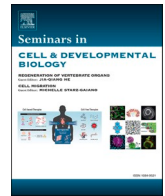




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journal homepage: www.elsevier.com/locate/semcdbThe gut microbiota and nervous system: Age-defined and age-defying[☆]Annelise A. Madison^{a,b}, Janice K. Kiecolt-Glaser^{a,c,*}^a The Institute for Behavioral Medicine Research, The Ohio State University College of Medicine, USA^b Department of Psychology, The Ohio State University, USA^c Department of Psychiatry and Behavioral Health, The Ohio State University College of Medicine, USA

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ABSTRACT

Even healthy older adults experience gastrointestinal (GI) and neurological changes. In fact, the aging process of these two systems are interrelated due the extensive, multifaceted communication network connecting them, termed the gut-brain axis. Age-related modification of the GI environment can influence the bacterial species that survive and thrive there. Additionally, the lifestyle common to older adults in the West, including sedentariness, polypharmacy, and a poor diet, can compound the effect of aging on the GI tract, gut microbiota, and nervous system. Emerging animal and human findings suggest that GI organisms play a major role in gut-brain communication, ultimately shaping neurological aging trajectories by either helping to maintain nervous system function into late life or promoting pathology. Aging and age-related behaviors help to define the gut microbiota's composition and function, but, conversely, the gut microbiota may help to determine late-life functionality and may be harnessed to limit the prevalence of steep neurological decline and diseases. Focusing primarily on clinical research, this review first defines the gut-brain axis, then details age-related GI and nervous system changes, and discusses the impact of age-related lifestyle factors on the GI and nervous systems. The remainder of this review describes cutting-edge research that positions the gut microbiota as an arbiter of age-related neurological decline.

1. Introduction

Neurological disorders have become so common among older adults that pathology can seem like the norm. In fact, one prospective population-based study that followed more than 12,000 midlife adults showed that one in two women and one in three men developed dementia, stroke, or Parkinson's disease (PD) over a 26-year period [1]. The researchers noted that interventions that delay disease onset by one to three years could reduce lifetime risk for these diseases by 25–50% [1], as pathological decline often occurs in the final few years of life. Indeed, as life expectancy continues to increase, the challenge is to preserve functionality and health during these additional years of life (i.e., health span). While some cognitive and neurological decline occurs in mid-to-late life, significant impairment and disease is not inevitable with aging.

To treat neurological pathology, identify those at risk, and maximize health span, it is important to pinpoint factors that shape neurological

aging trajectories. One important regulator of neurological aging is surprisingly not of human origin: gastrointestinal (GI) organisms, especially bacteria, can communicate both directly and indirectly with the nervous system. In the other direction, age-related physiological and lifestyle changes also shape the gut bacteria – a cycle that either fast-tracks to frailty or sustains neurological function well into late life.

The bacterial cells that inhabit and regulate the gut environment do not age in the same manner as human cells; however, their composition can shift throughout the lifespan. Epochs of significant shifts in gut bacteria composition align with periods of neurodevelopment and neurodegeneration [2]. These compositional changes are not inevitable with each birthday, but they do track with physical functionality and frailty [3]. After a brief description of the gut microbiota and nervous system's bidirectional communication (i.e., the gut-brain axis), this review describes primarily clinical findings to discuss: (1) the impact of aging and age-related lifestyle factors on the gut and nervous system, and (2) the gut microbiota's influence on neurological aging.

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2. The gut-brain axis

On a moment-to-moment basis, the gut and brain communicate with one another, and gut bacteria are integral to the conversation. GI bacteria communicate with the central nervous system (CNS) via several mechanisms, including immune activation, stimulation of vagal nerve afferents, alteration of tryptophan metabolism, and release of metabolites and neurotransmitters [4]. Indeed, the gut microbiota can communicate to and through the peripheral nervous system (e.g., the vagus nerve). In the opposite direction, central and peripheral nervous system activity, often manifested in mood and behavior, can exert top-down influence on the gut microbiota; for instance, a stressful examination period was associated with harmful gut microbiota shifts [5]. Overall, the gut microbiota sits at the interface of gut-to-brain and brain-to-gut crosstalk, shaping and being shaped by the discussion.

Epidemiological evidence of GI and neurological comorbidities bears out the physiological gut-brain linkage (Fig. 1, Arrow 1). Delayed gastric emptying and constipation are often some of the first symptoms of PD and can precede the characteristic motor symptoms by five years or more [6]. Colonic biopsies in patients with PD show the presence of Lewy bodies in the intestinal nervous tissue, which may herald this signature pathology in the brain [7]. Indeed, prospective evidence has implicated the gut in the pathophysiology of neurodegenerative disorders: recent meta-analytic evidence indicates that those with inflammatory bowel disease have 41% increased risk of developing PD, compared to their age- and sex-matched peers [8]. Similarly, cohort studies suggest that patients with inflammatory bowel disease or irritable bowel syndrome may be more likely to develop non-Alzheimer's dementia [9,10], and Alzheimer's dementia [9,11] than their peers. In fact, those with inflammatory bowel disease developed dementia an average of seven years before their peers [10]. On a macro level, these prevalent comorbidities demonstrate the strong link between the gastrointestinal and neurological health.

3. The aging gut

During the aging process, the gut environment changes form and function, and these changes dictate which bacterial species survive and thrive. The pancreas secretes less bile, the mucosal lining is less robust, gastric emptying takes longer, motility decreases, and whole-gut transit time increases (Fig. 1, Box B) [12–14]. Notably, the intestinal barrier may become more permeable with age [15], allowing certain bowel contents like bacterial endotoxin into the periphery, which can promote chronic low-grade inflammation. Digestion and appetite also change with age: compared to younger adults, healthy older adults had less of an appetite, slower gastric emptying, and poorer autonomic nervous system function after eating [16]. GI structural pathology is common in late life. The small intestine stretches, leading to weaker intestinal tension [17]. Also, 50% of 90-year-olds had a colonic diverticulum, or a painful, inflamed intestinal pouch, compared to only 5% of 50-year-olds [13]. However, diagnosing digestive disorders can be more difficult in older adults due to decreased pain sensitivity, self-medicating, and incomplete symptom reporting. Even among those who do not meet diagnostic criteria for a GI disorder, there is widespread digestive distress: functional constipation linearly increases from around 20% of 65-year-olds to just under 40% of those over age 85 [18]. Also, 43% of Italian adults over age 60 reported gut-related symptoms in the past week, including abdominal pain, indigestion, reflux, heartburn, burping, and vomiting [19].

These morphological and functional changes may be tied to gut bacterial population shifts (Fig. 1, Arrow 2). For instance, longer transit times are associated with constipation and harder stools [20] as well as lower microbiota diversity and higher protein fermentation in the distal colon [21], which can harm health. Also, the abundance of one problematic specie, *H. pylori*, rises in later life and is a primary culprit of gastritis and peptic ulcers [13].

However, harmful shifts in the gut microbiota are not an inherent part of the aging process. There is some evidence that when people are healthy, age may not make as much of a difference in gut microbiota composition, except during times of rapid neurodevelopment (i.e., late adolescence and emerging adulthood) [22]. In both young [23] and older adulthood [24], there is high microbiota variability between individuals, but relative stability within an individual. Age may not linearly predict gut microbiota composition, but a study of Northern Italian young adults, older adults, and centenarians revealed that the oldest-old exhibited a much more pro-inflammatory microbiota than the younger groups [25]. This finding corresponds with the phenomenon of “inflamm-aging”, or the vicious cycle of chronic low-grade inflammation and cellular senescence characteristic of the aged [26].

The presence of certain bacterial strains may hint at age, a “microbiomic clock” of sorts. Using metagenomic profiles from over 4000 healthy people aged 18–90, researchers constructed an algorithm that predicted individuals' ages within about six years of their real age [27]. Most species had a clear directional relationship with age, either increasing or decreasing the estimated age; few had a neutral or mixed effect. Three species that predicted a lower age belonged to the *Bifidobacterium* genus, which, when used as a probiotic, has reduced depressive and anxiety symptoms as well as inflammation in irritable bowel syndrome [28,29]. Also, six important species that predicted a lower age produce the short-chain fatty acid butyrate, which regulates gut-brain axis function. In a large cross-sectional study of a Japanese sample (0–104 years old), a clustering technique based solely on gut microbiota composition revealed five main groups, suggesting a handful of transitional periods throughout the aging process occurring at ages 3, 33, 42, 77, and 94 [30].

Outside of developmental and transitional periods, major microbiota shifts within an individual may indicate or result from a disease or its treatment (e.g., antibiotics and proton pump inhibitors, which we later discuss). Indeed, age-related gut microbiota alterations have been associated with many physical maladies, including frequent infection, colorectal cancer, cardiovascular disease, and the nebulous diagnosis of “frailty” [31]. In fact, functionality, or frailty, may track more closely with gut microbiota composition than chronological age does. Independent of age, self-reported frailty predicted a distinct community of microbiota, characterized by lower diversity and an abundance of three bacterial genera that may increase gut barrier permeability, symbiotically intensify their virulence, and promote chronic low-grade inflammation, further promoting accelerated aging [3]. Thus, regardless of age, low functionality may promote certain gut microbiota that cement frailty (Fig. 1, Box C) [32,33].

4. The aging nervous system

Although dementia and other neurological disorders are not part of the healthy aging process, some functional nervous system decline occurs naturally throughout the lifespan (Fig. 1, Box A) [34]. Brain volume and cerebral blood flow decrease, and nerves do not fire as quickly or efficiently. Spinal vertebrae become more brittle and may overgrow and constrict the spinal cord and nerve branches, leading to decreased sensation. Peripheral nerves also conduct impulses more slowly as myelin sheaths degenerate. Additionally, the older nervous system does not recover or regenerate as quickly or fully after injury. These neurological changes have cognitive implications: starting in early-to-mid adulthood, aspects of fluid intelligence like processing speed begin to decline [35]. However, crystallized intelligence, such as vocabulary, is preserved throughout much of older adulthood [35].

Age also impacts the autonomic nervous system. Parasympathetic activity declines with age [36]. Specifically, the vagus nerve does not exert as much inhibitory control over the heart in late life [36]. Heart rate variability, or the inconsistency of the interval between heart beats, indexes vagal tone. Higher heart rate variability signifies the ability to flexibly adapt to a changing environment. In contrast, low heart rate

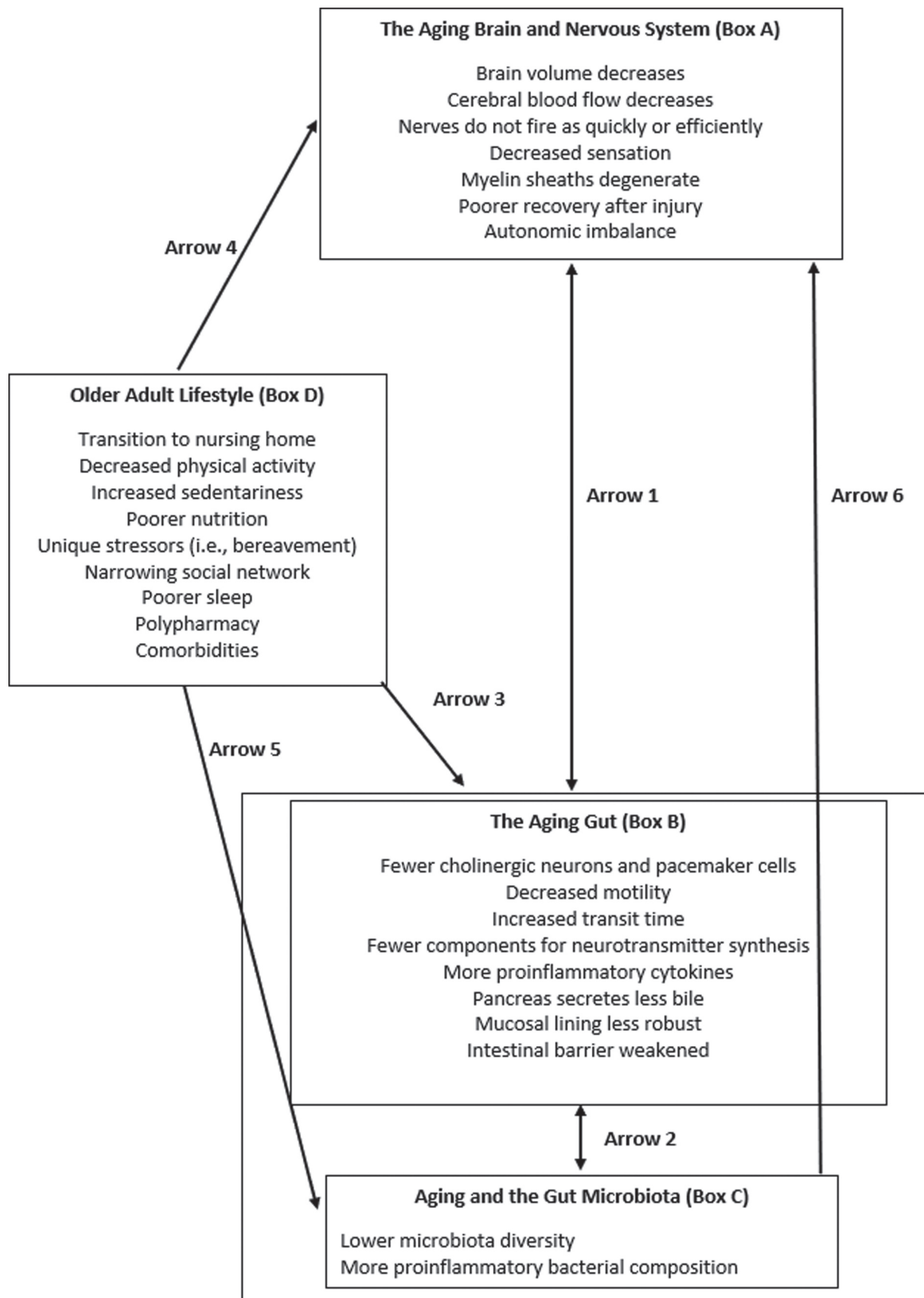


Fig. 1. Iterative Relationships between Aging, the Gut and its Microbiota, and the Nervous System. Age and age-related behaviors mold neurological (Arrow 4) and gastrointestinal aging (Arrow 3), thereby determining which gut micro-organisms can reside there (Arrows 2 and 5). In turn, the gut microbiota facilitate gut-brain communication (Arrow 1) and shape neurological aging trajectories (Arrow 6), either defying steep age-related decline and disease or cementing pathology.

variability, or a metronomic heartbeat, foreshadows a variety of age-related diseases and early mortality [37,38]. With age, heart rate variability reliably decreases [36]. Simultaneously, sympathetic nervous system activity increases, as evidenced by increasing systolic blood pressure [39]. The combination of high sympathetic activity and low parasympathetic activity denotes autonomic imbalance, which taxes the body by promoting heightened and prolonged stress responses – even in contexts in which there is no immediate threat. Notably, this age-related autonomic imbalance is gut-relevant, as parasympathetic and sympathetic nerve bundles innervate the enteric nervous system. Older adults' sympathetic dominance may fuel many age-related issues, including constipation, appetite changes, hypertension, erectile dysfunction, and insomnia.

Paralleling the GI motility deficits noted above, the geriatric colon has fewer enteric neurons and pacemaker cells (i.e., interstitial cells of Cajal), fewer components involved in neurotransmitter synthesis, and more proinflammatory cytokines [17]. In particular, aging decreases the number of cholinergic neurons, which are responsible for contraction, especially in the distal colon, but spares nitrergic neurons, which control smooth muscle relaxation [40]. Compared to younger individuals, the elderly have more abnormal enteric ganglia with “cavities” [41], suggestive of neurodegeneration.

Taken together, prior research demonstrates that some neurological and GI structural and functional decline is expected even in healthy aging, potentially rendering gut-brain communication less efficient or effective. However, poor health behaviors can aggravate age-related deterioration, in some cases promoting GI or neurological diseases, or both. The gut microbiota responds to age-related behavioral and environmental shifts and may help to drive these resulting physiological changes.

5. Age-related factors

Compared to genetics, environmental factors exert a much stronger influence on the gut microbiota [42]. The elderly have profound lifestyle and environmental changes that mold the gut microbiota (Fig. 1, Box D). Examples include sedentary living, fewer social connections, medications, sleep difficulties, and stressors that are largely unique to this age group (e.g., spousal bereavement, caregiving, health concerns), which we discuss in this section. Older adults in the West, in particular, often have lifestyles that undermine gut microbiota health and stability including an inflammatory diet, repetitive antibiotics use, and polypharmacy – detailed below. Because these changes are so entwined with chronological age itself, it is difficult to tease out the pure effect of age versus the effect of age-related factors on the gut microbiota. However, some older adults deviate from these norms, maintaining a highly active and engaged lifestyle, which can explain some of the variance in biological aging, physical and mental health, and gut microbiota composition among people of the same age. Simply put, poor health behaviors can accelerate the aging process. Fortunately, health behaviors are modifiable, representing a window of opportunity to shift gut microbiota composition and influence gut-brain axis function. This section explores age-related environmental and lifestyle influences on the GI and neurological outcomes (Fig. 1, Arrows 3–5).

5.1. Place of residence

The elderly population is unique in that a notable proportion of individuals transition from the community to nursing homes. Although only about 5% of older adults live in a nursing home at any given time, stints in nursing home facilities become more common with age; for instance, the probability of living in the community is about 100% for a 50-year-old, but declines to less than 50% for a 95-year-old [43]. When tracked over time, a 50-year-old has between a 53% and 59% chance of ever staying in a nursing home, and this percentage is higher for females [43]. Those who enter into nursing homes do so around age 76 and stay

for just over one year, on average [43], although many stay for much shorter stints to rehabilitate after surgery.

Nursing home care has evolved in the U.S. with increased programming, socialization, and cognitive stimulation than in past decades [44]. Even so, when older adults who are not cognitively impaired transition to a nursing home, they can experience “relocation stress syndrome,” or a constellation of symptoms such as anxiety, confusion, and loneliness. Unfortunately, this stress can persist and develop into depression: one year-long study among Norwegian nursing home residents found that 21% had clinically significant depressive symptoms at baseline and follow-up, 45% of them continued to be depressed at follow-up, and 15% developed clinically significant depressive symptoms; even worse, depression predicted mortality [45].

Depression, especially when chronic, can foreshadow and accompany cognitive decline [46]. Moreover, despite nursing home directors' best efforts, residents' diet, physical activity, socialization, and daily activities may be more circumscribed and less self-directed than community-dwellers', which can harm neurological and cognitive function [44]. Indeed, a prospective population-based study followed non-demented community-dwelling elderly individuals for 22 years and found that those who transitioned to a nursing home had steeper cognitive decline before and after institutionalization compared to their peers who continued to live in the community, and these results were robust to the exclusion of those who developed dementia [44].

Gut health may deteriorate after the transition to nursing homes as well, perhaps due to sedentariness and limited dietary choices. A study of 178 Irish elderly individuals ($M = 78$ years old) found that community-dwellers' – but not long-term care residents' – gut microbiota was very similar to healthy young individuals' [47]. Length of duration of long-term care was negatively associated with microbiota diversity [47], suggesting a causal relationship. Additionally, long-term care residents had elevated inflammatory markers and poorer health [47]. Although not well studied, these gut microbiota shifts may have functional consequences: for instance, over a three-month period, 7% of nursing home residents developed constipation [48]. Increasing the complexity of maintaining homeostasis, polypharmacy, discussed in greater detail below, is common among nursing home residents. In one nationally-representative sample of U.S. nursing home residents, individuals took eight medications per day, on average [49].

Even though those who are more physically and cognitively impaired are more likely to enter long-term care, this line of research suggests that the nursing home lifestyle itself may contribute to decline – despite recent programming improvements. Nursing home living is riddled with other risk factors for accelerated GI and neurological aging that are detailed below, such as polypharmacy, antibiotic use, limited diet, and sedentariness, and therefore it is a multipronged risk factor that demonstrates the impact of older adults' lifestyle on the aging process.

5.2. Diet

In older age, diet tends to be more restricted, rendering it difficult for older adults to meet their nutritional needs. Altered sensory and perception, depression, cognitive decline, or living alone can fuel dietary changes. Older adults' propensity for disordered eating behavior, termed anorexia of aging [50], can lead to under- or even mal-nutrition, weakened immune function, and frailty [12]. The prevalence of age-related anorexia is 25% in community-dwellers and a disturbingly high 85% in nursing home populations [50], and most treatments are ineffective. Not surprisingly, malnutrition is also more common among nursing home residents, as 6% of community-dwellers and 14% of nursing home residents suffer from malnutrition [51]. Whereas over-eating, weight gain, and obesity often drive morbidity and mortality among younger adults, undereating, weight loss, and malnutrition do so among older adults.

Further complicating matters is that older and younger adults' nutritional needs differ. One reason is that inflammation is

metabolically costly, and even in the absence of disease, chronic low-grade inflammation in late life is the norm. For instance, one common inflammatory marker that portends cardiovascular risk, C-reactive protein, doubles between ages 25 and 55 [52]. Chronic diseases like arthritis, acute diseases like pneumonia, or acute injuries like a broken bone further elevate inflammation, often leading to disease-related malnutrition [53]. This state is closely tied to neurodegeneration, as inflammation and related malnutrition accompany and worsen neurological disorders [53]. In contrast, anti-inflammatory diets with an abundance of fresh fruits and vegetables, such as the Mediterranean-Dietary Approach to Systolic Hypertension (MIND) diet, are associated with slower age-related cognitive decline and reduced Alzheimer's disease risk [54,55]. Those who were the most adherent to MIND dietary principles were, on average, 7.5 years younger in cognitive age, than those who were the least adherent [55].

The gut microbiota plays an important intermediary role in the diet-disease pathway. In fact, diet powerfully shapes the gut microbiota composition. Even a short-term dietary manipulation shifted gut microbiota composition, but shortly after the dietary manipulation ended, it reverted back to its initial state [56]. Therefore, longer-term dietary changes may be necessary for more permanent microbial community changes. For instance, in an impressive, five-country year-long Mediterranean diet intervention among pre-frail or non-frail elderly participants, those who adhered to the diet had bacterial taxa associated with lower frailty and inflammation, improved cognitive function, and increased short-chain fatty acid production, suggesting that longer-term dietary changes can promote healthy aging through microbiota alterations [57]. In fact, diet may help to explain the differential microbiota profiles of nursing home residents and community dwellers: in one study, nursing home residents ate a low fiber, high fat diet and community-dwellers ate a high fiber, low-to-mid fat diet, and these dietary differences explained variance in gut microbiota composition [47]. Adjusting for place of residence, diet predicted health, and this relationship was mediated by microbiota diversity [47]. Taken together, the significant alteration in dietary habits and nutritional status observed in older adults likely explains much of the variance in microbiota composition, and ultimately health outcomes.

5.3. Stressors

Although resilience, positive emotions, and emotional well-being increase with age [58], elderly individuals experience many stressors. Among Taiwanese older adults, perceived stress decreased with age while stress exposure increased [59]. In fact, perceived stress and stress exposure were only weakly correlated, with health-related stressors most predictive of stress perceptions [59]. In another study, the most commonly reported stressors among community-dwelling older adults were declines in mobility, concern for the world, pain, and wanting to spend more time with children or grandchildren [60]. Older adults, especially those facing health challenges, may experience end-of-life related distress and concerns about being burdensome, which increase risk for lethal suicide attempts. Other common stressors experienced by the elderly are caregiving and spousal death.

Bereavement and other late-life stressors may shape cognitive and neurological aging trajectories. Bereaved adults performed worse on a cognitive test battery that assessed attention, processing speed, and verbal fluency, compared to age-, gender-, education-, and intelligence-matched peers [61]. Importantly, bereaved adults' poorer mood fully accounted for these cognitive differences [61]. A longer-term stressor in late life is caregiving for a spouse, especially a spouse with dementia, a chronic and progressive disease that can require round-the-clock care. There is mixed evidence concerning caregiving's effect on cognition, with some finding a negative effect [62–64] and others finding a positive effect [65], likely due to several methodological and sample differences, including caregivers' age. Mechanistically, chronic stress can accelerate the immune system's aging process and promote chronic low-grade

inflammation. Although inflammation naturally rises with age, our lab found that spousal dementia caregivers had quadruple the rate of increase of a common inflammatory marker over a six-year period compared to noncaregivers [66]. This peripheral inflammation tracks with inflammation in the central nervous system [67], which facilitates neurodegeneration [68]. Also, depression, which itself is intimately tied to inflammation, may also mediate cognitive decline [64].

The GI impact of late-life stressors has not been well-studied. Over thirty years ago, one research team observed that bereaved older adults had a greater number of GI illnesses than controls [69], but little subsequent research among older adults has built on this finding. In a more recent study with middle-aged caregivers of patients with chronic diseases, a shocking 49% had irritable bowel syndrome [70], demonstrating the strong connection between chronic stress and GI health throughout the lifespan. More data are needed to track older adults' GI health related to life stressors, but it is possible that stress synergistically interacts with older age to harm gut health. No stressors common to late life have been explored in relation to the microbiota. However, in both mice and undergraduates, both social and non-social stress impacts the gut microbiota's composition [5,71]. Stress-related shifts in the gut microbiota may promote parallel cognitive, neurological, and GI decline among caregivers and bereaved individuals – a theory worth testing.

5.4. Narrowing social network

On average, social networks shrink in late life, as older adults prioritize the most emotionally meaningful relationships rather than new or less important relationships [72]. Consequently, having fewer social ties is not inherently pathological, unless the older individual feels lonely — defined as a discrepancy between desired and actual quantity and depth of relationships [73]. Meta-analytic evidence indicates that loneliness is as stable as personality traits throughout the lifespan [74]. Loneliness decreases throughout childhood and remains stable throughout adolescence, midlife, and late life [74]. Regardless of prevalence, loneliness in mid to late life can accelerate the aging process and promote mental and physical pathology. Concurrent loneliness and life stress can synergistically undermine health. Loneliness can speed hippocampal neurodegeneration and cognitive decline [75,76]. Among cognitively-normal older adults, greater loneliness was associated with more tau pathology in the right entorhinal cortex, a neurological correlate of Alzheimer's disease [77].

Loneliness's physical health consequences are well-mapped [73], but its relationship with gut disorders is not. That said, among animals and humans, social relationships relate to the gut microbiota. In wild baboons, rates of social interaction predicted composition of the gut microbiota, independent of diet, kinship, and shared environment [78]. Similarly, socially-transmitted gut microbiota seeds the microbiota of young adult bees, protecting them from parasitic infection [79]. Cohabiting humans share microbiota [80,81], with implications for those living alone as well as in long-term care facilities. Moreover, the quality of relationships matters more so than simply living together and having similar health behaviors: even after accounting for dietary factors, couples who report close relationships, but not those with more distant relationships, had more similar gut microbiota than siblings, suggesting that sustained intimate relationships affect the microbiota [82]. This similarity is one mechanism behind marriage's influence on health and the aging process [83].

5.5. Sedentariness and lack of physical activity

Sedentary lifestyles are common among the elderly. Both subjective and objective measurements reveal the magnitude of sedentary living, although self-reported sitting time is often underestimated. Whereas 60% of adults aged 60 and over reported sitting for more than four hours per day, an objective measure found that 67% were sedentary for more than 8.5 h daily [84].

There is sufficient evidence to implicate sedentariness in early mortality, metabolic syndrome, and obesity among older adults [85]. Additionally, one meta-analysis found that sedentary behavior was associated with an increased risk of dementia [86]. Findings from randomized, controlled trials featuring exercise interventions largely support the idea that physical activity causally influences cognitive function among older adults [87]. Specifically, moderate intensity aerobic and resistance training lasting 45–60 min per session several days per week achieves the greatest cognitive benefit [87]. Exercise interventions may have the most noticeable impact on executive function among the oldest-old [88]. Shedding light on potential mechanisms, sustained aerobic exercise programs may boost brain-derived neurotrophic levels and lessen neuroinflammation among those with neurological disorders, fostering nervous system plasticity and repair [89,90].

Paralleling exercise's neurological benefit, gut health also improves. Among healthy young adults in a crossover trial, individuals had faster whole gut transit times when they spent one hour per day jogging (34 h) or riding a bicycle (37 h) than when they spent the same hour sitting (51 h) [91]. More frequent and consistent bowel movements rid the intestines of toxins, and therefore repeated low- to moderate-intensity exercise can halve colon cancer risk [92]. It also may reduce the risk of diverticulosis and inflammatory bowel disease [92]. Exercise can also lessen symptoms in those with active GI disease and lower recurrence risk in those with remitted GI disease. In a 6-month observational study among those with remitted inflammatory bowel disease, those who exercised more had a decreased risk for relapsing [93]. Additionally, a ten-week moderate-intensity running program among those with inflammatory bowel disease boosted health-related quality of life by 19% and significantly improved bowel symptoms, compared to those who were randomized to activity as usual [94].

The gut microbiota responds to exercise. Women who meet the daily physical activity threshold set by the World Health Organization exhibit more health-promoting bacteria than their sedentary peers [95]. Moreover, the microbiota of professional athletes differs not only in composition, but also in functionality of that of sedentary individuals [96]. Specifically, the microbiota of athletes was better able to synthesize amino acid, metabolize carbohydrates, and produce short-chain fatty acids, factors associated with elevated muscle turnover and health [96].

5.6. Sleep

Many older adults experience nontrivial sleep difficulties, going to bed and rising an average of two hours earlier, waking more frequently during the night, and having less deep, slow-wave sleep, than younger adults [97]. A study of 9000 participants aged 65 and older revealed that a majority of elderly reported at least one enduring sleep complaint [98]. In a longitudinal study of 6899 adults aged 65 and older, 38% reported symptoms of insomnia at baseline and an additional 15% did so three years later [99].

Sleep is an important time for memory consolidation and nervous system maintenance and repair. Thus, poor sleep is a risk factor for cognitive decline and dementia. In one European multicenter study, mid- and late-life insomnia were associated with increased risk for dementia; importantly, long sleep duration was also a risk factor, suggesting that there is an optimal mid-range sleep duration [100]. In particular, less rapid-eye movement (REM) sleep predicted incident dementia; dementia risk increased by 9% with each percentage decrease in REM sleep [101]. Also, sleep-disordered breathing (i.e., sleep apnea) can fuel poor sleep, often waking people multiple times per hour. Compared to elderly women without sleep-disordered breathing, those with sleep-disordered breathing were more likely to develop mild cognitive impairment or dementia over the next five years (31% vs. 45%, respectively) [102]. Disturbed sleep is also associated with an increased risk for functional GI disorders, particularly irritable bowel syndrome [103].

Again, the gut microbiota may be one culprit of these sleep-related neurological and GI outcomes. Gut bacterial composition, function, and gene expression fluctuate throughout the day and night, in accordance with sleep schedule, meals, and activity level [104]. Although short-term sleep restrictions may not impact the gut microbiota [105], longer-term sleep matters: over a one-month period, adults who slept more, awoke fewer times throughout the night, or spent a greater proportion of their time in bed asleep (i.e., sleep efficiency) had higher gut microbiota diversity, which correlated with more cognitive flexibility [106]. Additionally, greater sleep efficiency was correlated with more richness in certain bacterial phyla, which also related to an inflammatory marker and abstract thinking [106], suggesting that sleep, gut bacteria, immune function, and cognition are all linked. A sleep deficiency can also fuel poor dietary choices, which themselves can impact the gut microbiota as discussed above.

Notably, the link between sleep and the microbiota may be bidirectional. Meta-analytic evidence indicates that probiotic treatment, especially treatment with one strain of bacteria for at least 8 weeks among healthy participants, improves self-reported, but not objective, sleep quality [107]. Thus, the jury is still out on whether the sleep-gut microbiota connection is self-reinforcing.

5.7. Polypharmacy

Thirty percent of all pharmaceuticals are prescribed to the elderly [108]. Many older individuals must manage multiple chronic conditions with numerous, potentially interacting medications. Almost 40% of U.S. nursing home residents take nine or more medications [49], and over 35% of ambulatory elderly adults use at least five prescription medications [109]. Some of these medications may be unnecessary; studies of both outpatient and in-patient older populations conclude that around half take unnecessary medication [110,111]. This pervasive medication usage impacts the microbiota; in hospitalized elderly patients, number of drugs was negatively correlated with microbiota diversity, and medication usage was associated with the abundance of 15 taxa [112]. In particular, proton pump inhibitors (PPIs; over-the-counter medications that significantly block gastric acid release) and psychiatric medication had the strongest association with single taxa abundance [112]. Polypharmacy is especially problematic among the elderly because the liver's volume and blood flow decreases with age, impairing the body's ability to clear drugs that are metabolized in the liver [13].

Because infections are common in the elderly and carry a higher risk of complications and death than they do in younger adults, the threshold for antibiotic therapy is quite low. An analysis of Medicare Part D prescription data from 2007 through 2009 revealed significant regional differences in rates of antibiotic use among the elderly with the highest (21%) in the South and the lowest (17%) in the West [113]. An antibiotic's effect on the gut microbiota depends on which organisms it targets as well as its intestinal absorption; generally speaking, broad-spectrum antibiotics that are poorly absorbed in the small intestine can substantially reduce microbiota diversity – a change that is not easily remedied and can set the stage for opportunistic infections [114].

GI medications may amplify neurological consequences of aging. For example, PPIs are more widely and chronically used among the elderly to remedy heartburn or gastroesophageal reflux (<10% use among young adults versus almost 40% use among those over 80) – with rates increasing each year [115]. PPIs decrease stomach acidity to such an extent that remarkable shifts in the gut microbiota occur [116], potentially impacting gut-brain communication. They can cross the gut barrier and blood-brain barrier, and once in the brain, they can facilitate the accumulation of amyloid beta proteins [117] – a biological signature of dementia. Also, because PPIs alter nutrient absorption, they can contribute to nutrient deficiencies that impair cognition (i.e., Vitamin B12). Indeed, emerging findings link PPI usage with increased risk for dementia and cognitive complaints – especially among individuals who are older [118] or more vulnerable (e.g., breast cancer survivors [119]).

Beyond PPI usage, a 12-year case-control study among the South Korean community-dwelling elderly revealed that the odds of developing dementia increased significantly with each additional prescribed medication [120].

6. The impact of gut microbiota on neurological aging

The above evidence suggests that aging and age-related health behaviors impact GI and neurological health as well as the gut microbiota. Cutting-edge research positions the gut microbiota as a central node, and perhaps even a causal driver, of these age-related disease outcomes. In this section, we attend to evidence suggesting that the gut microbiota influences neurological function (Fig. 1, Arrow 6).

6.1. The central nervous system

Early in life, the gut microbiota plays a critical role in the formation and maintenance of neurons, microglia maturation and ongoing function, myelination, and the formation of the blood-brain barrier [121–124]. Studies in germ-free or antibiotic-treated young animals demonstrate that the gut microbiota regulates CNS development; these animals have dysregulated neurotransmitter systems as well as deficiencies in learning, memory, recognition, and emotional behavior [125]. Aging corresponds with poorer microglial and blood-brain barrier function, suggesting that the gut microbiota is a potential mechanism of cognitive decline in the elderly.

To date, the most convincing evidence of the gut microbiota's causal influence on the brain and behavior comes from two types of interventions: microbiota transfer therapy and probiotic therapy. Some experimental paradigms have humanized a previously germ-free rat GI tract via the transplantation of human fecal matter. In these studies, fecal matter from an anxious or depressed human triggers anxiety- and depressive-like behaviors in rats [4,126]. Our two-year observational study among primarily middle-aged women indicated that those with more permeable gut barriers at baseline reported more depressive symptoms one and two years later, compared to their peers with better barrier function [127]. Although fecal microbiota transfer therapy provides a better test of causality, it is challenging due to the risk of adverse events even with careful donor screening. Despite these obstacles, in an open-label trial of microbiota transfer therapy among children with autism, GI and autism symptoms significantly improved [128]. Intriguingly, two years post-transplant, GI health and microbiota diversity was preserved while autism symptoms continued to improve [128]. Among older patients with liver cirrhosis, fecal microbiota transplants were well-tolerated with fewer hospitalizations and better cognitive function even months after the transplant [129].

There is also some preliminary evidence that probiotic supplementation can boost neurological and cognitive function. In one study, probiotics restored the integrity of the intestinal wall [130], effectively reducing systemic inflammation. Probiotics may also keep pathogenic bacterial populations in check. In one randomized controlled trial among community-dwelling older adults, 12 weeks of probiotic supplementation reduced the abundance of proinflammatory gut bacteria, boosted brain-derived neurotrophic factor, and increased cognitive flexibility [131]. Similarly, another randomized, double-blind, placebo-controlled trial showed that multiple sclerosis patients who received probiotics were less disabled and depressed and had lower inflammatory and oxidative stress markers after 12 weeks of supplementation [132]. Even so, there is conflicting meta-analytic evidence about whether probiotics bolster cognitive function among those with dementia or mild cognitive impairment [133,134].

6.2. Autonomic nervous system

The gut microbiota also interacts with the peripheral nervous system, most noticeably the autonomic branch. Remarkably, gut bacteria can

recognize and respond to human stress hormones [135], which may help to explain remodeled gut environments and opportunistic gut infections during periods of stress. Even more intriguingly, gut bacteria can release neurotransmitters such as GABA and serotonin, as well as catecholamines in the gut lumen [136]. Gut bacteria also release short-chain fatty acids, products of dietary fiber fermentation in the large intestine, which can regulate sympathetic nervous system activity [137]. Rat models suggest that probiotics can reduce the sensitivity, or prevent stress-induced hypersensitivity or excitability, of enteric neurons [138].

Autonomic imbalance, or too much sympathetic activity and too little parasympathetic activity, can result in hypertension. High sympathetic drive may promote hypertension while also stiffening the gut, decreasing GI blood flow, and unfavorably shifting bacterial communities [139]. Indeed, hypertensive patients have less diverse and less rich gut microbiota communities [140], and there is preliminary evidence that correcting this microbiota imbalance with the antibiotic minocycline [141] or probiotics [142] can normalize blood pressure. Of note, one randomized, triple-blind, placebo-controlled trial among hypertensive women showed that probiotic supplementation reduced sympathetic dominance, helping to restore balance to the autonomic nervous system [143].

In the other direction, the sympathetic nervous system not only innervates the enteric muscles, but also the gut mucosa and gut-associated lymphoid tissue where the gut's immune system resides. Through its extensive, multilevel control over the gut environment, the sympathetic nervous system can modulate intestinal inflammation [144], thereby helping to determine which gut microbes will survive and thrive. In contrast, a principle component of the parasympathetic nervous system, the vagus nerve, can dampen peripheral inflammation and reduce intestinal permeability [145], perhaps also impacting the gut microbiota. The vagus nerve facilitates communication between gut bacteria and the brain, and in animal models, severing the vagus nerve often circumvents the behavioral and mood-related benefits of probiotic supplementation [146]. In short, the relationship between the autonomic nervous system and gut microbiota is multifaceted and recursive.

7. Future directions

The above evidence suggests that promoting a diverse, resilient, and anti-inflammatory gut microbiota may facilitate healthy neurological aging, largely preserving cognitive and neurological function well into late life. Although certain bacterial species (e.g., those that produce lactic acid and short-chain fatty acids) promote general health, the science has not yet progressed to having robust converging evidence linking certain probiotics as treatments or preventatives for specific neurodegenerative diseases. Identifying exactly which microbes reduce or increase risk for certain diseases is challenging because their function may be more important than their mere presence, and their importance may depend on their interaction with other microbes. Much more research is needed before targeted probiotic therapy is a primary or even supplementary treatment or preventative strategy.

Also, fecal microbial transplants will only become more widely validated and accepted as a viable treatment strategy for neurological disorders if there are more randomized, blinded, controlled trials with careful tracking and reporting of adverse events, rather than open-label, uncontrolled trials. In particular, adverse events should be linked with both donor and recipient characteristics to aid in better screening and risk factor identification.

Besides probiotics or a more invasive fecal microbial transplant, certain health behaviors like exercise can shift the gut microbiota composition in a pro-health direction. In this research domain, one five-country European randomized, controlled trial is particularly noteworthy because it correlated Mediterranean diet adherence with gut bacteria as well as inflammation and cognitive function [57], suggesting that diet-associated gut microbiota shifts are partially responsible for healthy neurological aging outcomes. To truly harness the gut

microbiota's power over healthy aging trajectories and learn to control it via health behavior modifications, more research like this is needed.

8. Conclusions

There is no ubiquitous neurological aging process; instead, an individual's late life functionality depends on multiple interactive factors, some of which are modifiable (e.g., health behaviors). Emerging evidence indicates that despite its distance from the brain, the lower GI tract is intimately linked to brain health. In particular, the gut microbes that reside there facilitate communication between the gut and the brain, and therefore may play a central role in neurological aging. As such, exploring what influences and results from microbe-facilitated gut-brain communication is a vast new frontier for translational science and ultimately preventative medicine. Certainly, the gut microbiota is defined, in part, by the aging process and age-associated lifestyle factors (and less so by genetics), but it may also be channeled to defy the steep late-life neurological decline that is prevalent in the West, which often includes neurodegenerative disease. Thus, the gut microbiota is deeply entwined with neurological aging: it is both age-defined and age-defying.

Conflicts of interest

Declarations of interest: none.

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