Influences of Dopaminergic System Dysfunction on Late-Life Depression

Warren D. Taylor, MD, MHSc, David H. Zald, PhD, Jennifer C. Felger, PhD, Seth Christman, MD, Daniel O. Claassen, MD, Guillermo Horga, MD, Jeffrey M. Miller, Katherine Gifford, PsyD, Baxter Rogers, PhD, Sarah M. Szymkowicz, PhD, Bret R. Rutherford, MD

Abstract

Deficits in cognition, reward processing, and motor function are clinical features relevant to both aging and depression. Individuals with late-life depression often show impairment across these domains, all of which are moderated by the functioning of dopaminergic circuits. As dopaminergic function declines with normal aging and increased inflammatory burden, the role of dopamine may be particularly salient for late-life depression. We review the literature examining the role of dopamine in the pathogenesis of depression, as well as how dopamine function changes with aging and is influenced by inflammation. Applying a Research Domain Criteria (RDoC) Initiative perspective, we then review work examining how dopaminergic signaling affects these domains, specifically focusing on Cognitive, Positive Valence, and Sensorimotor Systems. We propose a unified model incorporating the effects of aging and low-grade inflammation on dopaminergic function.
functioning, with a resulting negative effect on cognition, reward processing, and motor function. Interplay between these systems may influence development of a depressive phenotype, with an initial deficit in one domain reinforcing decline in others. This model extends RDoC concepts into late-life depression while also providing opportunities for novel and personalized interventions.

INTRODUCTION

Late-life depression (LLD), or Major Depressive Disorder (MDD) in older adults, is a source of disability, increased risk for suicide, and elevated mortality [1]. LLD is a heterogeneous disorder, including individuals with an earlier life onset and recurrent episodes, and individuals with their first depressive episode occurring in late life. Cerebrovascular changes are common in LLD [2] and some individuals may experience neurodegenerative processes [3]. Given this heterogeneity, the clinical presentation of LLD often differs from depression in younger adults [4], with cognitive deficits including executive dysfunction, motivational deficits, and comorbid physical disability and mobility impairment being common [5]. As dopaminergic processes mediate or influence these behaviors, this constellation of symptoms suggests that dopaminergic dysfunction may be a common contributor to LLD symptoms.

The specific mechanisms, degree of influence, and reversibility of dopaminergic circuit contributions to LLD are unclear. Human studies of dopamine signaling in MDD often focus on reward processing in younger adults to the exclusion of cognitive and sensorimotor domains relevant for older adults. Normal aging and age-related proinflammatory processes are further associated with declines in dopaminergic molecular functioning and impairment in dopamine signaling [6–8], while depression itself may accelerate aging processes [9]. The confluence of age-related declines and pre-existing dopaminergic system functional alterations may increase vulnerability to depression and exacerbate the presentation of episodes in later life.

This manuscript synthesizes work elucidating the role of dopamine within a Research Domain Criteria (RDoC) framework, focusing on cognitive function, reward processing, and sensorimotor system function. We focus on evidence supporting dopaminergic contributions to these domains in the context of depression, aging, and inflammation. As work in this area is relatively sparse, we review studies of younger populations when geriatric data are unavailable. We then present an integrative model positing that aging, in concert with pro-inflammatory shifts, decreases dopamine signaling. Resultant changes in behaviors supported by these circuits then combine and interact to influence LLD phenotypes. Finally, we discuss the potential significance and treatment implications of this line of research in older adults.
DOPAMINERGIC SYSTEM CHANGES SEEN IN DEPRESSION AND THE EFFECTS OF AGING AND INFLAMMATION

Dopamine Circuit Anatomy

Dopamine-producing neurons originate in brainstem nuclei, with well-described projections through the medial forebrain bundle that innervate disparate cortical and subcortical regions [10] (Table 1; Figure 1). Key pathways include 1) the mesocortical pathway projecting from the ventral tegmental area to frontal and temporal cortices, important for attention, executive function, and working memory. 2) The mesolimbic pathway projects from the ventral tegmental area to the ventral striatum (VS) / nucleus accumbens (NAc) and is involved in motivation and reward processes. 3) The nigrostriatal pathway, projecting from the substantia nigra, pars compacta to the caudate and putamen of the dorsal striatum, plays a role in the planning and execution of motor function. Despite this classical delineation of function, and regional variations in some dopamine effects, modern work associates the firing of all midbrain dopamine cell groups with reward-based learning supporting goal-directed behaviors [11]. Animal models suggest that dopamine is also co-released with norepinephrine from locus coeruleus neurons [12,13]. While dopamine is a precursor of norepinephrine, locus coeruleus release of dopamine may be important for hippocampal-dependent memory processes [14,15].

Dopaminergic System Differences in Depression

Most studies examining dopamine’s role in MDD focus on aspects of reward processing mediated by mesolimbic projections [16]. While published data are consistent that dopamine release in the NAc influences motivation and approach responses [17–19], it has been challenging to precisely specify the nature of dopaminergic disturbances in MDD. Studies of D2/D3 receptor binding using PET in young or midlife populations are mixed, with some finding increased receptor availability in MDD, potentially reflecting decreased dopaminergic activity and homeostatic receptor upregulation [20–22], while others report no differences [23–25]. In contrast, PET and postmortem studies of adult MDD [26,27] and PET studies in geriatric LLD [28] consistently demonstrate lower dopamine transporter (DAT) availability in the putamen, NAc, ventral tegmental area, and superior midbrain. This reduction in DAT availability has been interpreted as possible compensatory downregulation due to low dopamine signaling. Functional MRI studies using reward tasks in MDD can report divergent results, although decreased striatal activation to reward emerges as a reasonably consistent finding in meta-analyses [29,30]. Variability across broader cortico-striatal networks innervated by dopamine may be related to heterogeneity within the clinical diagnosis of MDD and a lack of focus on specific symptoms or behavior.

Given MDD’s heterogeneity, a superior approach may be to focus on endophenotypes characterized by prominent behavior or symptoms influenced by dopamine. Relevant phenotypes where dopaminergic system dysfunction may play a role include MDD characterized by prominent anhedonia [20] or psychomotor retardation [21]. LLD phenotypes, including LLD characterized by prominent apathy, may be particularly informative as dopaminergic function declines with aging. Although often associated with Alzheimer’s disease [31], apathy is particularly common in LLD, occurring in 30–40% of...
patients [32]. Apathy may be more common in LLD patients with a later-life onset or who are amongst the oldest-old [33,34]. Such a focus on pertinent clinical phenotypes may help identify the relationship between measures of dopamine signaling and key features of MDD.

**Dopaminergic System Changes with Aging**

Aging is associated with widespread changes in dopamine signaling. There is a significant loss of dopaminergic neurons in the substantia nigra [35] during aging potentially with additional cell loss in parts of the ventral tegmental area [36]. Post-mortem and in vivo neuroimaging studies demonstrate that aging is also associated with decreased dopamine receptor binding potential and loss of dopamine transporters (DAT) [6–8]. This decline results in an average loss in D2-like receptor concentrations on the order of 9% per decade from early adulthood [8]. Even without Parkinson’s disease (PD), 25% of older adults have a striatal DAT binding threshold more than 3 standard deviations below that of younger subjects [37]. Vesicular monoamine transporter 2 (VMAT2) binding also declines with aging, which is important as VMAT2 transports dopamine and other monoamines from the cytosol into synaptic vesicles. Age-related D2/D3 receptor binding loss is not uniform across brain regions. Temporal and frontal cortical regions exhibit higher rates of decline at 6–16% per decade, while the parahippocampal gyrus, caudate, putamen, thalamus and amygdala exhibit slower declines of 3–5% per decade [7]. This diminishment of dopaminergic tone contributes to decreased processing speed [38] and reaction time [39], fine motor dysfunction [40], slowed gait, and impaired balance [41,42].

Such age-related changes in dopamine function, occurring diffusely across the striatum and other regions including the midbrain, anterior cingulate cortex, and insula [43–45], are distinguishable from denervation patterns seen in PD [43,46]. Similarly, histological changes in the substantia nigra differ between PD and normal aging [47]. As dopamine synthesis shows weaker rates of decline than other measure of dopamine function [8], normal aging may be characterized by a compensatory process wherein dopamine synthesis increases in order to maintain function.

**Effects of Inflammation on Dopaminergic System Function**

Aging is associated with increased markers of chronic, low-grade inflammation [48], referred to as “inflammaging” [49]. This low-grade inflammation may have multiple causes, including aging of the immune system, inadequate elimination of cellular debris, mitochondrial changes, and harmful products produced by oral or gut microbiota [50,51]. This increase in inflammation affects multiple systems, including negatively impacting dopamine system functioning. It is associated with a host of poor medical outcomes [51] and may trigger a deleterious cascade contributing to depression [2,52]. Higher levels of circulating inflammatory markers including c-reactive protein (CRP), tumor necrosis factor (TNF), and interleukin-6 (IL-6) are common immunological abnormalities observed in elders and associated with LLD [53,54]. In the aging brain, this pro-inflammatory shift is characterized by increased numbers of activated and primed microglia and decreased anti-inflammatory molecules [55].
Inflammaging is associated with adverse structural CNS changes commonly observed in LLD [2,56], including increased cerebrovascular risk, often characterized by white matter hyperintensity (WMH) burden, and decreased hippocampal volumes [57]. Chronic pro-inflammatory activation may increase depression vulnerability [58] through additional pathways, including hypothalamus–pituitary–adrenal axis activation, decreased glucocorticoid sensitivity of immune cells, altered neurotransmitter metabolism, decreased neurogenesis and impaired neuroplasticity [59,60]. Inflammatory cytokines may adversely affect dopaminergic systems by limiting tetrahydrobiopterin (BH4) availability and decreasing dopamine synthesis, as is evident in aging [61]. They may also impair dopamine release and reuptake mechanisms [62]. Studies involving administration of inflammatory cytokines or cytokine inducers (e.g., vaccination, endotoxin) highlight the clinical effects of inflammation on dopamine-mediated behaviors [63]. Administration of inflammatory cytokine therapies such as interferon alpha (IFN)-alpha are notorious for causing clinical depression and high rates of anhedonia, fatigue, psychomotor and sleep disturbances, symptoms associated with reduced dopamine function [62,64,65]. These clinical effects of cytokine therapies are accompanied by altered glucose metabolism and dopamine turnover in the basal ganglia [64,65] that correlate with symptoms of reduced motivation. This clinical evidence of decreased dopamine turnover parallels nonhuman primate data that depressive symptoms arising in response to IFN are accompanied by declines in dopamine metabolism [63]. Moreover, both patients receiving IFN-alpha and healthy controls given experimental endotoxin exhibited decreased neural activation in the basal ganglia during reward tasks [65,66]. Such functional changes may reflect broader circuit disruption as administration of IFN-alpha therapy negatively disrupts basal ganglia-prefrontal circuitry [67,68].

COGNITIVE SYSTEMS: FOCUS ON COGNITIVE CONTROL AND PROCESSING SPEED

Cognitive System Findings in LLD

While attention and concentration deficits are a diagnostic criterion for MDD, research on these symptoms often utilize tasks assessing selective, sustained, or divided attention, finding that these processes are impaired in depression [69]. Depressed adults often report subjective cognitive difficulties, including attentional deficits, that do not always correspond to objective cognitive performance measures [70,71]. Instead, subjective difficulties may be related to maladaptive strategies or negative attentional biases common in LLD, such as rumination [72], that then influence regulation of emotional states [73].

In contrast, executive dysfunction and cognitive control deficits are better studied in LLD, where they are common [74] and predict poorer acute antidepressant response [75–77]. Cognitive control is a superordinate function that marshals subordinate cognitive processes such as attentional control, working memory and episodic memory to allow for the flexible adaptation of cognition and behavior in the context of current goals [78,79]. While executive function deficits in LLD are associated with accelerated brain aging and WMH
severity [80,81], we propose that dopaminergic system alterations also influence cognitive performance.

Decreased processing speed may be the “core cognitive deficit” in LLD [82,83]. Processing speed is a dominant characteristic of the efficiency of lower-order cognitive functions that are needed to support higher-order executive functions [84,85]. Such inefficient processes may hinder the ability to accomplish higher-order executive functions, thus producing or compounding cognitive control difficulties. Decreased processing speed is consistently reported in LLD [74,82,83], mediates the effects of depression on daily functioning [86], and is associated with increased dementia risk [87].

**Role of Dopamine in Cognitive Processes**

Dopamine clearly influences cognitive performance, directly mediating performance in some domains and modulating the extent of age-related cognitive decline in other domains [88]. In aging adults, dopamine receptor density, DAT availability, and DA synthesis capacity are all associated with performance on tasks of executive function and cognitive control, working memory, episodic memory, and processing speed [38,88,89]. Generally, intact dopaminergic function, such as preserved (average or greater) dopamine transporter or DA synthesis capacity, is associated with better cognitive performance. Although other neurotransmitters including acetylcholine also have well-established roles in cognition, for some domains this link to dopamine appears selective. For example, dopaminergic but not anticholinergic pharmacological challenges modulate processing speed [38]. Age-related deterioration of monoaminergic system function may contribute to declines in performance, and this may be particularly important for more demanding tasks [90]. When performing a challenging cognitive task, compared to baseline younger adults exhibited less D1 striatal receptor binding potential [91], likely reflecting displacement due to competition with endogenous DA. In contrast, older adults did not exhibit any change in binding potential during the task [91], suggesting that a less-responsive dopaminergic system may be a component of age-related cognitive decline [88].

As both dopamine system function and cognitive performance decline with age, a “correlative triad” proposes that dopaminergic declines contribute to age-related cognitive decline [92,93]. While this hypothesis holds true for working memory [94,95], for other cognitive domains the interactive effects of aging and dopamine function depend on other moderators or their effects on performance may be independent [89,90,96,97]. Despite this complexity, decreased dopaminergic tone may be an important contributor to cognitive slowing and executive dysfunction in LLD. These effects on cognitive performance may be modifiable, as levodopa (L-DOPA) improves processing speed in LLD [98] and processing speed, executive function and attention in PD [99].

**Impact of Inflammation on Cognition**

Substantial work supports that inflammation contributes to cognitive decline and dementia [100,101]. While much of this focus is on neuroinflammation, systemic inflammation also clearly plays a role. The risk of dementia is elevated in chronic medical conditions characterized by pro-inflammatory states, including obesity and diabetes [102]. Higher
levels of peripherally-measured inflammatory cytokines such as IL-6 are associated with
cognitive impairment in elderly people [103,104] and higher risk of cognitive decline
[103]. While inflammation may affect cognition independently of dopamine [100,101],
higher proinflammatory marker levels in older adults are associated with impairment in
cognitive domains mediated by dopamine, including executive function and processing
speed [105,106]. In LLD, inflammatory markers are associated not only with prevalence
[107] and future development of depression [53] but also with depressive cognitions [58].

**POSITIVE VALENCE SYSTEMS: FOCUS ON MOTIVATION AND EFFORT**

**Role of Dopamine on Positive Valence Systems (PVS)**

PVS underlie the response to positive or motivational stimuli. Clinically, deficits in these
systems manifest as anhedonia, a core symptom of depression that is proposed as a critical
depression endophenotype [108,109]. While anhedonia is most simply defined as a “loss of
pleasure,” the term is often used more broadly to also encompass motivational deficits, and
can be operationalized as a reduced willingness to commit effort to obtain rewarding stimuli
[110], impaired reward-based learning and decision making [111], diminished time spent in
activities, and reduced willingness to expend effort for rewards [112,113]. Such motivational
anhedonia may be described as apathy, a common symptom in LLD [32] defined as a
disturbance in motivation leading to reduced goal-directed behavior [31].

These behaviors reflect impaired reward processing, or how individuals use reinforcement-
related perceptions to guide goal-directed behaviors [114]. Reward processing includes
multiple subcomponents (Table 2) [112,114,115]. While not all reward processing
components are equally well studied, they appear to have distinct but overlapping
neuroanatomical bases. For example, decision making requires weighing the benefit or value
of potential rewards against the effort cost required to achieve them [116–118]. The anterior
VS encodes subjective value, increasing or decreasing activity based on the probability of
reward or cost, respectively. In turn, action and the initiation of effortful action activates the
dorsomedial VS [119]. Other processes extend beyond the striatum. For example, apathy
involves not only VS and NAcc function, but also the dorsal anterior cingulate cortex and the
orbitofrontal, dorsomedial, and dorsolateral prefrontal cortices [31,120].

Animal studies reveal the complexity of dopamine’s effect on reward and motivation,
including prediction error learning. A key function of the brain is to predict future
environmental states, facilitating interactions and responses to environmental stimuli
[121,122]. A prediction error is a mismatch between a prior expectation and reality,
signaling a need to update future expectations [122]. Phasic burst firing of DA neurons
signal the presence of underpredicted rewards, as well as underpredicted cues of potential
rewards, providing the positive prediction error signal that lies at the heart of temporal
difference reinforcement learning [11,123]. In the opposite direction, pauses in dopamine
cell firing occur when expected rewards do not occur. Depletion of dopamine or blockage of
this prediction error signaling may act like a negative prediction error, indicating a failure to
receive a reward, and may contribute to extinction of previously reinforced behaviors [124].
During behavior, synaptic levels of dopamine dynamically increase as expected rewards become more temporally or spatially proximal [125, 126]. This ramping of synaptic dopamine levels appears to reflect terminal release in a manner that is partially independent from dopamine neuron spiking and exerts an influence on motivated behavior beyond that of phasic prediction error signals [127]. Increases in synaptic dopamine levels, as caused by reward cues, facilitate the speed of initiation and vigor of reward seeking, approach and operant behaviors aimed at obtaining rewards [125, 128–130]. Such motor facilitation may reflect the critical translation of motivational value of potential rewards into action. At a more explicit decision-making level, these findings parallel dopamine’s ability to increase the willingness to expend effort to obtain rewards [18, 113], or in behavioral economic terms, the ability of dopamine to attenuate the effort discounting of subjective value [131].

Dopamine cell firing and dopamine release are not simply reflective of the level of effort required to act. Upcoming effort costs result in a measurable, albeit modest, decline in dopamine neuron firing [132], consistent with a degree of effort discounting of the subjective value of potential rewards. Somewhat paradoxically, recent data suggest that effort expended to gain a reward enhances dopamine neuron reward prediction error firing upon reward receipt, which is translated into more rapid reward learning [133]. This post-effort dopaminergic response may be particularly important for reinforcing “hard earned” rewards over easier or passive rewards.

Relationships between dopaminergic measures and reward-processing variables differ with age and clinical status. For instance, relations between effort discounting and D2/D3 binding potential (BPND) in the VS and midbrain as assessed by [18F]-fallypride PET change across the adult lifespan [45]. In a meta-analysis of associations between value discounting and dopamine measures, there was greater evidence of relationships with reward discounting for different types of costs when analyzing data from individuals with psychiatric disorders, suggesting the particular importance of the influence of dopaminergic variables in clinical populations [45].

**PVS Findings in LLD**

Reward deficits may be particularly germane for patients with LLD. In younger adults, depressed individuals often exhibit impairment across many reward domains, including reduced reward sensitivity [30, 134], impaired ability to use information on the magnitude and probability of the reward to guide choices [110], decreased willingness to expend effort [110, 135–137], and deficient reward learning [138, 139]. A recent meta-analysis associated adult MDD with small-to-medium effect size impairment in option valuation and reinforcement learning, reflecting both impaired cost-benefit decision making as well as difficulty adjusting future behavior (definitions in Table 2) [114]. Medium to large effect size impairment in reward bias has also been observed, with depressed individuals being less likely to select more frequently rewarded stimuli [138]. While research in LLD is comparatively scarce, depressed older adults with a history of suicidal behavior exhibit high delay discounting of rewards [140].

More is known about changes in reward processing with normal aging. While behavioral and neural responses to the anticipation and consummation of rewards are similar between
younger and older adults [141,142], older adults exhibit a higher sensitivity to loss relative to reward information [143]. Reward learning is also negatively affected, as aging is associated with a reduced ability to adapt to changes in reward contingencies [143]. Older populations exhibit additional changes in the decision making process, although there is heterogeneity in these age-related changes. For instance, the ventromedial prefrontal cortex (vmPFC) shows a reduced subjective value signal in older adults displaying suboptimal decision-making even though there is no overall decline in vmPFC subjective reward signaling across the lifespan in healthy adults [144,145]. A greater perceived cost of cognitive effort [146] is observed in older adults, which may be linked to declines in cognitive resources with aging [147]. There may be similar parallels for physical effort in relation to co-existing motoric difficulties that contribute to increased fatigability, a common complaint of many elders that predicts disability [148,149].

**Effects of Dopaminergic System Modulation on PVS**

Through a combination of neuroimaging and pharmacological manipulations, translational research supports dopamine’s role in reward-related behavior, including decision making, goal-related action initiation, vigor and willingness to overcome effort, and reward learning [113,117,150–155]. For example, reward prediction error signal in the VS is enhanced by administration of L-DOPA [156], and in older subjects L-DOPA enhances probabilistic reward learning and ventral striatal representations of expected reward [157]. Administration of L-DOPA promotes response vigor for rewards, while D2 receptor antagonism reduces the impact of reward on explicit decisions to expend effort [158,159]. Individuals with higher dopamine synthesis capacity measured with [18F]-DOPA make more decisions to expend cognitive effort for rewards than those with lower dopamine synthesis capacity, while methylphenidate promotes a greater willingness to expend effort and a greater sensitivity to rewards relative to costs in their decision making [160,161]. However, a limitation of this literature is that most studies were conducted in psychiatrically healthy populations, so the translation to LLD is uncertain.

Although there is a similar limitation in considering populations with neurological disease, studies in PD demonstrate that individuals with dopaminergic system dysfunction can have positive valence deficits rectified through administration of dopamine enhancing agents. Most notably, while individuals with PD often exhibit reward learning impairments, these deficits can be restored by dopamine replacement [162,163]. Similarly, in PD patients, L-DOPA increases willingness to work for rewards independent of facilitating movement [164]. Rodent models of PD and studies of PD patients reveal that dopamine replacement therapy rectifies deficits in the vigor of responses [165,166].

Similar pharmacological enhancement of dopaminergic activity may have clinical utility in depressed patients. A recent single-dose blinded study examined amisulpride [167], a selective D2/D3 receptor antagonist that preferentially blocks presynaptic autoreceptors at low doses, thus increasing dopamine release. Amisulpride administration to younger adult depressed individuals normalized reward-related brain activation and functional connectivity across multiple regions involved in reward processing, including the NAc, perihippocampal gyrus, and midcingulate cortex [167].
Impact of Inflammation on PVS

Impaired reward processing in MDD also provides a possible mechanism by which inflammation contributes to depressive symptoms. Increased inflammatory cytokines, including TNF, in both blood and CSF are associated with anhedonia severity and reduced motivation in MDD [168,169]. Anhedonia was also the most responsive symptom to antagonism of TNF with infliximab in both treatment-resistant MDD and bipolar disorder patients characterized by increased inflammation [170,171]. As with the studies described above involving administration of exogenous inflammatory stimuli [65–68], recent reports indicate that biomarkers of endogenous inflammation are associated with both impaired neural activation and altered functional connectivity of basal ganglia and prefrontal regions. For example, unmedicated healthy MDD patients with high levels of both CRP and inflammatory cytokines exhibited low functional connectivity between PVS regions including VS and vmPFC [172]. This inflammation-associated effect on low VS-vmPFC connectivity in turn correlated with anhedonia severity [172,173]. In MDD patients who underwent a Monetary Incentive Delay Task (MIDT), those with higher CRP levels exhibited decreased VS neural activation during reward anticipation [174].

SENSORIMOTOR SYSTEMS: MOTOR FUNCTION

Sensorimotor System Changes with Aging and Findings in LLD

Motor deficits are common with aging, including slowed movement, coordination deficits [175], and difficulties with balance and gait [176]. These problems are often related to medical comorbidities common in LLD, including cerebrovascular disease, chronic obstructive pulmonary disease, and arthritis [177,178]. Motor deficits are further associated with falls [179], disability [180], and mortality [181–183]. Depressed older adults are at increased risk for motor problems [180,181,184] and this relationship may be bidirectional. For example, the tendency towards seclusion and decreased activity, a common observation in LLD, may lead to muscle loss and gait slowing; similarly, motor deficits including slowed gait speed may contribute to depression vulnerability [185–187]. Subcortical white matter disease, including WMHs, may contribute both to depression and gait slowing in older adults [2,188]. Gait slowing may also be a physical manifestation of slowed processing speed, with both measures increasing mortality risk in older adults [189]. Depression may further magnify this risk [190].

Role of Dopamine in Sensorimotor Processing

Although many factors contribute to physical limitations, age-related changes in motor function are associated with dopamine system dysfunction. Decreased striatal dopamine transmission capacity is associated with increased reaction time [39], fine motor dysfunction [40], slowed gait and impaired balance [41,42]. In healthy adults, lower striatal DAT binding (which provides an index of presynaptic dopamine innervation in aging) is associated with poorer balance, postural control [41] and decreased gait speed, explaining 23% of the variance in gait [42]. Diminished DAT binding is also associated with exaggerated slips on a challenging walking course [191] and predicts recurrent falls in elderly subjects [192].
These observations are not simply reflecting preclinical PD. As noted above, declines in dopaminergic functioning observed with normal aging are distinct from the denervation pattern typical of PD [43–46]. While subtle Parkinsonian-like phenomena may be observed with normal aging, age-related non-specific slowing is distinct from the signs and symptoms of PD. Despite differing neurobiological mechanisms, as in PD, slowed gait speed in LLD is responsive to enhancement of dopaminergic neurotransmission with L-DOPA [98].

**Impact of Inflammation on Motor Function**

Older adults with poor physical performance exhibit lower muscle strength and higher levels of proinflammatory cytokines than their higher-functioning peers [193]. Inflammaging is similarly associated with poorer functional and mobility status, including slowed gait speed [194,195]. Similar to the effects on other systems, administration of IFN-alpha results in motor slowing, which in turn is associated with depressive symptom severity and fatigue [196]. Although inflammation may contribute to motor deficits through multiple mechanisms [197], converging evidence suggests that inflammatory cytokines can impair striatal dopaminergic tone, with psychomotor slowing as a clinical correlate [63]. Progressive gait slowing in older adults is associated with trajectories of depression and inflammation measured by CRP and IL-6 [198], with the triad of slow gait, inflammation, and depression predicting elevated mortality [190]. Higher levels of IL-6, IL-10, and the IL-6/IL-10 ratio are further associated with sarcopenia and predict reduced lower extremity strength in mobility-limited older adults [199,200].

**INTEGRATIVE MODEL OF AGING AND DOPAMINERGIC DYSFUNCTION IN LLD**

A straightforward model is that dopamine system dysfunction contributes to alterations in cognitive, positive valence, and/or sensorimotor systems that combine and interact, leading to cognitive difficulties, behavioral deactivation and frank depressive symptoms (Figure 2). The clinical presentation may depend on which circuits are primarily affected. While aging and inflammation contribute to dopaminergic system dysfunction, microvascular changes commonly observed in LLD [2] may also adversely affect dopaminergic function by damaging dopaminergic neuronal projections. Thus, dopaminergic system dysfunction may be more common in some LLD phenotypes characterized by cerebrovascular processes. Altered dopaminergic system function may itself then further influence the clinical presentation.

Impairment in one system may have deleterious effects on behaviors mediated by other systems. In other words, deficits in a specific circuit may influence cognitive or behavioral symptoms mediated by other dopaminergic circuits, contributing to worsened depressive symptoms and development of LLD. For example, cognitive control is adversely affected by motivational deficits [79]. Cognitive control processes require more effort than automatic ones to achieve goals, so differences in the willingness to expend effort influence cognitive control performance [201]. Greater motivation is also associated with better cognitive task performance across the lifespan [202] and in depressed groups [74,78,79]. While incentives improve task performance [203], their effect is contingent on intact reward function. The
The relationship between cognitive and PVS may be bidirectional, as impaired cognitive control may adversely affect reward learning [204].

Cognitive dysfunction often co-exists with gait or postural impairment [205]. “Higher level” gait control is mediated by frontal subcortical circuits that underlie executive functions [206] and cognitive control processes may compensate for motor deficits [207]. Walking while distracted or cognitively engaged (a ‘dual-task’ gait) is associated with gait disturbances and increased falls risk [208], and in turn is improved by L-DOPA [98]. Motor impairments similarly interact with reward processing and other PVS. Increased incentives are associated with motor task performance [209,210] and the motor cortex facilitates the integration of a reward’s subjective value with incentive-motivated performance [209].

As a primary mechanism underlying these relationships, we hypothesize that slowed processing speed and impaired cognitive control increase the effort cost to achieve a goal. This increased effort cost in turn increases fatiguability and the level of motivation needed to work towards goals. Motivation is further challenged by any deficits in reward sensitivity. Poorer motor function may have a bidirectional relationship with fatigability, requiring even greater effort for any task and thus favoring inaction. Jointly, these deficits contribute to behavioral deactivation and reduced physical activity, resulting in deconditioning, sarcopenia, and increased physical fatigability.

**SIGNIFICANCE OF EXAMINING DOPAMINERGIC SYSTEMS IN LLD**

The clinical picture described above is common in LLD, and dopaminergic system dysfunction may be a frequent underlying contributor to its development. While we utilize an RDoC-based conceptualization, the current RDoC iteration has been criticized for neglect of developmental factors, including senescence and aging [5]. As highlighted by our discussion of aging effects on molecular dopaminergic system function, this is a critical omission as neural systems change during aging. Further, as most aging research is conducted in psychiatrically healthy populations, it highlights a gap in our knowledge of how psychiatric illness may alter the trajectory of molecular or neural processes during aging. This is also a limitation of our scientific model, as much of the work we cite in support of our theories derives from younger adults or from studies of normal aging. We need to more comprehensively examine the interrelationships between brain aging, changes in dopaminergic system function, behavior and psychopathology.

Delineating dopaminergic system contributions to LLD can inform treatment targets and guide personalize treatment. Several second-generation antipsychotics exhibiting efficacy in mood disorders are partial dopamine agonists, including aripiprazole, brexpiprazole, and caripirazine. While selective dopamine agonists such as pramipexole or ropinirole have inconsistently shown efficacy as adjuncts in treatment-resistant MDD [211,212], sample sizes in these studies are small and typically do not include older adults. This raises the question of whether such drugs may be more effective in populations with dopaminergic system dysfunction, whether due to aging or inflammation. Drugs that modulate dopaminergic systems without direct receptor agonism may also have utility. Methylphenidate, a stimulant that inhibits the reuptake of dopamine and norepinephrine,
is an effective augmentation agent for LLD [213]. Preliminary evidence also supports benefit of L-DOPA in subjects with LLD characterized by psychomotor slowing [98]. Beyond psychopharmacology, linking behavioral features to dysfunction in RDoC domains allows for a personalized treatment approach where therapeutic strategies can be deployed depending on the clinical presentation, such as ‘Engage’ psychotherapy for LLD [214]. Other approaches may address cognitive impairment through computerized training designed to enhance information processing by promoting neuroplasticity [215], or using behavioral activation for PVS dysfunction and exercise/physical therapy for sensorimotor deficits.

**Future Approaches and Challenges**

A thorough characterization of dopaminergic function in LLD requires not only traditional diagnostic assessments and measures of depression severity, but also dimensional assessments of behavior such as anhedonia and apathy. Neuropsychological evaluations should include batteries enriched for domains affected by dopamine, such as processing speed, working memory, and executive function. Further assessments should evaluate reward function, motivation and motor function, including gait and fine motor performance.

Interrogation of the dopaminergic system at the molecular level using PET imaging has substantial promise for understanding LLD. Radioligands can assess dopamine synthesis ([18F]-FDOPA), dopamine receptor binding ([11C]-raclopride, [18F]-fallypride, [11C]-(+)-PHNO), and DAT function ([11C]-altropane, ([11C]-PE2I). However, there is variability across tracers in availability, specificity, off-target binding, and in the anatomic regions visualized. Moreover, it is challenging to probe all aspects of dopaminergic system function in a single sufficiently powered study due to both radiation exposure limits and the high cost of PET radioligands. These limitations require novel trial designs and likely an acceptance that a single study will be unable to thoroughly probe all aspects of dopamine’s molecular functioning.

There is also opportunity for novel MRI approaches such as neuromelanin MRI (NM-MRI). Neuromelanin is a product of dopamine synthesis that accumulates in midbrain nuclei over the lifespan [216,217]. NM-MRI signal intensity increases with age [218] but decreases through degeneration of dopamine neurons [219,220]. NM-MRI may serve as an *in vivo* proxy of dopaminergic function as it is sensitive to variation in NM post-mortem concentrations and relates to dopamine function measured by [11C]raclopride in the striatum during an amphetamine challenge [221].

**Conclusions**

Dopaminergic function declines with aging and may mediate common signs and symptoms in LLD. However, a significant amount of data supporting this hypothesis is derived from work in younger populations where the influence of age cannot be clearly assessed. A better understanding of how dopaminergic system dysfunction contributes to variability in the clinical, cognitive, and motor presentation of LLD provides an opportunity for the development or repurposing of drugs enhancing dopaminergic function and better identification of who may most benefit from them. It can also inform personalized non-
pharmacological treatment approaches including cognitive remediation or interventions focused on mobility.

Acknowledgements:
This research was supported by National Institute of Health grants K24 MH110598, R01 MH123660 and R01 MH123662. Dr. Taylor would additionally like to acknowledge salary support from the Tennessee Valley Healthcare System Geriatric Research Education and Clinical Center (GRECC).

REFERENCES
1. Taylor WD. Clinical practice. Depression in the elderly. N Engl J Med 2014; 371: 1228–36. [PubMed: 25251617]
2. Taylor WD, Aizenstein HJ, Alexopoulos GS. The vascular depression hypothesis: Mechanisms linking vascular disease with depression. Molecular Psychiatry 2013; 18: 963–74. [PubMed: 23439482]
3. Byers AL, Yaffe K. Depression and risk of developing dementia. Nat Rev Neurol 2011; 7: 323–31. [PubMed: 21537355]
4. Hybels CF, Landerman LR, Blazer DG. Age differences in symptom expression in patients with major depression. Int J Geriatr Psychiatry 2012; 27: 601–11. [PubMed: 21773997]
5. Rutherford BR, Taylor WD, Brown PJ, Sneed JR, Roose SP. Biological Aging and the Future of Geriatric Psychiatry. J Gerontol A Biol Sci Med Sci 2017; 72: 343–52. [PubMed: 27994004]
6. Kaasinen V, Vilkan H, Hietala J, Nagren K, Helenius H, Olsson H et al. Age-related dopamine D2/D3 receptor loss in extrastriatal regions of the human brain. Neurobiol Aging 2000; 21: 683–8. [PubMed: 11016537]
7. Seaman KL, Smith CT, Juarez EJ, Dang LC, Castrellon JJ, Burgess LL et al. Differential regional decline in dopamine receptor availability across adulthood: Linear and nonlinear effects of age. Hum Brain Mapp 2019; 40: 3125–38. [PubMed: 30932295]
8. Karrer TM, Josek AK, Mata R, Morris ED, Samanez-Larkin GR. Reduced dopamine receptors and transporters but not synthesis capacity in normal aging adults: a meta-analysis. Neurobiol Aging 2017; 57: 36–46. [PubMed: 28599217]
9. Wolkowitz OM, Epel ES, Reus VI, Mellon SH. Depression gets old fast: do stress and depression accelerate cell aging? Depress Anxiety 2010; 27: 327–38. [PubMed: 20376837]
10. Dunlop BW, Nemeroff CB. The role of dopamine in the pathophysiology of depression. Arch Gen Psychiatry 2007; 64: 327–37. [PubMed: 17339521]
11. Schultz W Getting formal with dopamine and reward. Neuron 2002; 36: 241–63. [PubMed: 12383780]
12. Smith CC, Greene RW. CNS dopamine transmission mediated by noradrenergic innervation. J Neurosci 2012; 32: 6072–80. [PubMed: 22553014]
13. Devoto P, Flore G. On the origin of cortical dopamine: is it a co-transmitter in noradrenergic neurons? Curr Neuropharmacol 2006; 4: 115–25. [PubMed: 18615131]
14. Kempadoo KA, Mosharov EV, Choi SJ, Sulzer D, Kandel ER. Dopamine release from the locus coeruleus to the dorsal hippocampus promotes spatial learning and memory. Proc Natl Acad Sci U S A 2016; 113: 14835–40. [PubMed: 27930324]
15. Yamasaki M, Takeuchi T. Locus Coeruleus and Dopamine-Dependent Memory Consolidation. Neural Plast 2017; 2017: 8602690. [PubMed: 29123927]
16. Nestler EJ, Carlezon WA Jr. The mesolimbic dopamine reward circuit in depression. Biol Psychiatry 2006; 59: 1151–9. [PubMed: 16566899]
17. Soares-Cunha C, Coimbra B, David-Pereira A, Borges S, Pinto L, Costa P et al. Activation of D2 dopamine receptor-expressing neurons in the nucleus accumbens increases motivation. Nat Commun 2016; 7: 11829. [PubMed: 27337658]
18. Salamone JD, Pardo M, Yohn SE, Lopez-Cruz L, SanMiguel N, Correa M. Mesolimbic Dopamine and the Regulation of Motivated Behavior. Curr Top Behav Neurosci 2016; 27: 231–57. [PubMed: 26323245]

19. Tye KM, Mirzabekov JJ, Warden MR, Ferenczi EA, Tsai HC, Finkelstein J et al. Dopamine neurons modulate neural encoding and expression of depression-related behaviour. Nature 2013; 493: 537–41. [PubMed: 23235822]

20. Pecina M, Sikora M, Avery ET, Heffernan J, Pecina S, Mickey BJ et al. Striatal dopamine D2/3 receptor-mediated neurotransmission in major depression: Implications for anhedonia, anxiety and treatment response. Eur Neuropsychopharmacol 2017; 27: 977–86. [PubMed: 28870407]

21. Meyer JH, McNeely HE, Sagrati S, Boovariwala A, Martin K, Verhoeff NP et al. Elevated putamen D(2) receptor binding potential in major depression with motor retardation: an [11C]raclopride positron emission tomography study. Am J Psychiatry 2006; 163: 1594–602. [PubMed: 16946186]

22. Hamilton JP, Sacchet MD, Hjornevik T, Chin FT, Shen B, Kampe R et al. Striatal dopamine deficits predict reductions in striatal functional connectivity in major depression: a concurrent (11)C-raclopride positron emission tomography and functional magnetic resonance imaging investigation. Transl Psychiatry 2018; 8: 264. [PubMed: 30504860]

23. Parsley RV, Oquendo MA, Zea-Ponce Y, Rodenhisser J, Kegeles LS, Pratap M et al. Dopamine D(2) receptor availability and amphetamine-induced dopamine release in unipolar depression. Biol Psychiatry 2001; 50: 313–22. [PubMed: 11543733]

24. Schneier FR, Slifstein M, Whitton AE, Pizzagalli DA, Reinen J, McGrath PJ et al. Dopamine Release in Antidepressant-Naive Major Depressive Disorder: A Multimodal [(11)C]-[+]-PHNO Positron Emission Tomography and Functional Magnetic Resonance Imaging Study. Biol Psychiatry 2018; 84: 563–73. [PubMed: 30041971]

25. Li Z, He Y, Tang J, Zong X, Hu M, Chen X. Molecular imaging of striatal dopamine transporters in major depression—a meta-analysis. J Affect Disord 2015; 174: 137–43. [PubMed: 25497470]

26. Pizzagalli DA, Berretta S, Wooten D, Goer F, Pilobello KT, Kumar P et al. Assessment of Striatal Dopamine Transporter Binding in Individuals With Major Depressive Disorder: In Vivo Positron Emission Tomography and Postmortem Evidence. JAMA psychiatry 2019; 76: 854–61. [PubMed: 31042280]

27. Dubol M, Trichard C, Leroy C, Granger B, Tzavara ET, Martinot JL et al. Lower midbrain dopamine transporter availability in depressed patients: Report from high-resolution PET imaging. J Affect Disord 2020; 262: 273–7. [PubMed: 31732277]

28. Moriya H, Tiger M, Tateno A, Sakayori T, Masuoka T, Kim W et al. Low dopamine transporter binding in the nucleus accumbens in geriatric patients with severe depression. Psychiatry Clin Neurosci 2020; 74: 424–30. [PubMed: 32363761]

29. Zhang WN, Chang SH, Guo LY, Zhang KL, Wang J. The neural correlates of reward-related processing in major depressive disorder: a meta-analysis of functional magnetic resonance imaging studies. J Affect Disord 2013; 151: 531–9. [PubMed: 23856280]

30. Keren H, O’Callaghan G, Vidal-Ribas P, Buzzell GA, Brotman MA, Leibenluft E et al. Reward Processing in Depression: A Conceptual and Meta-Analytic Review Across fMRI and EEG Studies. Am J Psychiatry 2018; 175: 1111–20. [PubMed: 29921146]

31. van Dyck CH, Arnsten AFT, Padula PR, Brawman-Mintzer O, Lerner AJ, Porsteinson AP et al. Neurobiologic Rationale for Treatment of Apathy in Alzheimer’s Disease With Methylphenidate. Am J Geriatr Psychiatry 2021; 175: 51–62. [PubMed: 32461027]

32. Yuen GS, Bhutani S, Lucas BJ, Gunning FM, AbdelMalak B, Seirup JK et al. Apathy in late-life depression: common, persistent, and disabling. Am J Geriatr Psychiatry 2015; 23: 488–94. [PubMed: 25047306]

33. Krishnan KRR, Hays JC, Tupler LA, George LK, Blazer DG. Clinical and phenomenological comparisons of late-onset and early-onset depression. American Journal of Psychiatry 1995; 152: 785–8.

34. Mehta M, Whyte E, Lenze E, Hardy S, Roumani Y, Subashan P et al. Depressive symptoms in late life: associations with apathy, resilience and disability vary between young-old and old-old. Int J Geriatr Psychiatry 2008; 23: 238–43. [PubMed: 17676651]
35. Stark AK, Pakkenberg B. Histological changes of the dopaminergic nigrostriatal system in aging. Cell Tissue Res 2004; 318: 81–92. [PubMed: 15365813]
36. Siddiqi Z, Kemper TL, Killiany R. Age-related neuronal loss from the substantia nigra-pars compacta and ventral tegmental area of the rhesus monkey. J Neuropathol Exp Neurol 1999; 58: 959–71. [PubMed: 10499438]
37. Wong KK, Muller ML, Kuwabara H, Studenski SA, Bohnen NI. Olfactory loss and nigrostriatal dopaminergic denervation in the elderly. Neurosci Lett 2010; 484: 163–7. [PubMed: 20727944]
38. Eckart C, Bunzeck N. Dopamine modulates processing speed in the human mesolimbic system. NeuroImage 2013; 66: 293–300. [PubMed: 23142277]
39. van Dyck CH, Avery RA, MacAvoy MG, Marek KL, Quinlan DM, Baldwin RM et al. Striatal dopamine transporters correlate with simple reaction time in elderly subjects. Neurobiol Aging 2008; 29: 1237–46. [PubMed: 17363113]
40. Yang YK, Chiu NT, Chen CC, Chen M, Yeh TL, Lee IH. Correlation between fine motor activity and striatal dopamine D2 receptor density in patients with schizophrenia and healthy controls. Psychiatry Res 2003; 123: 191–7. [PubMed: 12928107]
41. Cham R, Perera S, Studenski SA, Bohnen NI. Striatal dopaminergic denervation and sensory integration for balance in middle-aged and older adults. Gait Posture 2007; 26: 516–25. [PubMed: 17196819]
42. Cham R, Studenski SA, Perera S, Bohnen NI. Striatal dopaminergic denervation and gait in healthy adults. Exp Brain Res 2008; 185: 391–8. [PubMed: 17973106]
43. Bohnen NI, Albin RL, Koepe RA, Wernette KA, Kilbourn MR, Minoshima S et al. Positron emission tomography of monoaminergic vesicular binding in aging and Parkinson disease. J Cereb Blood Flow Metab 2006; 26: 1198–212. [PubMed: 16421508]
44. Volkow ND, Wang GJ, Fowler JS, Ding YS, Gur RC, Gatley J et al. Parallel loss of presynaptic and postsynaptic dopamine markers in normal aging. Ann Neurol 1998; 44: 143–7. [PubMed: 9667606]
45. Rudow G, O'Brien R, Savonenko AV, Resnick SM, Zonderman AB, Pletnikova O et al. Morphometry of the human substantia nigra in ageing and Parkinson’s disease. Acta Neuropathol 2008; 115: 461–70. [PubMed: 18297291]
46. Roubenoff R, Harris TB, Abad LW, Wilson PW, Dallal GE, Dinarello CA. Monocyte cytokine production in an elderly population: effect of age and inflammation. J Gerontol A Biol Sci Med Sci 1998; 53: M20–6. [PubMed: 9467429]
47. Franceschi C, Bonafe M, Valensin S, Olivieri F, De Luca M, Ottaviani E et al. Inflammaging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci 2000; 908: 244–54. [PubMed: 10911963]
48. Alexopoulos GS, Morimoto SS. The inflammation hypothesis in geriatric depression. International Journal of Geriatric Psychiatry 2011; 26: 1109–18. [PubMed: 21370276]
49. Martinez-Cengottitabengoa M, Carrascon L, O’Brien JT, Diaz-Gutierrez MJ, Bermudez-Ampudia C, Sanada K et al. Peripheral Inflammatory Parameters in Late-Life Depression: A Systematic Review. Int J Mol Sci 2016; 17.
50. Ershler WB. Interleukin-6: a cytokine for gerontologists. J Am Geriatr Soc 1993; 41: 176–81. [PubMed: 8426042]
55. Sparkman NL, Johnson RW. Neuroinflammation associated with aging sensitizes the brain to the effects of infection or stress. Neuroimmunomodulation 2008; 15: 323–30. [PubMed: 19047808]

56. Taylor WD, McQuoid DR, Payne ME, Zannas AS, MacFall JR, Steffens DC. Hippocampus Atrophy and the Longitudinal Course of Late-life Depression. Am J Geriatr Psychiatry 2014; 22: 1504–12. [PubMed: 24378256]

57. Satizabal CL, Zhu YC, Mazoyer B, Dufouil C, Tzourio C. Circulating IL-6 and CRP are associated with MRI findings in the elderly: the 3C-Dijon Study. Neurology 2012; 78: 720–7. [PubMed: 22357713]

58. Gimeno D, Kivimaki M, Brunner EJ, Elovainio M, De Vogli R, Steptoe A et al. Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II Study. Psychol Med 2009; 39: 413–23. [PubMed: 18533059]

59. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat Rev Immunol 2016; 16: 22–34. [PubMed: 26711676]

60. Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. Psychol Bull 2014; 140: 774–815. [PubMed: 24417575]

61. Capuron L, Schroecksnadel S, Feart C, Aubert A, Higueret D, Barberger-Gateau P et al. Chronic low-grade inflammation in elderly persons is associated with altered tryptophan and tyrosine metabolism: role in neuropsychiatric symptoms. Biol Psychiatry 2011; 70: 175–82. [PubMed: 21277567]

62. Felger JC, Miller AH. Cytokine effects on the basal ganglia and dopamine function: the subcortical source of inflammatory malaise. Front Neuroendocrinol 2012; 33: 315–27. [PubMed: 23000204]

63. Felger JC, Treadway MT. Inflammation Effects on Motivation and Motor Activity: Role of Dopamine. Neuropsychopharmacology 2017; 42: 216–41. [PubMed: 27480574]

64. Capuron L, Pagnoni G, Demetrashvili MF, Lawson DH, Fornwalt FB, Woolwine B et al. Basal ganglia hypermetabolism and symptoms of fatigue during interferon-alpha therapy. Neuropsychopharmacology 2007; 32: 2384–92. [PubMed: 17327884]

65. Capuron L, Pagnoni G, Drake DF, Woolwine BJ, Spivey JR, Crowe RJ et al. Dopaminergic mechanisms of reduced basal ganglia responses to hedonic reward during interferon alfa administration. Arch Gen Psychiatry 2012; 69: 1044–53. [PubMed: 23026954]

66. Eisenberger NI, Berkman ET, Inagaki TK, Rameson LT, Mashal NM, Irwin MR. Inflammation-induced anhedonia: endotoxin reduces ventral striatum responses to reward. Biol Psychiatry 2010; 68: 748–54. [PubMed: 20719303]

67. Harrison NA, Brydon L, Walker C, Gray MA, Steptoe A, Critchley HD. Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. Biological Psychiatry 2009; 66: 407–14. [PubMed: 19423079]

68. Dipasquale O, Cooper EA, Tibble J, Voon V, Baglio F, Baselli G et al. Interferon-alpha acutely impairs whole-brain functional connectivity network architecture - A preliminary study. Brain Behav Immun 2016; 58: 31–9. [PubMed: 26697999]

69. Keller AS, Leikauf JE, Holt-Gosselin B, Staveland BR, Williams LM. Paying attention to attention in depression. Transl Psychiatry 2019; 9: 279. [PubMed: 31699968]

70. Serra-Blasco M, Torres JJ, Vicent-Gil M, Goldberg X, Navarra-Ventura G, Aguilar E et al. Discrepancy between objective and subjective cognition in major depressive disorder. Eur Neuropsychopharmacol 2019; 29: 46–56. [PubMed: 30503099]

71. Petersen JZ, Porter RJ, Miskowiak KW. Clinical characteristics associated with the discrepancy between subjective and objective cognitive impairment in depression. J Affect Disord 2019; 246: 763–74. [PubMed: 30623822]

72. DeJong H, Fox E, Stein A. Does rumination mediate the relationship between attentional control and symptoms of depression? J Behav Ther Exp Psychiatry 2019; 63: 28–35. [PubMed: 30639915]

73. Hendricks MA, Buchanan TW. Individual differences in cognitive control processes and their relationship to emotion regulation. Cogn Emot 2016; 30: 912–24. [PubMed: 25947896]

74. Gandelman JA, Albert K, Boyd BD, Park JW, Riddle M, Woodward ND et al. Intrinsic Functional Network Connectivity Is Associated With Clinical Symptoms and Cognition in Late-Life Depression. Biol Psychiatry Cogn Neurosci Neuroimaging 2019; 4: 160–70. [PubMed: 30392844]

Mol Psychiatry. Author manuscript; available in PMC 2022 March 31.
75. Alexopoulos GS, Kiosses DN, Heo M, Murphy CF, Shanmugham B, Gunning-Dixon F. Executive dysfunction and the course of geriatric depression. Biological Psychiatry 2005; 58: 204–10. [PubMed: 16018984]

76. Butters MA, Whyte EM, Nebles RD, Begley AE, Dew MA, Mulsant BH et al. The nature and determinants of neuropsychological functioning in late-life depression. Archives of General Psychiatry 2004; 61: 587–95. [PubMed: 15184238]

77. Pimontel MA, Culing-Reinleib ME, Morimoto SS, Sneed JR. Executive dysfunction and treatment response in late-life depression. International Journal of Geriatric Psychiatry 2012; 27: 893–9. [PubMed: 22009869]

78. Grahek I, Shenhav A, Musslick S, Krebs RM, Koster EHW. Motivation and cognitive control in depression. Neurosci Biobehav Rev 2019; 102: 371–81. [PubMed: 31047891]

79. Botvinick M, Braver T. Motivation and cognitive control: from behavior to neural mechanism. Annu Rev Psychol 2015; 66: 83–113. [PubMed: 25251491]

80. Christman S, Bermudez C, Hao L, Landman BA, Boyd B, Albert K et al. Accelerated brain aging predicts impaired cognitive performance and greater disability in geriatric but not midlife adult depression. Transl Psychiatry 2020; 10: 317. [PubMed: 32948749]

81. Respino M, Jaywant A, Kuceyeski A, Victoria LW, Hoptman MJ, Scult MA et al. The impact of white matter hyperintensities on the structural connectome in late-life depression: Relationship to executive functions. Neuroimage Clin 2019; 23: 101852. [PubMed: 31077981]

82. Sheline YI, Barch DM, Garcia K, Gersing K, Piper C, Welsh-Bohmer KA et al. Cognitive function in late life depression: relationships to depression severity, cerebrovascular risk factors and processing speed. Biological Psychiatry 2006; 60: 58–65. [PubMed: 16414031]

83. Neubes RD, Butters MA, Mulsant BH, Pollock BG, Zmuda MD, Houck PR et al. Decreased working memory and processing speed mediate cognitive impairment in geriatric depression. Psychological Medicine 2000; 30: 679–91. [PubMed: 10883722]

84. Lindenberger U, Mayr U, Kliegl R. Speed and intelligence in old age. Psychol Aging 1993; 8: 207–20. [PubMed: 8323725]

85. Sliwinski M, Buschke H. Processing speed and memory in aging and dementia. J Gerontol B Psychol Sci Soc Sci 1997; 52: P308–18. [PubMed: 9403520]

86. Brown PJ, Liu X, Sneed JR, Pimontel MA, Devanand DP, Roose SP. Speed of processing and depression affect function in older adults with mild cognitive impairment. Am J Geriatr Psychiatry 2013; 21: 675–84. [PubMed: 23567401]

87. Rapp MA, Reischies FM. Attention and executive control predict Alzheimer disease in late life: results from the Berlin Aging Study (BASE). Am J Geriatr Psychiatry 2005; 13: 134–41. [PubMed: 15703322]

88. Backman L, Lindenberger U, Li SC, Nyberg L. Linking cognitive aging to alterations in dopamine neurotransmitter functioning: recent data and future avenues. Neurosci Biobehav Rev 2010; 34: 670–7. [PubMed: 20026186]

89. Juarez EJ, Castrellon JJ, Green MA, Crawford JL, Seaman KL, Smith CT et al. Reproducibility of the correlational triad among aging, dopamine receptor availability, and cognition. Psychol Aging 2019; 34: 921–32. [PubMed: 31589058]

90. Salami A, Garrett DD, Wahlin A, Rieckmann A, Papenberg G, Karaliija N et al. Dopamine D2/3 Binding Potential Modulates Neural Signatures of Working Memory in a Load-Dependent Fashion. J Neurosci 2019; 39: 537–47. [PubMed: 30478031]

91. Karlsson S, Nyberg L, Karlsson P, Fischer H, Thilers P, Macdonald S et al. Modulation of striatal dopamine D1 binding by cognitive processing. NeuroImage 2009; 48: 398–404. [PubMed: 19539768]

92. Backman L, Ginovart N, Dixon RA, Wahlin TB, Wahlin A, Halldin C et al. Age-related cognitive deficits mediated by changes in the striatal dopamine system. Am J Psychiatry 2000; 157: 635–7. [PubMed: 10739428]

93. Volkow ND, Gur RC, Wang GJ, Fowler JS, Moberg PJ, Ding YS et al. Association between decline in brain dopamine activity with age and cognitive and motor impairment in healthy individuals. Am J Psychiatry 1998; 155: 344–9. [PubMed: 9501743]
94. Backman L, Karlsson S, Fischer H, Karlsson P, Brehmer Y, Rieckmann A et al. Dopamine D(1) receptors and age differences in brain activation during working memory. Neurobiol Aging 2011; 32: 1849–56. [PubMed: 19962789]

95. Erixon-Lindroth N, Farde L, Wahlin TB, Sovago J, Halldin C, Backman L. The role of the striatal dopamine transporter in cognitive aging. Psychiatry Res 2005; 138: 1–12. [PubMed: 15708296]

96. Nyberg L, Karlalija N, Salami A, Andersson M, Wahlin A, Kaboovand N et al. Dopamine D2 receptor availability is linked to hippocampal-caudate functional connectivity and episodic memory. Proc Natl Acad Sci U S A 2016; 113: 7918–23. [PubMed: 27339132]

97. Lovden M, Karlalija N, Andersson M, Wahlin A, Axelson J, Kohncke Y et al. Latent-Profile Analysis Reveals Behavioral and Brain Correlates of Dopamine-Cognition Associations. Cereb Cortex 2018; 28: 3894–907. [PubMed: 29028935]

98. Rutherford BR, Slifstein M, Chen C, Abi-Dargham A, Brown PJ, Wall MW et al. Effects of L-DOPA Monotherapy on Psychomotor Speed and [(11)C]Raclopride Binding in High-Risk Older Adults With Depression. Biol Psychiatry 2019; 86: 221–9. [PubMed: 31178096]

99. Roy MA, Doiron M, Talon-Croteau J, Dupre N, Simard M. Effects of Antiparkinson Medication on Cognition in Parkinson’s Disease: A Systematic Review. Can J Neurol Sci 2018; 45: 375–404. [PubMed: 29747716]

100. Heppner FL, Rossohoff RM, Becher B. Immune attack: the role of inflammation in Alzheimer disease. Nat Rev Neurosci 2015; 16: 358–72. [PubMed: 25991443]

101. Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL et al. Neuroinflammation in Alzheimer’s disease. Lancet Neurol 2015; 14: 388–405. [PubMed: 25792098]

102. Takeda S, Sato N, Uchio-Yamada K, Sawada K, Kuniida T, Takeuchi D et al. Diabetes-accelerated memory dysfunction via cerebrovascular inflammation and Abeta deposition in an Alzheimer mouse model with diabetes. Proc Natl Acad Sci U S A 2010; 107: 7036–41. [PubMed: 20231468]

103. Weaver JD, Huang MH, Albert M, Harris T, Rowe JW, Seeman TE. Interleukin-6 and risk of cognitive decline: MacArthur studies of successful aging. Neurology 2002; 59: 371–8. [PubMed: 12177370]

104. Wright CB, Sacco RL, Rundek T, Delman J, Rabbani L, Elkind M. Interleukin-6 is associated with cognitive function: the Northern Manhattan Study. J Stroke Cerebrovasc Dis 2006; 15: 34–8. [PubMed: 16501663]

105. Heringa SM, van den Berg E, Reijmer YD, Nijpels G, Stehouwer CD, Schalkwijk CG et al. Markers of low-grade inflammation and endothelial dysfunction are related to reduced information processing speed and executive functioning in an older population - the Hoon Study. Psychoneuroendocrinology 2014; 40: 108–18. [PubMed: 24485482]

106. Marsland AL, Gianaros PJ, Kuan DC, Sheu LK, Krajina K, Manuck SB. Brain morphology links systemic inflammation to cognitive function in midlife adults. Brain Behav Immun 2015; 48: 195–204. [PubMed: 25882911]

107. Bremmer MA, Beekman AT, Deeg DJ, Penninx BW, Dik MG, Hack CE et al. Inflammatory markers in late-life depression: results from a population-based study. J Affect Disord 2008; 106: 249–55. [PubMed: 17716746]

108. Pizzagalli DA. Depression, stress, and anhedonia: toward a synthesis and integrated model. Annu Rev Clin Psychol 2014; 10: 393–423. [PubMed: 24471371]

109. Hasler G, Drevets WC, Manji HK, Charney DS. Discovering endophenotypes for major depression. Neuropsychopharmacology 2004; 29: 1765–81. [PubMed: 15213704]

110. Treadway MT, Bossaller NA, Shelton RC, Zald DH. Effort-based decision-making in major depressive disorder: a translational model of motivational anhedonia. J Abnorm Psychol 2012; 121: 553–8. [PubMed: 22775583]

111. Kunisato Y, Okamoto Y, Ueda K, Onoda K, Okada G, Yoshimura S et al. Effects of depression on reward-based decision making and variability of action in probabilistic learning. J Behav Ther Exp Psychiatry 2012; 43: 1088–94. [PubMed: 22721601]

112. Rizvi SJ, Pizzagalli DA, Sproule BA, Kennedy SH. Assessing anhedonia in depression: Potentials and pitfalls. Neurosci Biobehav Rev 2016; 65: 21–35. [PubMed: 26959336]
113. Treadway MT, Zald DH. Reconsidering anhedonia in depression: lessons from translational neuroscience. Neurosci Biobehav Rev 2011; 35: 537–55. [PubMed: 20603146]

114. Halahakoon DC, Kieslich K, O’Driscoll C, Nair A, Lewis G, Roiser JP. Reward-Processing Behavior in Depressed Participants Relative to Healthy Volunteers: A Systematic Review and Meta-analysis. JAMA psychiatry 2020.

115. Husain M, Roiser JP. Neuroscience of apathy and anhedonia: a transdiagnostic approach. Nat Rev Neurosci 2018; 19: 470–84. [PubMed: 29946157]

116. Rangel A, Camerer C, Montague PR. A framework for studying the neurobiology of value-based decision making. Nat Rev Neurosci 2008; 9: 545–56. [PubMed: 18545266]

117. Salamone JD, Correa M. The mysterious motivational functions of mesolimbic dopamine. Neuron 2012; 76: 470–85. [PubMed: 23141060]

118. Kable JW, Glimcher PW. The neurobiology of decision: consensus and controversy. Neuron 2009; 63: 733–45. [PubMed: 19778504]

119. Suzuki S, Lawlor VM, Cooper JA, Arulpragasam AR, Treadway MT. Distinct regions of the striatum underlying effort, movement initiation and effort discounting. Nat Hum Behav 2021; 5: 378–88. [PubMed: 33230282]

120. Alexopoulos GS, Hoptman MJ, Yuen G, Kanellopoulos D, Seirup JK, Lim KO et al. Functional connectivity in apathy of late-life depression: a preliminary study. J Affect Disord 2013; 149: 398–405. [PubMed: 23261142]

121. Friston K A theory of cortical responses. Philos Trans R Soc Lond B Biol Sci 2005; 360: 815–36. [PubMed: 15937014]

122. den Ouden HE, Kok P, de Lange FP. How prediction errors shape perception, attention, and motivation. Front Psychol 2012; 3: 548. [PubMed: 23248610]

123. Steinberg EE, Keiflin R, Boivin JR, Witten IB, Deisseroth K, Janak PH. A causal link between prediction errors, dopamine neurons and learning. Nat Neurosci 2013; 16: 966–73. [PubMed: 23708143]

124. Wise RA. Dopamine, learning, and motivation. Nature Reviews Neuroscience 2004; 5: 483–94. [PubMed: 15152198]

125. Hamid AA, Pettibone JR, Mabrouk OS, Hetrick VL, Schmidt R, Vander Weele CM et al. Mesolimbic dopamine signals the value of work. Nat Neurosci 2016; 19: 117–26. [PubMed: 26595651]

126. Howe MW, Tierney PL, Sandberg SG, Phillips PE, Graybiel AM. Prolonged dopamine signalling in striatum signals proximity and value of distant rewards. Nature 2013; 500: 575–9. [PubMed: 23913271]

127. Berke JD. What does dopamine mean? Nat Neurosci 2018; 21: 787–93. [PubMed: 29760524]

128. du Hoffmann J, Nicola SM. Dopamine invigorates reward seeking by promoting cue-evoked excitation in the nucleus accumbens. J Neurosci 2014; 34: 14349–64. [PubMed: 25339748]

129. Niv Y, Daw ND, Joel D, Dayan P. Tonic dopamine: opportunity costs and the control of response vigor. Psychopharmacology (Berl) 2007; 191: 507–20. [PubMed: 17031711]

130. Satoh T, Nakai S, Sato T, Kimura M. Correlated coding of motivation and outcome of decision by dopamine neurons. J Neurosci 2003; 23: 9913–23. [PubMed: 14586021]

131. Castrellon JJ, Meade J, Greenwald L, Hurst K, Samanez-Larkin GR. Dopaminergic modulation of reward discounting in healthy rats: a systematic review and meta-analysis. Psychopharmacology (Berl) 2021; 238: 711–23. [PubMed: 33215269]

132. Walton ME, Bouret S. What Is the Relationship between Dopamine and Effort? Trends Neurosci 2019; 42: 79–91. [PubMed: 30391016]

133. Tanaka S, O’Doherty JP, Sakagami M. The cost of obtaining rewards enhances the reward prediction error signal of midbrain dopamine neurons. Nat Commun 2019; 10: 3674. [PubMed: 31417077]

134. Huys QJ, Pizzagalli DA, Bogdan R, Dayan P. Mapping anhedonia onto reinforcement learning: a behavioural meta-analysis. Biol Mood Anxiety Disord 2013; 3: 12. [PubMed: 23782813]
135. Yang XH, Huang J, Zhu CY, Wang YF, Cheung EF, Chan RC et al. Motivational deficits in effort-based decision making in individuals with subsyndromal depression, first-episode and remitted depression patients. Psychiatry Res 2014; 220: 874–82. [PubMed: 25262638]

136. Clery-Melin ML, Schmidt L, Lafargue G, Baup N, Fossati P, Pessiglione M. Why don’t you try harder? An investigation of effort production in major depression. PLoS One 2011; 6: e23178. [PubMed: 21853083]

137. Hershenberg R, Satterthwaite TD, Daldal A, Katchmar N, Moore TM, Kable JW et al. Diminished effort on a progressive ratio task in both unipolar and bipolar depression. J Affect Disord 2016; 196: 97–100. [PubMed: 26919058]

138. Pizzagalli DA, Iosifescu D, Hallett LA, Ratner KG, Fava M. Reduced hedonic capacity in major depressive disorder: evidence from a probabilistic reward task. J Psychiatri Res 2008; 43: 76–87. [PubMed: 18433774]

139. Vrieze E, Pizzagalli DA, Demyttenaere K, Hompes T, Sienaert P, de Boer P et al. Reduced reward learning predicts outcome in major depressive disorder. Biol Psychiatry 2013; 73: 639–45. [PubMed: 23228328]

140. Dombrovski AY, Siegle GJ, Szanto K, Clark L, Reynolds CF, Aizenstein H. The temptation of suicide: striatal gray matter, discounting of delayed rewards, and suicide attempts in late-life depression. Psychol Med 2012; 42: 1203–15. [PubMed: 21999930]

141. Samanez-Larkin GR, Gibbs SE, Khanna K, Nielsen L, Carstensen LL, Knutson B. Anticipation of monetary gain but not loss in healthy older adults. Nat Neurosci 2007; 10: 787–91. [PubMed: 17468751]

142. Rademacher L, Salama A, Grunder G, Spreckelmeyer KN. Differential patterns of nucleus accumbens activation during anticipation of monetary and social reward in young and older adults. Soc Cogn Affect Neurosci 2014; 9: 825–31. [PubMed: 23547243]

143. Eppinger B, Hammerer D, Li SC. Neuromodulation of reward-based learning and decision making in human aging. Ann N Y Acad Sci 2011; 1235: 1–17. [PubMed: 22023564]

144. Seaman KL, Brooks N, Karrer TM, Castrellon JJ, Perkins SF, Dang LC et al. Subjective value representations during effort, probability and time discounting across adulthood. Soc Cogn Affect Neurosci 2018; 13: 449–59. [PubMed: 29618082]

145. Halfmann K, Hedgcock W, Kable J, Denburg NL. Individual differences in the neural signature of subjective value among older adults. Soc Cogn Affect Neurosci 2016; 11: 1111–20. [PubMed: 26089342]

146. Hess TM, Smith BT, Sharifian N. Aging and effort expenditure: The impact of subjective perceptions of task demands. Psychol Aging 2016; 31: 653–60. [PubMed: 27831709]

147. Devine ST, Otto AR, Bolenz F, Reiter AM, Eppinger B. Cognitive resource limitations shift effort trade-offs across the lifespan. PsyArXiv 2019.

148. Manty M, de Leon CF, Rantanen T, Era P, Pedersen AN, Ekman A et al. Mobility-related fatigue, walking speed, and muscle strength in older people. J Gerontol A Biol Sci Med Sci 2012; 67: 523–9. [PubMed: 22016363]

149. Avlund K, Rantanen T, Schroll M. Tiredness and subsequent disability in older adults: The role of walking limitations. J Gerontol A Biol Sci Med Sci 2006; 61: 1201–5. [PubMed: 17167163]

150. Salamone JD, Correa M, Yohn S, Lopez Cruz L, San Miguel N, Alatorre L. The pharmacology of effort-related choice behavior: Dopamine, depression, and individual differences. Behav Processes 2016; 127: 3–17. [PubMed: 26899746]

151. Robles CF, Johnson AW. Disruptions in effort-based decision-making and consummatory behavior following antagonism of the dopamine D2 receptor. Behav Brain Res 2017; 320: 431–9. [PubMed: 27984049]

152. Wardle MC, Treadway MT, Mayo LM, Zald DH, de Wit H. Amping up effort: effects of d-amphetamine on human effort-based decision-making. J Neurosci 2011; 31: 16597–602. [PubMed: 22090487]

153. Treadway MT, Buckholtz JW, Cowan RL, Woodward ND, Li R, Ansari MS et al. Dopaminergic mechanisms of individual differences in human effort-based decision-making. J Neurosci 2012; 32: 6170–6. [PubMed: 22553023]
154. Caravaggio F, Fervaha G, Browne CJ, Gerretsen P, Remington G, Graff-Guerrero A. Reward motivation in humans and its relationship to dopamine D2/3 receptor availability: A pilot study with dual [(11)C]-raclopride and [(11)C]-(+)-PHNO imaging. J Psychopharmacol 2018; 32: 357–66. [PubMed: 29442593]

155. Flagel SB, Clark JJ, Robinson TE, Mayo L, Czuj A, Willuhn I et al. A selective role for dopamine in stimulus-reward learning. Nature 2011; 469: 53–7. [PubMed: 21150898]

156. Pessiglione M, Seymour B, Flandin G, Dolan RJ, Frith CD. Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. Nature 2006; 442: 1042–5. [PubMed: 16929307]

157. Chowdhury R, Guitart-Masip M, Lambert C, Dayan P, Huys Q, Duzel E et al. Dopamine restores reward prediction errors in old age. Nat Neurosci 2013; 16: 648–53. [PubMed: 23525044]

158. Beierholm U, Guitart-Masip M, Economides M, Chowdhury R, Duzel E, Dolan R et al. Dopamine modulates reward-related vigor. Neuropsychopharmacology 2013; 38: 1495–503. [PubMed: 23419875]

159. Michely J, Viswanathan S, Hauser TU, Delker L, Dolan RJ, Grefkes C. The role of dopamine in dynamic effort-reward integration. Neuropsychopharmacology 2020; 45: 1448–53. [PubMed: 32268344]

160. Hofmans L, Papadopetra D, van den Bosch R, Maatta JI, Frobose MI, Zandbelt BB et al. Methylphenidate boosts choices of mental labor over leisure depending on striatal dopamine synthesis capacity. Neuropsychopharmacology 2020; 45: 2170–9. [PubMed: 32919405]

161. Westbrook A, van den Bosch R, Maatta JI, Hofmans L, Papadopetra D, Cools R et al. Dopamine promotes cognitive effort by biasing the benefits versus costs of work. Science 2020; 367: 1362–6. [PubMed: 32193325]

162. Sharp ME, Foerde K, Daw ND, Shohamy D. Dopamine selectively remediates ‘model-based’ reward learning: a computational approach. Brain 2016; 139: 355–64. [PubMed: 26685155]

163. Foerde K, Figner B, Doll BB, Woyke IC, Braun EK, Weber EU et al. Dopamine Modulation of Intertemporal Decision-making: Evidence from Parkinson Disease. J Cogn Neurosci 2016; 28: 657–67. [PubMed: 26836514]

164. Chong TT, Bonnelle V, Manohar S, Veromann KR, Muhammed K, Tofaris GK et al. Dopamine enhances willingness to exert effort for reward in Parkinson’s disease. Cortex 2015; 69: 40–6. [PubMed: 25967086]

165. Muhammed K, Manohar S, Ben Yehuda M, Chong TT, Tofaris G, Lennox G et al. Reward sensitivity deficits modulated by dopamine are associated with apathy in Parkinson’s disease. Brain 2016; 139: 2706–21. [PubMed: 27452600]

166. Panigrahi B, Martin KA, Li Y, Graves AR, Vollmer A, Olson L et al. Dopamine Is Required for the Neural Representation and Control of Movement Vigor. Cell 2015; 162: 1418–30. [PubMed: 26359992]

167. Liu Y, Admon R, Mellem MS, Belleau EL, Kaiser RH, Clegg R et al. Machine Learning Identifies Large-Scale Reward-Related Activity Modulated by Dopaminergic Enhancement in Major Depression. Biol Psychiatry Cogn Neurosci Neuroimaging 2020; 5: 163–72. [PubMed: 31784354]

168. Rengasamy M, Marsland A, McClain L, Kovats T, Walko T, Pan L et al. Longitudinal relationships of cytokines, depression and anhedonia in depressed adolescents. Brain Behav Immun 2021; 91: 74–80. [PubMed: 32919038]

169. Felger JC, Haroon E, Patel TA, Goldsmith DR, Womack EC, Woolwine BJ et al. What does plasma CRP tell us about peripheral and central inflammation in depression? Mol Psychiatry 2020; 25: 1301–11. [PubMed: 29895893]

170. Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA psychiatry 2013; 70: 31–41. [PubMed: 22945416]

171. Lee Y, Mansur RB, Brietzke E, Carmona NE, Subramaniapillai M, Pan Z et al. Efficacy of adjunctive infliximab vs. placebo in the treatment of anhedonia in bipolar I/II depression. Brain Behav Immun 2020; 88: 631–9. [PubMed: 32380271]
172. Felger JC, Li Z, Haroon E, Woolwine BJ, Jung MY, Hu X et al. Inflammation is associated with decreased functional connectivity within corticostriatal reward circuitry in depression. Mol Psychiatry 2016; 21: 1358–65. [PubMed: 26552591]

173. Yin L, Xu X, Chen G, Mehta ND, Haroon E, Miller AH et al. Inflammation and decreased functional connectivity in a widely-distributed network in depression: Centralized effects in the ventral medial prefrontal cortex. Brain Behav Immun 2019; 80: 657–66. [PubMed: 31078690]

174. Burrows K, Stewart JL, Kaplucki R, Figueroa-Hall L, Spechler PA, Zheng H et al. Elevated peripheral inflammation is associated with attenuated striatal reward anticipation in major depressive disorder. Brain Behav Immun 2021.

175. Seidler RD, Alberts JL, Stelmach GE. Changes in multi-joint performance with age. Motor Control 2002; 6: 19–31. [PubMed: 11842268]

176. Nevitt MC, Cummings SR, Kidd S, Black D. Risk factors for recurrent nonsyncopal falls. A prospective study. Jama 1989; 261: 2663–8. [PubMed: 2709546]

177. Karpman C, DePew ZS, LeBrasseur NK, Novotny PJ, Benzo RP. Determinants of gait speed in COPD. Chest 2014; 146: 104–10. [PubMed: 24522522]

178. Dawson J, Linsell L, Zondervan K, Rose P, Randall T, Carr A et al. Epidemiology of hip and knee pain and its impact on overall health status in older adults. Rheumatology (Oxford) 2004; 43: 497–504. [PubMed: 14762225]

179. Verghese J, Holtzer R, Lipton RB, Wang C. Quantitative gait markers and incident fall risk in older adults. J Gerontol A Biol Sci Med Sci 2009; 64: 896–901. [PubMed: 19349593]

180. Guralnik JM, Ferrucci L, Pieper CF, Leveille SG, Markides KS, Ostir GV et al. Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. J Gerontol A Biol Sci Med Sci 2000; 55: M221–31. [PubMed: 10811152]

181. Penninx BW, Ferrucci L, Leveille SG, Rantanen T, Pahor M, Guralnik JM. Lower extremity performance in nondisabled older persons as a predictor of subsequent hospitalization. J Gerontol A Biol Sci Med Sci 2000; 55: M691–7. [PubMed: 11078100]

182. Abellan van Kan G, Rolland Y, Andrieu S, Bauer J, Beauchet O, Bonnefoy M et al. Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people an International Academy on Nutrition and Aging (IANA) Task Force. J Nutr Health Aging 2009; 13: 881–9. [PubMed: 19924348]

183. White DK, Neogi T, Nevitt MC, Peloquin CE, Zhu Y, Boudreau RM et al. Trajectories of gait speed predict mortality in well-functioning older adults: the Health, Aging and Body Composition study. J Gerontol A Biol Sci Med Sci 2013; 68: 456–64. [PubMed: 23051974]

184. Montero-Odasso M, Schapira M, Soriano ER, Varela M, Kaplan R, Camera LA et al. Gait velocity as a single predictor of adverse events in healthy seniors aged 75 years and older. J Gerontol A Biol Sci Med Sci 2005; 60: 1304–9. [PubMed: 16282564]

185. Demakakos P, Cooper R, Hamer M, de Oliveira C, Hardy R, Breeze E. The bidirectional association between depressive symptoms and gait speed: evidence from the English Longitudinal Study of Ageing (ELSA). PLoS One 2013; 8: e68632. [PubMed: 23874698]

186. Sanders JB, Bremmer MA, Deeg DJ, Beekman AT. Do depressive symptoms and gait speed impairment predict each other’s incidence? A 16-year prospective study in the community. J Am Geriatr Soc 2012; 60: 1673–80. [PubMed: 22905679]

187. Stahl ST, Altman HM, Dew MA, Albert SM, Butters M, Gildengers A et al. The Effects of Gait Speed and Psychomotor Speed on Risk for Depression and Anxiety in Older Adults with Medical Comorbidities. J Am Geriatr Soc 2021; 69: 1265–71. [PubMed: 33387385]

188. Rosario BL, Rosso AL, Aizenstein HJ, Harris T, Newman AB, Satterfield S et al. Cerebral White Matter and Slow Gait: Contribution of Hyperintensities and Normal-appearing Parenchyma. J Gerontol A Biol Sci Med Sci 2016; 71: 968–73. [PubMed: 26755683]

189. Sanders JB, Bremmer MA, Comijs HC, van de Ven PM, Deeg DJH, Beekman ATF. Gait Speed and Processing Speed as Clinical Markers for Geriatric Health Outcomes. Am J Geriatr Psychiatry 2017; 25: 374–85. [PubMed: 28063852]
190. Brown PJ, Roose SP, Zhang J, Wall M, Rutherford BR, Ayonayon HN et al. Inflammation, Depression, and Slow Gait: A High Mortality Phenotype in Later Life. J Gerontol A Biol Sci Med Sci 2016; 71: 221–7. [PubMed: 26392405]

191. Cham R, Perera S, Studenski SA, Bohnen NI. Age-related striatal dopaminergic denervation and severity of a slip perturbation. J Gerontol A Biol Sci Med Sci 2011; 66: 980–5. [PubMed: 21746736]

192. Bohnen NI, Muller ML, Kuwabara H, Cham R, Constantine GM, Studenski SA. Age-associated striatal dopaminergic denervation and falls in community-dwelling subjects. J Rehabil Res Dev 2009; 46: 1045–52. [PubMed: 20157861]

193. Calvani R, Marini F, Cesari M, Buford TW, Manini TM, Pahor M et al. Systemic inflammation, body composition, and physical performance in old community-dwelling. J Cachexia Sarcopenia Muscle 2017; 8: 69–77. [PubMed: 27897412]

194. Penninx BW, Kritchevsky SB, Newman AB, Nicklas BJ, Simonsick EM, Rubin S et al. Inflammatory markers and incident mobility limitation in the elderly. J Am Geriatr Soc 2004; 52: 1105–13. [PubMed: 15209648]

195. Verghese J, Holtzer R, Oh-Park M, Derby CA, Lipton RB, Wang C. Inflammatory markers and gait speed decline in older adults. J Gerontol A Biol Sci Med Sci 2011; 66: 1083–9. [PubMed: 21719612]

196. Majer M, Welberg LA, Capuron L, Pagnoni G, Raison CL, Miller AH. IFN-alpha-induced motor slowing is associated with increased depression and fatigue in patients with chronic hepatitis C. Brain Behav Immun 2008; 22: 870–80. [PubMed: 18258414]

197. Wilson D, Jackson T, Sapey E, Lord JM. Frailty and sarcopenia: The potential role of an aged immune system. Ageing Res Rev 2017; 36: 1–10. [PubMed: 28223244]

198. Verghese J, Holtzer R, Lipton RB, Wang C. High-sensitivity C-reactive protein and mobility disability in older adults. Age Ageing 2012; 41: 541–5. [PubMed: 22417984]

199. Custodero C, Anton SD, Beavers DP, Mankowski RT, Lee SA, McDermott MM et al. The relationship between interleukin-6 levels and physical performance in mobility-limited older adults with chronic low-grade inflammation: The ENRGISE Pilot study. Arch Gerontol Geriatr 2020; 90: 104131. [PubMed: 32554219]

200. Rong YD, Bian AL, Hu HY, Ma Y, Zhou XZ. Study on relationship between elderly sarcopenia and inflammatory cytokine IL-6, anti-inflammatory cytokine IL-10. BMC Geriatr 2018; 18: 308. [PubMed: 30541467]

201. Westbrook A, Kester D, Braver TS. What is the subjective cost of cognitive effort? Load, trait, and aging effects revealed by economic preference. PLoS One 2013; 8: e68210. [PubMed: 23894295]

202. Yee DM, Adams S, Beck A, Braver TS. Age-Related Differences in Motivational Integration and Cognitive Control. Cogn Affect Behav Neurosci 2019; 19: 692–714. [PubMed: 30980339]

203. Locke HS, Braver TS. Motivational influences on cognitive control: behavior, brain activation, and individual differences. Cogn Affect Behav Neurosci 2008; 8: 99–112. [PubMed: 18405050]

204. Shohamy D, Wagner AD. Integrating memories in the human brain: hippocampal-midbrain encoding of overlapping events. Neuron 2008; 60: 378–89. [PubMed: 18957228]

205. Camicioli R, Wang Y, Powell C, Minitski A, Rockwood K. Gait and posture impairment, parkinsonism and cognitive decline in older people. J Neural Transm (Vienna) 2007; 114: 1355–61. [PubMed: 17641815]

206. Thompson PD. Gait disorders accompanying diseases of the frontal lobes. Adv Neurol 2001; 87: 235–41. [PubMed: 11347226]

207. Holtzer R, Verghese J, Xue X, Lipton RB. Cognitive processes related to gait velocity: results from the Einstein Aging Study. Neuropsychology 2006; 20: 215–23. [PubMed: 16594782]

208. Belur P, Hsiao D, Myers PS, Earhart GM, Rawson KS. Dual-task costs of texting while walking forward and backward are greater for older adults than younger adults. Hum Mov Sci 2020; 71: 102619. [PubMed: 32452436]

209. Galaro JK, Celnik P, Chib VS. Motor Cortex Excitability Reflects the Subjective Value of Reward and Mediates Its Effects on Incentive-Motivated Performance. J Neurosci 2019; 39: 1236–48. [PubMed: 30552182]

Mol Psychiatry. Author manuscript; available in PMC 2022 March 31.
210. Summa S, Tamagnone I, Asprea G, Capurro C, Sanguineti V. Modulation of motor performance by a monetary incentive: A pilot study. Conf Proc IEEE Eng Med Biol Soc 2015; 2015: 238–41.

211. Cusin C, Iovieno N, Iosifescu DV, Nierenberg AA, Fava M, Rush AJ et al. A randomized, double-blind, placebo-controlled trial of pramipexole augmentation in treatment-resistant major depressive disorder. J Clin Psychiatry 2013; 74: e636–41. [PubMed: 23945458]

212. Gershon AA, Amiaz R, Shem-David H, Grunhaus L. Ropinirole Augmentation for Depression: A Randomized Controlled Trial Pilot Study. J Clin Psychopharmacol 2019; 39: 78–81. [PubMed: 30489382]

213. Lavretsky H, Reinlieb M, St Cyr N, Siddarth P, Ercoli LM, Senturk D. Citalopram, methylphenidate, or their combination in geriatric depression: a randomized, double-blind, placebo-controlled trial. Am J Psychiatry 2015; 172: 561–9. [PubMed: 25677354]

214. Alexopoulos GS, Raue PJ, Banerjee S, Marino P, Renn BN, Solomonov N et al. Comparing the streamlined psychotherapy “Engage” with problem-solving therapy in late-life major depression. A randomized clinical trial. Mol Psychiatry 2020.

215. Morimoto SS, Wexler BE, Liu J, Hu W, Seirup J, Alexopoulos GS. Neuroplasticity-based computerized cognitive remediation for treatment-resistant geriatric depression. Nat Commun 2014; 5: 4579. [PubMed: 25093396]

216. Zecca L, Tampellini D, Gerlach M, Riederer P, Fariello RG, Sulzer D. Substantia nigra neuromelanin: structure, synthesis, and molecular behaviour. Mol Pathol 2001; 54: 414–8. [PubMed: 11724917]

217. Liang CL, Nelson O, Yazdani U, Pashakhsh P, German DC. Inverse relationship between the contents of neuromelanin pigment and the vesicular monoamine transporter-2: human midbrain dopamine neurons. J Comp Neurol 2004; 473: 97–106. [PubMed: 15067721]

218. Shibata E, Sasaki M, Tohyama K, Kanbara Y, Otsuka K, Ehara S et al. Age-related changes in locus ceruleus on neuromelanin magnetic resonance imaging at 3 Tesla. Magn Reson Med Sci 2006; 5: 197–200. [PubMed: 17332710]

219. Castellanos G, Fernandez-Seara MA, Lorenzo-Betancor O, Ortega-Cubero S, Puigvert M, Uranga J et al. Automated neuromelanin imaging as a diagnostic biomarker for Parkinson’s disease. Mov Disord 2015; 30: 945–52. [PubMed: 25772492]

220. Kawaguchi H, Shimada H, Kodaka F, Suzuki M, Shinotoh H, Hirano S et al. Principal Component Analysis of Multimodal Neuromelanin MRI and Dopamine Transporter PET Data Provides a Specific Metric for the Nigral Dopaminergic Neuronal Density. PLoS One 2016; 11: e0151191. [PubMed: 26954690]

221. Cassidy CM, Zucca FA, Girgis RR, Baker SC, Weinstein JJ, Sharp ME et al. Neuromelanin-sensitive MRI as a noninvasive proxy measure of dopamine function in the human brain. Proc Natl Acad Sci U S A 2019; 116: 5108–17. [PubMed: 30796187]
Figure 1. Dopaminergic Circuit Anatomy

The figure illustrates dopaminergic pathways in the human brain, with involved regions and functions detailed in Table 1. Relevant glutamate (Glu) and gamma-aminobutyric acid (GABA) projections are also illustrated for comparison. Amyg = amygdala; Caud = caudate; DA = dopamine; Hipp = hippocampus; NAcc = nucleus accumbens; Put = putamen; SN = substantia nigra; VP = ventral pallidum; VTA = ventral tegmental area. Original figure from Treadway and Zald [113], used with permission.
The scientific model proposes that aging and increases in pro-inflammatory cytokines observed with aging and medical illness negatively affect many aspects of dopamine system function. In turn, this decline in dopamine system signaling contributes to deficits in cognitive, positive valence, and sensorimotor systems. Symptoms in one system may initially be predominant and magnified by other risk factors related to that individual’s genetic, medical, or social background. However, these systems are interdependent and deficits in one system can contribute to difficulties in other systems. This process increases vulnerability to depressive episode in later life and, in context of other risk factors, may contribute to the development of frank depressive episodes.

Abbreviations: DA = dopamine; DAT = dopamine transporter

Figure 2. Model of dopaminergic system contributions and interactions to behavior in late-life depression
Table 1.

Dopaminergic Circuit Anatomy and Function

| Pathway       | Origin                      | Projections                                 | Primary Function            | Potential Deficits                     |
|---------------|-----------------------------|---------------------------------------------|------------------------------|----------------------------------------|
| Mesocortical  | Ventral Tegmental Area      | Frontal & Temporal Cortices                 | Cognitive / Executive Function | Slowed processing speed                |
|               |                             | • Anterior Cingulate Cortex                 |                              | Executive dysfunction                   |
|               |                             | • Entorhinal Cortex                        |                              | Working memory deficits                |
|               |                             | • Prefrontal Cortex                        |                              |                                        |
| Mesolimbic    | Ventral Tegmental Area      | Ventral Striatum (VS)                      | Reward Processing            | Reward function deficits               |
|               |                             | • Nucleus Accumbens (NAc)                  |                              | Impaired motivation                    |
|               |                             | Hippocampus                                |                              |                                        |
|               |                             | Amygdala                                   |                              |                                        |
| Nigrostriatal | Substantia Nigra, pars compacta | Dorsal Striatum                           | Motor Function               | Impairment in planning and execution of motor function |
|               |                             | • Caudate                                  |                              |                                        |
|               |                             | • Putamen                                  |                              |                                        |
### Table 2.

Reward Processing Subcomponents and Terminology

| Cognitive Operation | Description |
|---------------------|-------------|
| 1. Valuation        | Process by which the benefits of a potential outcome are computed. This includes integration of different types of information including the individual’s current need state, and discounting of value based on probability of receiving the reward, costs of obtaining the reward goal, and temporal delays before the reward is available. |
| 2. Decision-Making  | Process resulting in the selection of an option |
|                     | - Option Generation: Generation of potential options based on current external information and past experience |
|                     | - Option Comparison and Selection: Process of comparing the relative computed value of different options leading to the selection of an action |
|                     | - Reward Bias: The tendency to choose more frequently rewarded stimuli |
| 3. Anticipation     | Preparatory phase characterized by arousal before the reward is obtained and which may facilitate actions aimed at obtaining the reward goal |
| 4. Action and Effort| Engagement in action to achieve the reward goal |
|                     | - Reward Response Vigor: The speed or intensity that an individual executes an action to achieve the reward goal |
| 5. Consummation     | Hedonic response to achieving the reward (i.e., pleasure) |
| 6. Reinforcement Learning | Adjustment of valuation of future options based on prior outcomes |
|                     | - Prediction Error: Difference in the value of an expected reward outcome and the actual outcome |

Primary subcomponents are numbered, with more specific subprocesses being listed as bullet points underneath the primary subcomponents. Conceptualization of reward processing drawn from: [112,114,115]