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Influences of Dopaminergic System Dysfunction on Late-Life Depression

Warren D. Taylor, MD, MHSc[a,b], **David H. Zald, PhD**[c], **Jennifer C. Felger, PhD**[d], **Seth Christman, MD**[a], **Daniel O. Claassen, MD**[e], **Guillermo Horga, MD, PhD**[f], **Jeffrey M. Miller, MD**[f], **Katherine Gifford, PsyD**[d], **Baxter Rogers, PhD**[g], **Sarah M. Szymkowicz, PhD**[a], **Bret R. Rutherford, MD**[f]

[a]Department of Psychiatry and Behavioral Sciences, Vanderbilt University Medical Center, Nashville, TN

[b]Geriatric Research, Education, and Clinical Center, Veterans Affairs Tennessee Valley Health System, Nashville Tennessee

[c]Department of Psychiatry Rutgers Biomedical and Health Sciences, Rutgers University, Piscataway, NJ

[d]Department of Psychiatry and Behavioral Sciences, Emory University, Atlanta, GA

[e]Department of Neurology, Vanderbilt University Medical Center, Nashville TN

[f]Department of Psychiatry, Columbia University Vagelos College of Physicians and Surgeons and New York State Psychiatric Institute, New York, NY

[g]Department of Radiology and Radiological Sciences, Vanderbilt University Medical Center, Nashville, TN

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

Correspondence: Warren D. Taylor, MD, MHSc, Vanderbilt University Medical Center, 1601 23rd Avenue South , Nashville, TN 37212, USA, warren.d.taylor@vanderbilt.edu, Telephone: (615) 322-1073, Fax: (615) 875-0686.

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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 terms 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 (BP_{ND}) in the VS and midbrain as assessed by [^{18}F]-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 [^{18}F]-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

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 ([^{18}F]-FDOPA), dopamine receptor binding ([^{11}C]-raclopride, [^{18}F]-fallypride, [^{11}C]-(+)-PHNO), and DAT function ([^{11}C]-altropane, ([^{11}C]-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 [^{11}C]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.

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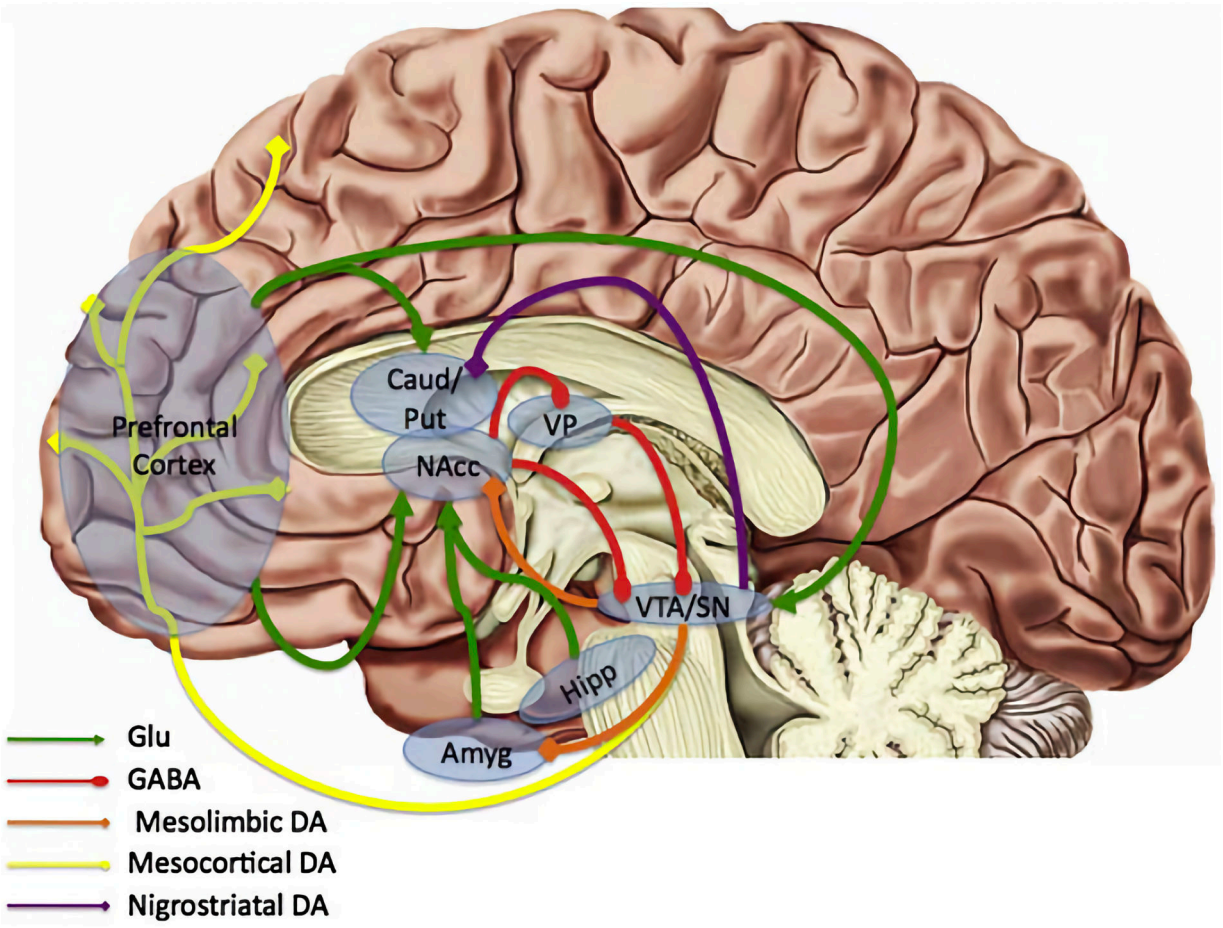

Figure 1. Dopaminergic Circuit Anatomy

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.

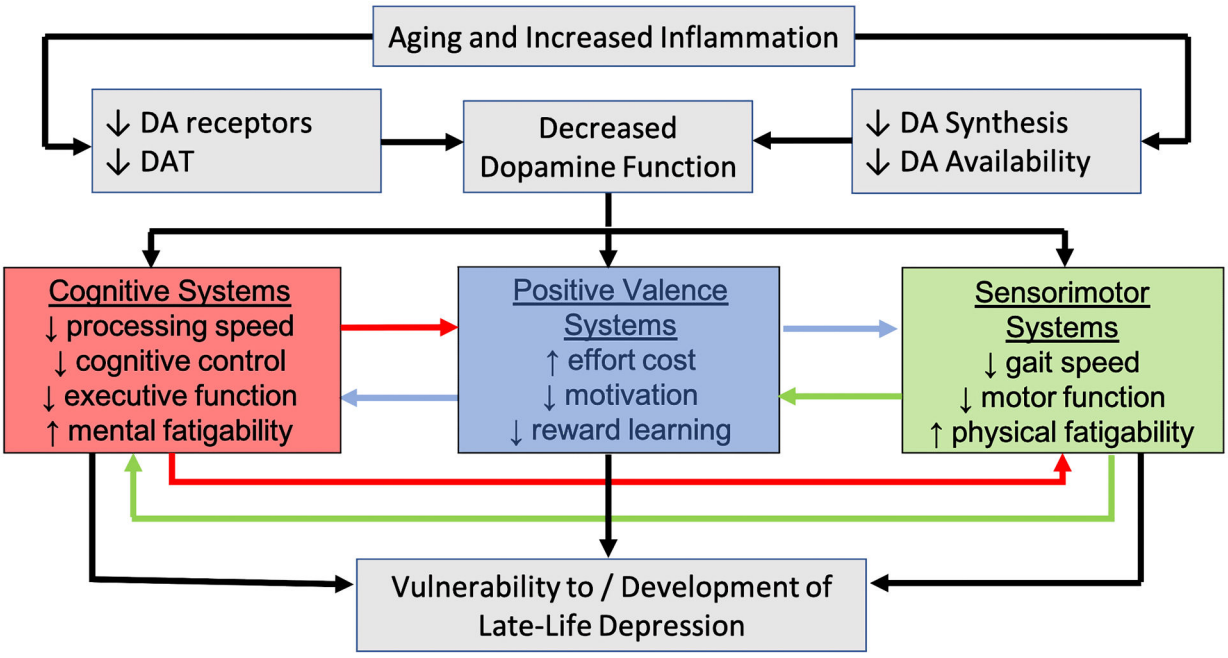

Figure 2. Model of dopaminergic system contributions and interactions to behavior in late-life depression

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

Table 1.

Dopaminergic Circuit Anatomy and Function

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

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]