decision-making and financial risk taking can be extended to real-world scenarios. To date, the relatively few cognitive neuroscience studies that have tested these relationships in aging have shown general agreement between performance on financial reward tasks and real-world financial measures (Knutson, Samanez-Larkin, & Kuhnen, 2011; Y. Li et al., 2015; Samanez-Larkin et al., 2010). Future studies may focus on predicting the conditions under which older adults are vulnerable to suboptimal decision-making. If changes in affective focus in aging partly counteract the detrimental effects of dopamine loss, older adults may be differentially impacted in decisions that occur in conditions in which the positivity effect is suppressed. For example, the positivity effect may be diminished for decisions made in high cognitive load conditions, where there is excessive or irrelevant information presented.

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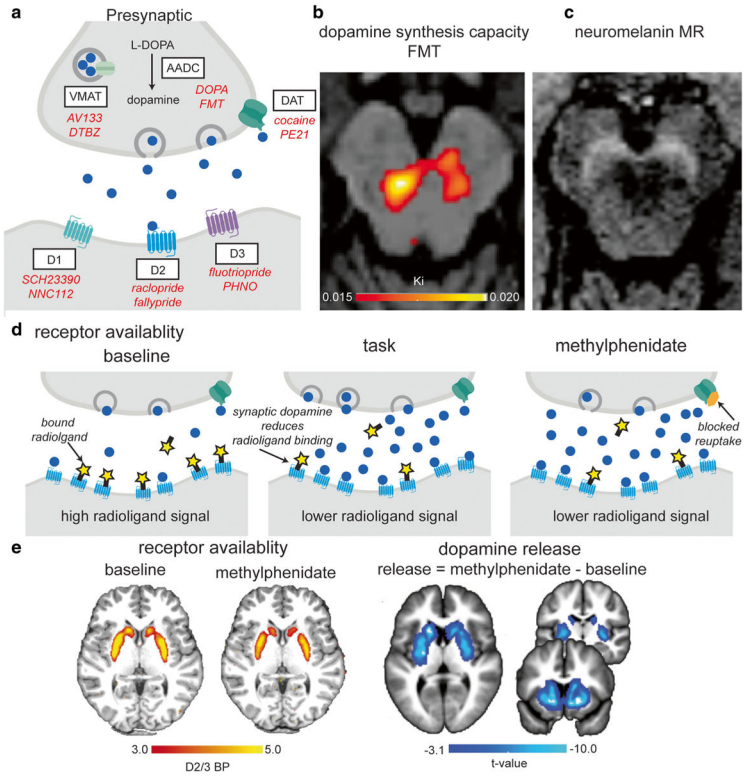

Fig. 1.

In vivo measurement of the dopamine system. **a** PET tracers target pre and postsynaptic components of dopamine function. Presynaptic targets include the vesicular monoamine transporter (VMAT), the dopamine synthesis enzyme aromatic amino acid decarboxylase (AADC), and the dopamine transporter (DAT). Postsynaptic targets include D1, D2, and D3 dopamine receptors. Examples of PET tracers for each of these targets are in red italics. **b** Fluoro-l-m-tyrosine (FMT) PET image overlaid on a T1-weighted structural image displays dopamine synthesis capacity for a single subject in the midbrain. **c** Neuromelanin-sensitive MR image displays neuromelanin rich regions in white. This single subject image was acquired at UC Berkeley using a 3D T1-weighted multiecho Fast Low Angle Shot (FLASH) sequence on a 3T Siemens TIM/Trio and displays substantia nigra signal in the midbrain. **d** Dopamine release can be measured within-subject by comparing baseline dopamine receptor availability with receptor availability following task-performance or drug administration. At baseline, when endogenous levels of dopamine (blue dots) are low, the PET radioligand (yellow stars) competitively binds to dopamine receptors. This competitive binding is reduced when synaptic dopamine increases via release (center) or via blockade of the transporter following methylphenidate administration (right). (E) Two [^{11}C]raclopride scans are displayed for a single subject at baseline (placebo) and following oral methylphenidate administration. Reductions in nondisplaceable binding potential (BPND) are evident throughout striatum for the single subject and on the group level (n = 40, adapted from Berry, Shah, Furman, et al., 2018) and represent dopamine release. (Color figure online)

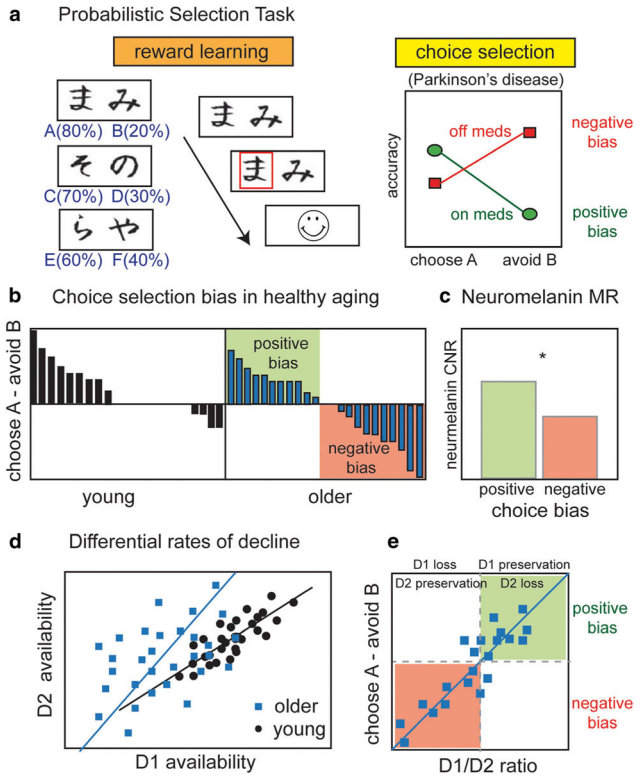

Fig. 2.

Interindividual variability and the probabilistic selection task. Data displayed in panels C-E are hypothetical and are presented to illustrate predictions. **a** The probabilistic selection task (PST) is composed of a probabilistic reward learning phase and a choice selection phase. Studies in Parkinson's patients suggest hypodopaminergic function biases choice selection towards actions that reduce punishment (i.e., negative bias; adapted from Frank et al., 2004). Pharmacologically restoring dopamine shifts bias towards actions that maximize reward (i.e. positive bias). **b** Studies in healthy aging reveal greater interindividual variability in choice biases in aging (adapted from Simon et al., 2010). **c** Subgroups of older adults with positive choice bias versus negative choice bias may have underlying differences in the integrity of the dopamine system that can be assessed with neuromelanin MR contrast-to-noise ratio in the midbrain (CNR). **d** Aging is associated with reduced D1 and D2/3 receptor availability. The rate of decline in receptor subtypes may vary across individual causing substantial between-subject variability in aging. Future studies should test the possibility that D1 receptors decline at faster rates than D2/3 receptors. **e** Choice selection bias on PST may be predicted from the relative ratio of D1 and D2/3 receptors in older adults. (Color figure online)

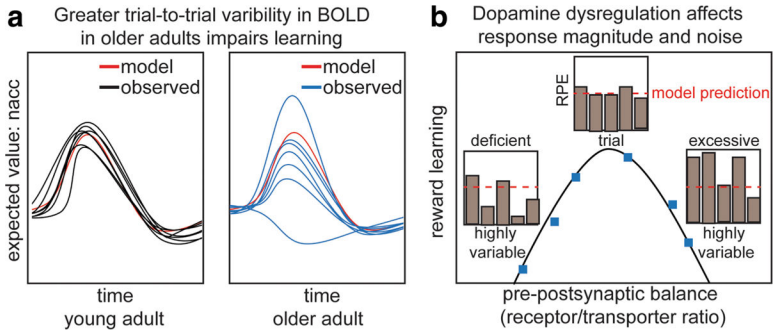

Fig. 3.

Effects of dysregulated dopamine function on intraindividual variability. Data displayed in panels **a**–**b** are hypothetical and are presented to illustrate predictions. **a** Within-subject variability in the precision of dopaminergic responses may be associated with noisier representations of expected value in the nucleus accumbens (NAcc) and slower learning of cue-reward contingencies. A young adult may show consistent, accurate responses across trials (black), while an older adult may show increased variability (blue). **b** Dysregulation of presynaptic and postsynaptic balance may cause changes in the precision of reward prediction errors (RPEs) leading to greater within-subject trial-to-trial variability in dopaminergic responses. Subjects with greater dysregulation (ascending and descending arm of the inverted U) may show greater trial-to-trial variability. Subjects with relatively preserved dopamine receptors, but reduced transporters (descending arm) may show excessive responses, while subjects with reduced receptors and preserved transporters may show deficient responses. (Color figure online)

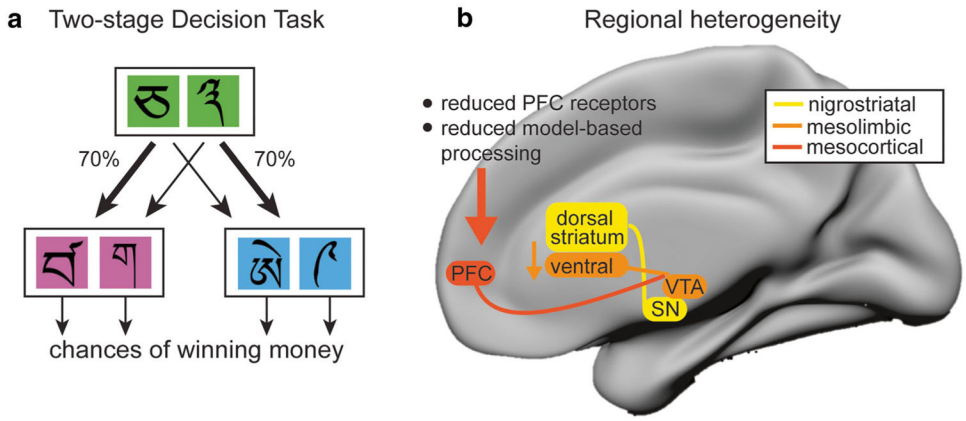

Fig. 4.

Regional dopamine function and goal-directed decision-making. **a** The two-stage Markov decision-making task (Daw et al., 2011) involves a first decision phase which leads probabilistically to one of two second-stage decisions. The use of model-based versus model-free learning strategies varies across individuals. **b** Regional comparisons of dopamine receptors within individuals suggests greater losses in PFC D2/3 receptors relative to ventral striatum receptors in aging. It is currently not known whether reduction in prefrontal cortex (PFC) dopamine function is associated with shifts away from model-based strategies. Aging is also associated with reductions in inter-regional correlations of D1 receptor binding (Rieckmann et al., 2011). These findings suggest that aging is accompanied by a divergence in receptor regulation within nigrostriatal pathways connecting substantia nigra (SN) and dorsal striatum and mesocortical/mesolimbic pathways originating in the ventral tegmental area (VTA). (Color figure online)

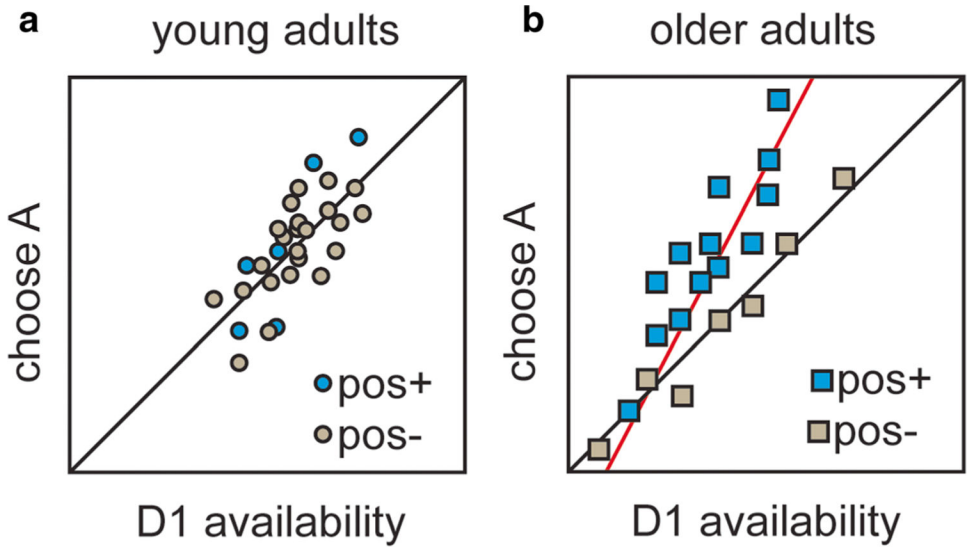

Fig. 5.

Individual differences in choice selection to approach reward may be modulated by both dopamine and affective attentional biases. Data displayed in panels **a**–**b** are hypothetical and are presented to illustrate predictions. Older adults are more likely to show biased attention towards positive rather than negatively valenced stimuli. Here, representational positivity effect is binarized to visualize its possible influence on performance for high positivity subjects (pos+ represented in blue) and positivity absent subject (pos− in beige). **a** For young adults whose representational positivity effect is minimal, the influence of D1 availability on performance will be primary. **b** For older adults high in positivity, representational biases may interact with dopamine to influence choice behavior. Subjects with systematic changes in representation may show increased proclivity to approach reward (choose A) despite lower D1 availability, leading to a steeper regression line (red). (Color figure online)