

Chapter 8

Gut Microbiota and Microbiota-Related Metabolites as Possible Biomarkers of Cognitive Aging



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1 Gut Microbiota and Cognitive Aging

1.1 *The “Gut-Brain Axis” in Dementia*

In the last decade, several studies have highlighted that the intestinal microbiome, i.e. the ensemble of bacteria symbiotically living with the host in the gut lumen, may influence the physiopathology of a large number of human diseases, not involving only the gastrointestinal system [1–3]. For example, alterations of the composition of gut microbiota may promote the progression of chronic liver disease [4], chronic renal failure [5] and even the formation of kidney stones [6]. By modulating insulin sensitivity, anabolism and systemic inflammation, the gut microbiota could also have relevance in the onset of age-related bone diseases and sarcopenia [7, 8].

In this context, the existence of a possible “gut-brain axis” influencing cognition in aging has been hypothesized [9, 10]. A large number of animal studies, recently reviewed elsewhere [10], have demonstrated that alterations of the gut microbiota composition, the so-called dysbiosis, can be associated with reduction of performances at cognitive tasks and, conversely, the administration of probiotics or

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functional foods can prevent cognitive decline in transgenic models of Alzheimer's disease. The hypothesized mechanisms involved in these phenomena include bacterial production of amyloid proteins able to promote β -amyloid deposition in the brain tissue, modulation of vagal nerve activity, production of bacterial metabolites that may act as endocrine modulators or neurotransmitters, modulation of neuroinflammation and microbiota-mediated transformation of nutrients into substances exerting toxic or protective activity on brain cells [10, 11].

Therefore, the current scientific literature suggests that the intestinal microbiome can influence the onset of dementia and its progression in multiple ways, making the "gut-brain axis" a promising area of research for the future.

1.2 Clinical Relevance of the "Gut-Brain Axis" in Humans with Dementia

Despite the results of pre-clinical studies, the translation of the "gut-brain axis" concept into human health is still uncertain. In fact, only a few investigators have comprehensively compared the intestinal microbiota composition of older patients with cognitive complaints (ranging from mild cognitive impairment to overt dementia) with that of healthy active older subjects (Table 8.1). The results of these studies suggest the presence of reduced gut microbiota biodiversity (i.e., lower numbers of species) and specific compositional signatures, such as over-representation of *Bacteroides* and Enterobacteriaceae and under-representation of *Dialister*, in subjects with cognitive symptoms [12–15]. In the largest of these studies, comparing the fecal microbiota composition of 34 older patients with dementia and 94 age-matched controls, dementia was associated with increased biodiversity, reduced representation of *Bacteroides*, and an increased Firmicutes/Bacteroidetes ratio [16]. These associations were independent of other known biomarkers of dementia, including ApoE ϵ 4 polymorphism, presence of lacunar infarcts at brain computed tomography (CT) or amyloid deposition detected by positron-emission tomography (PET) [16].

These findings, although promising, should be interpreted with caution. Most of the existing studies were observational, with a cross-sectional design preventing to draw solid conclusions on causal inference. Low sample sizes of these studies also represent an issue (Table 8.1) and generalizability to the general population with cognitive impairment or dementia is not automatic.

These limitations could be overcome by rigorous and well-designed intervention studies, implying the manipulation of the intestinal microbiome by administration of probiotics or functional foods. However, despite the large number of human trials with pre- or probiotics, studies specifically focused on dementia are still lacking [17]. The few studies published to date included only subjects without cognitive complaints [17] or with advanced dementia [18–20], and thus had a low chance of detecting significant variations in cognitive performance. Moreover, the investigators

Table 8.1 Overview of the main human studies comparing the fecal microbiota composition between subjects suffering from dementia or cognitive symptoms with healthy older subjects

First author, journal, year, [Ref]	Setting and country	Number and characteristics of participants	Mean age	Gut microbiota-related parameters differing between cases and controls	Implications
Cattaneo A, Neurobiol Aging, 2017 [12]	18 memory clinics in Northern Italy	73 patients with dementia (40 amyloid-positive and 33 amyloid-negative) 10 controls	71 ± 7 (cases) 68 ± 8 (Controls)	Abundance of <i>Eubacterium rectale</i> (anti-inflammatory) Abundance of <i>Escherichia/Shigella</i> (pro-inflammatory)	The fecal microbiota of patients with dementia has a higher pro-inflammatory activity than controls
Vogt NM, Sci Rep, 2017 [13]	Memory Clinic and Registry for Prevention of Alzheimer's disease in the United States	25 patients with Alzheimer's disease 25 controls	71 ± 7 (cases) 69 ± 8 (controls)	Overall biodiversity (α -diversity) Inter-individual variability (β -diversity) Abundance of the Firmicutes and Bacteroidetes phyla Abundance of 13 taxa, including <i>Bifidobacterium</i> , <i>Alistipes</i> , <i>Bilophila</i> and <i>Clostridium</i>	Subjects with Alzheimer's disease have a distinct composition of fecal microbiome, with reduced biodiversity and abundance of putative anti-inflammatory taxa
Manderino L, J Int Neuropsychol Soc, 2017 [14]	Community recreation and wellness center in the United States	43 healthy community dwellers (25 with intact cognitive functions and 18 with previously unknown mild cognitive impairment)	64 ± 7	Abundance of 4 bacterial phyla (Bacteroidetes, Firmicutes, Proteobacteria, Verrucomorbia)	The gross composition of fecal microbiota in terms of phylum abundance is correlated with cognitive performance; the strongest correlation is observed for Verrucomorbia abundance
Zhuang ZQ, J Alzheimers Dis, 2018 [15]	4 hospital outpatient clinics in China	43 patients with dementia 43 controls	70 ± 9 (cases and controls)	Inter-individual variability (β -diversity) Abundance of several species including <i>Bacteroides</i> , <i>Actinobacteria</i> , <i>Ruminococcus</i> , <i>Lachnospiraceae</i> , <i>Selenomonadales</i>	Subjects with dementia have a distinct fecal microbiota composition than controls at both community and species level
Saji N, Sci Rep, 2019 [16]	Memory clinic in Japan	34 patients with dementia 94 controls	76 (interquartile range 69–81)	Overall biodiversity (α -diversity) Firmicutes/Bacteroidetes ratio Abundance of <i>Bacteroides</i> , <i>Bifidobacterium</i> and Lactobacillales	The gut microbiota composition was associated with the status of suffering from dementia independently of other known and well-established biomarkers of dementia

in these studies concentrated on microbiological and inflammation-related, rather than on clinical outcomes [18–20]. In the only study which assessed cognition as the primary outcome, the intervention consisted in a 12-week resistance training program associated with the administration of a *Bifidobacterium* spp blend, so that the improvement of executive functions detected in the intervention arm could not be attributed with complete certainty to the benefits of gut microbiome manipulation [21].

In this scenario, the possibility of obtaining a clinically relevant modulation of cognitive symptoms with microbiome-targeted interventions in older patients still remains speculative.

1.3 Gut Microbiota at the Cross-Road Between Environment and Human Pathophysiology

An increasing body of evidence suggests that the human microbiome composition is strongly influenced by environmental factors [1]. These factors include dietary patterns and habits [2], exercise [22], drugs [23, 24], the presence of diseases [23, 24], climate and pollution [25]. Moreover, the gut microbiota composition is shaped in each human being according to his or her genetic background, and is greatly influenced by immune system functionality [1, 20]. Aging itself represents a process able to influence the gut microbiota composition in an independent way, implying a progressive reduction of biodiversity and resilience to stressors [26]. Finally, growing evidence indicates that the output of metagenomics analyses of fecal microbiota is dependent on the bacterial load, which is ultimately associated with stool moisture [27, 28]. Intestinal motility, number of bowel movements and hydration status are thus important variables influencing the microbiome composition.

In the largest population-based study to date, investigating the human gut microbiota composition and its determinants, the authors were able to identify a long list of environmental factors associated with a distinct microbiological signature [29]. These results put into question the role of the intestinal microbiome as an independent mediator of human health and disease. They also suggest the existence of complex relationships between the environment and the host physiopathology, with gut microbiota possibly positioned at the cross-road [8, 30]. In fact, it is very difficult to consider all of the possible environmental factors influencing the microbiome composition, acting as potential confounders in pathophysiological associations [1, 30].

From a clinical perspective, this means that the disease-associated microbiome alterations most likely represent only one component of a large network of pathophysiological factors [30]. It also helps to understand why microbiome-targeted interventions, including administration of probiotics and functional foods, rarely provide clinically significant results outside the field of gastroenterology. If the microbiome is a cross-road mediator between the environment and host pathophysiology, then environmental interventions have a greater potential of influencing dis-

ease onset and course than microbiome manipulations targeted to a single or a limited number of bacterial species.

Despite these possible limitations, the intestinal microbiome remains a promising target for anti-aging interventions [31], particularly in the field of cognitive disorders, in which studies conducted in mouse models have provided encouraging results [10]. However, much research must still be done before we can recommend therapeutic strategies centered on the microbiome for patients with cognitive impairment, mainly because of objective difficulties in identification and preparation of probiotic blends or functional foods able to induce significant modification in the overall structure of gut communities [32].

Possibly, the nearest goal in this field of medicine is the use of gut microbiota composition and gut microbiota-related metabolites as biomarkers of disease. The existing studies exploring the relationship between microbiome and dementia highlight that a certain number of abnormalities in microbiome composition and functionality may be of potential interest as biomarkers. To be useful as biomarker of cognitive function, a physiological parameter should be measurable, correlated with cognitive performance or other indicators of cognitive impairment, able to predict the onset and course of cognitive impairment as well as the therapeutic response to treatments [33, 34]. Correlation with other measures of disease and prediction of outcomes are thus necessary before a biomarker can enter into clinical practice [33, 34]. Unfortunately, most of the research on the gut-brain axis has been focused on correlations rather than predictions [1]. However, there are many microbiome-related parameters deserving careful evaluation as possible biomarkers of cognitive aging in future studies.

2 Gut Microbiota Composition as Biomarker of Cognitive Function

2.1 Microbiome Biodiversity

The latest next-generation sequencing techniques (16S rRNA microbial profiling, shotgun metagenomics) allow detection of virtually all different taxa harbored in biological samples [35, 36]. After bioinformatics processing, the output of these analyses retrieves several indexes of biodiversity, such as the Shannon Index, the Simpson Index or the Chao1 Index [37]. In microbial ecology, biodiversity (also called alpha diversity) is defined as species richness and relative species abundance in space and time [38]. Thus, the more elevated are biodiversity indices, the higher is the number of species harbored in the fecal sample [37].

A high fecal microbiome biodiversity is generally considered to be a marker of good health status, implying a virtuous symbiotic equilibrium between microbial communities and host [3]. Conversely, reduced fecal microbiome biodiversity is generally associated with poor health status, and represents the main feature of gut

microbiota dysbiosis [3]. For example, studies performed in patients with critical illnesses admitted to intensive care units globally show a high level of fecal microbiota dysbiosis, with reduced species richness [39]. Moreover, older patients with prolonged hospital stay who develop *Clostridium difficile* infection, one of the most frequent healthcare-associated infections, exhibit a reduced level of fecal microbiota biodiversity, compared with those who have milder health problems and shorter hospital stays [40].

However, an elevated fecal microbiota biodiversity is not necessarily associated with a healthy microbiota. When patients are treated with systemic antibiotic therapy, a transient increase in gut microbiota biodiversity may be observed due to overexpansion of microbial populations, mainly pathobionts that are not sensitive to the administered treatment [41, 42]. Stressful events such as exercise to exhaustion, may also promote increased gut microbiota biodiversity due to increased colonization and expansion of opportunistic pathogens at the expense of symbionts [22]. Thus, a finding of increased biodiversity in fecal microbiota should be carefully interpreted, especially in the light of which taxa are present and their relative abundance.

In mouse models of senescence or dementia, the association between gut microbiota biodiversity and cognitive performance has provided inconsistent results. For example, in a group of senescence-accelerated mouse prone 8 (SAMP8) mice exhibiting symptoms of severe cognitive dysfunction, the gut microbiota biodiversity measured by Chao1 and Shannon indices was significantly reduced in comparison with controls [43]. However, another study showed that older mice with mild symptoms of cognitive dysfunction exhibited an increased, rather than decreased, gut microbiota biodiversity in comparison with younger mice [44]. Antibiotic-induced reduction of gut microbiota biodiversity resulted in worsened cognitive performance of mice in one study [45] but was associated with reduced A β amyloid deposition in transgenic mouse models of Alzheimer's disease [46, 47]. In germ-free mice, harboring no intestinal microbiota, a massive reduction of A β amyloid brain deposition was also documented in comparison with controls [48].

In humans, the association between gut microbiota biodiversity and cognitive functions has been assessed in different settings. In patients with cirrhosis undergoing liver transplantation, a high gut microbiota diversity was associated with reduced risk of encephalopathy and thus cognitive symptoms [49]. However, species richness in gut microbiota was unable to predict long-term cognitive outcomes in a group of unselected patients with cirrhosis [50]. In obese subjects, the Shannon index of fecal microbiota was correlated with anatomical and functional parameters of brain magnetic resonance imaging (R2* and fractional anisotropy of the hypothalamus, caudate nucleus and hippocampus) and cognitive performance related to speed, attention and flexibility [51].

In a group of 85 HIV-infected subjects naïve to antiretroviral therapy, fecal microbiota biodiversity was significantly lower in the presence of HIV-associated neurological disease with cognitive symptoms [52]. However, this difference was not independent of educational level and HIV-infection-related clinical data, such as CD4 T-cell count, suggesting that gut microbiota dysbiosis is not pathophysiologically involved in the cognitive dysfunction [52].

In the largest human study to date, Verdi et al. [53] analyzed the fecal microbiota of 1551 individuals over the age of 40 and correlated microbial variables with the cognitive performance assessed by several tests (verbal fluency, Mini-Mental State Examination, Deary-Liewald Reaction Time test, Paired Associated Learning from the Cambridge Neuropsychological Test Automated Battery). Among the results of these tests, only the Deary-Liewald Reaction Time test score was inversely associated with alpha diversity independently of covariates, suggesting that the possible link between gut microbiota biodiversity and cognition may be mediated by several other environmental and host-related factors [53].

Fecal microbiota biodiversity was analyzed in patients with dementia in only three studies [13, 16, 54]. Araos et al. analyzed the fecal microbiota of 85 long-term-care facility residents with advanced dementia, demonstrating a very high level of dysbiosis with reduced species richness in all subjects [54]. Their results suggest that advanced dementia may be associated with low alpha diversity indices but the absence of a control group in the study design prevents solid conclusions. In another study performed in 25 patients with dementia and 25 controls, the Shannon index was significantly reduced in cases (Table 8.1) [13], supporting the possible association between reduced alpha diversity and cognitive symptoms. However, in the most recent and largest study comparing alpha diversity between 34 demented patients and 94 controls, Saji and colleagues documented that the Shannon index was significantly lower in controls, rather than in demented patients (Table 8.1) [16].

Overall, the current literature state-of-art does not support the use of fecal microbiota biodiversity indices as biomarkers of cognitive aging. The studies performed on this topic are too scarce, with reduced sample sizes, and have therefore provided inconclusive results with interpretations that may be challenging. However, they do suggest that an association between alpha diversity and cognitive symptoms may exist, although this is not independent of covariates. Future studies should better investigate this association, considering larger sample sizes, thorough selection of covariates and the use of longitudinal designs to assess whether variations in gut microbiome composition can predict variations in cognitive function.

2.2 *Firmicutes to Bacteroidetes Ratio*

Bioinformatics processing of next-generation sequencing metagenomics output allows identification of the number of bacterial taxa harbored in fecal samples as well as assignment of each of these to the corresponding taxonomic level and calculation of their relative abundance [35, 36]. These data are generally used to determine the relative abundance of the two most represented phyla in fecal microbiota, i.e., Bacteroidetes and Firmicutes, and their ratio. The Firmicutes/Bacteroidetes ratio is an index representing the overall qualitative composition of the fecal microbiota. The intestinal microbiota can in fact physiologically assume different states, called enterotypes, with a predominance of either Bacteroidetes or Firmicutes,

according to individual factors and dietary habits [55]. The Firmicutes/Bacteroidetes ratio increases from infancy to adult life and then declines again with senescence [56]. The predominance of Firmicutes in fecal microbiota composition has also been associated with the presence of metabolic imbalances, especially obesity, insulin resistance and metabolic syndrome [57, 58]. In fact, it generally increases with increasing body mass indices [59]. The Firmicutes/Bacteroidetes ratio has thus become an important parameter in the evaluation of the relationship between gut microbiota, obesity and obesity-related disorders [57].

An altered Firmicutes/Bacteroidetes ratio can however also represent an index of dysbiosis in other diseases, including dementia. In mice genetically prone to dementia (3xtg breed), gut microbiota analyses revealed a marked elevation of the Firmicutes/Bacteroidetes ratio compared to controls [60]. In mice with diet-induced obesity, over-expression of Firmicutes and reduced expression of Bacteroidetes was associated with impaired cognitive performance, especially in recognition memory and spatial memory tasks [61]. Finally, in older mice, an increase in the Firmicutes/Bacteroidetes ratio was associated with compromised cognition and increased anxiety behaviors, and this was not observed in younger mice [44].

The Firmicutes/Bacteroidetes ratio was calculated in human beings with dementia in only two studies, where it appeared significantly higher than in healthy controls [15, 16]. However, in a population of cognitively healthy older adults, Manderino et al. showed that greater proportions of Firmicutes and smaller proportions of Bacteroidetes in fecal microbiota were associated with better performances at cognitive tests [14].

Thus, the current literature state-of-art seems to support the concept that the presence of cognitive impairment may be associated with variations in the Firmicutes/Bacteroidetes ratio in fecal microbiota, making this parameter a promising potential biomarker of cognitive aging, deserving investigation in future studies. The capacity of this ratio to predict the onset and worsening of cognitive symptoms in human beings, and its association with obesity and metabolic imbalance should be particularly assessed.

2.3 Abundance of Specific Taxa in Fecal Microbiota

Apart from the overall composition of the fecal microbiota, variations in the representation of specific taxa may show a significant association with the presence of cognitive symptoms. The outputs of metagenomics analyses and their bioinformatics elaborations generally retrieve, for each detected bacterial taxon, a ratio of relative abundance, representing the proportion of bacteria belonging to that taxon on the total bacterial load of the sample [28]. Thus, these relative abundances do not represent the absolute quantities of bacteria harbored in each sample, and this concept should be considered for interpreting any result [28]. However, relative abundances could represent promising biomarkers of health status, especially if their association with diseases is reproducible across different studies.

The main bacterial taxa found over-represented or under-represented in fecal samples of either patients or animal models with cognitive symptoms, cognitive impairment or dementia, according to the current literature state-of-art, are summarized in Table 8.2. The findings of studies on mouse models [43, 60, 62–64] showed some degree of inconsistency. For example, in mice with cognitive impairment, Christensenellaceae and Ruminococcaceae were found to be depleted in one study [43] and over-represented in another [60]. However, depletion of Bifidobacteria and over-representation of Anaeroplasmatales were both associated with dementia in two studies [60, 63]. The largest study which compared senescence-accelerated mouse prone 8 with senescence-accelerated mouse resistant 1 breeds, showed that the presence of cognitive symptoms was associated with depletion of 26 taxa and over-representation of only one taxon [43].

Human studies which investigated the relative abundances of specific microbial taxa in fecal microbiota composition in relation to cognitive performance were performed in healthy subjects [19, 53, 65, 66], patients with cirrhosis [67–69], Parkinsonism [70, 71], or dementia/cognitive impairment [12–16]. An overview of taxa that resulted in significant differences between subjects with and without signs of cognitive dysfunction is presented in Table 8.2. In a large population of twins aged 40 or older, Verdi and colleagues showed that under-representation of taxa belonging to the Burkholderiales order was associated with worse performance at cognitive tests independently of covariates such as frailty and treatment with proton pump inhibitors [53]. These findings suggest that microbiota depletion of Burkholderiales may represent a promising biomarker of cognitive aging, although the cross-sectional design of the study prevents drawing any conclusions on prediction of cognitive outcomes. In their studies on patients with cirrhosis, Bajaj and colleagues found other putative microbial biomarkers of cognitive impairment [67–69], namely Alcaligenaceae, Porphyromonadaceae and Enterobacteriaceae with positive associations, and Lactobacillales and Lachnospiraceae having negative associations with the condition (Table 8.2). These studies provide interesting data on the possible usefulness of gut microbiota-related parameters for predicting cognitive outcomes. However, they were conducted using a population of patients exhibiting a high burden of gut microbiota dysbiosis, due to cirrhosis. Therefore, their results may not be immediately transferred to the elderly population with cognitive impairment or dementia.

Decreased relative abundance of Lachnospiraceae, *Butyricoccus* and *Clostridium* XIVb, and increased relative abundance of Lactobacillaceae and Christensenellaceae were associated with the presence of cognitive impairment in two distinct studies performed on patients with Parkinsonism [70, 71]. Interestingly, a decreased relative abundance of Lachnospiraceae associated with cognitive symptoms was also observed in patients with cirrhosis and, most importantly, in one of the few studies specifically conducted in the field of human dementia [15, 69]. Similarly, a decreased relative abundance of *Clostridium* XIVb was also detected in the study by Vogt and colleagues [13], in which the fecal microbiota of 25 patients with Alzheimer’s disease was compared with that of 25 healthy controls (Table 8.1).

Table 8.2 Overview of the main bacterial taxa found as over- or under-represented in the fecal microbiota of animal models or human beings with cognitive symptoms, cognitive impairment or dementia

Mouse studies		Human studies	
Over-representation in cognitive impairment/dementia	Under-representation in cognitive impairment/dementia	Over-representation in cognitive impairment/dementia	Under-representation in cognitive impairment/dementia
Anaeroplasmatales [60, 64]	<i>Bifidobacterium</i> [60, 64]	Alcaligenaceae [67]	<i>Adlerkreutzia</i> [13]
<i>Anaerostipes</i> [64]	Christensenellaceae [43]	<i>Alisipes</i> [13]	Bacteroidaceae [15, 16]
Christensenellaceae [60]	<i>Desulfovibrio</i> [43]	<i>Bacteroides</i> [13]	<i>Bifidobacterium</i> [13]
Cyanobacteria [64]	Lachnospiraceae [43]	<i>Bilophila</i> [13]	Burkholderiales [53]
Erysipelotrichaceae [63]	<i>Prevotella</i> [43]	<i>Blautia</i> [13]	<i>Butyrivococcus</i> [70]
<i>Helicobacter</i> [65]	Ruminococcaceae [43]	<i>Caldiserica</i> [66]	<i>Clostridium</i> XIVb [13, 69, 70]
<i>Odoribacter</i> [65]	<i>Subdoligranulum</i> [43]	Christensenellaceae [71]	<i>Dialister</i> [13]
Proteobacteria [63]		Enterobacteriaceae [68]	<i>Eubacterium</i> [12]
Ruminococcaceae [60]		Enterococcaceae [15]	Lachnospiraceae [15, 69, 71]
<i>Sutterella</i> [63]		<i>Escherichia/Shigella</i> [12]	Lactobacillales [68]
Tenericutes [64]		<i>Gemella</i> [13]	<i>Parabacteroides</i> [19]
<i>Turricobacter</i> [60]		<i>Helicobacter</i> [72]	<i>Phascolarctobacterium</i> [19]
		Lactobacillaceae [71]	Ruminococcaceae [19, 69]
		<i>Phascolarctobacterium</i> [13]	<i>Turricobacter</i> [13]
		Porphyromonadaceae [67, 68]	Veillonellaceae [15]
		Prevotellaceae [65]	Verrucomorbia [14]
		Proteobacteria [14]	
		Ruminococcaceae [15, 65]	
		Tenericutes [66]	
		<i>Thermodesulfobacterium</i> [66]	

Some taxa are listed both as over- or under-represented because of some inconsistency across the results of different studies

Thus, the abundance of Lachnospiraceae and Clostridium XIV b may deserve greater attention in future studies as possible biomarkers of cognitive aging.

The study by Vogt and colleagues [13] was also the most accurate one to date in the identification of microbial taxa with altered relative abundance in Alzheimer's disease, and with significant correlation of these with other biomarkers, including p-tau and β -amyloid deposition. Specifically, the relative abundance of *Blautia*, *Bacteroides*, *Phascolarctobacterium*, *Alistipes*, *Bilophila* and *Gemella* was increased in Alzheimer's disease, while the relative abundance of *Clostridium*, *Bifidobacterium*, *Dialister*, *Adlerkreutzia* and *Turicibacter* was decreased [13]. Future, larger studies should better clarify whether these bacteria may assume the role of microbial biomarkers of dementia or cognitive impairment.

It is also noteworthy that a significant association between the representation of some taxa in the fecal microbiome and imaging biomarkers of cognitive dysfunction [66] or genetic risk factors for Alzheimer's disease (APOE polymorphisms) [65] has been detected in two distinct studies. Other investigations recently reviewed by Franceschi et al. [72] also suggest that the presence of *Helicobacter pylori* in the intestinal microbiome could be involved in the development of Alzheimer's disease, by promoting systemic chronic inflammation or molecular mimicry mechanisms. These aspects will need further confirmation in future studies but may represent the bases for the discovery of other microbial biomarkers of dementia and cognitive impairment.

In summary, the current literature state-of-art suggests a list of possible gut microbiota-related biomarkers of cognitive aging, shown in Table 8.2. However, the evidence is too scarce to recommend the use of fecal microbiota analyses as a method to identify the risk of cognitive impairment or dementia. In addition, these studies were conducted in heterogeneous settings, included small numbers of participants and had a cross-sectional design, preventing study of the association of microbiome composition with clinical outcomes. Finally, some inconsistencies are present among the results of different studies, reinforcing the need to develop larger and sounder investigations in this field.

3 Microbiota-Related Metabolites as Biomarkers of Cognitive Function

3.1 The Role of Microbial Metabolites as Biomarkers in the Gut-Brain Axis

Many substances synthesized by components of the gut microbiota, either as metabolic byproducts or constituents of bacterial structures, may have a role in influencing the gut-brain axis functionality in cognitive function [10]. These substances, their characteristics and possible pathophysiological relevance have been recently reviewed by many authors [73–77]. These include neurotransmitters [73, 74],

metabolites derived by amino acid catabolism [75], short-chain fatty acids (SCFAs) and other lipids [76], components of the outer membrane of bacteria [76] and even bacterial amyloid proteins [77]. Despite their possible involvement in the development and course of dementia, only a limited number of them could have potential usefulness as biomarkers of cognitive aging. In fact, neurotransmitters, such as acetylcholine, norepinephrine, histamine and γ -aminobutyric acid, are also synthesized by the host, and their microbial origin cannot be easily detected with standard laboratory methods [73]. Bacterial amyloid proteins may be involved in the pathophysiology of Alzheimer's disease by promoting the formation of β -amyloid protein aggregates in the brain by molecular mimicry but they cannot easily be detected in biological samples [77]. Metabolites derived by amino acid catabolism and SCFAs have recently received considerable attention by researchers and show, in some cases, correlations with cognitive function [75, 76]. However, some technical issues associated with laboratory methods of detection are currently limiting their study and implementation in clinical practice.

Along with substances synthesized by the intestinal microbiota, there are also a number of substances derived from diet and transformed by certain metabolotypes of gut microbiota that may have a relevant pathophysiological involvement in the gut-brain axis [8, 10]. However, since the intake of the precursors of these substances is variable and not easy to standardize in the diet, their use as biomarkers is in doubt. The most known of these substances is trimethylamine N-oxide (TMAO), which is produced by the metaorganismal metabolism of dietary choline and has been implicated in the pathogenesis of several human diseases, including cardiovascular, cerebrovascular and metabolic diseases [78]. Other microbial products of nutrients introduced with diet include polyphenol metabolites and urolithins [8]. Finally, recent studies link cognitive performance to vitamin K status, which is partly produced by the intestinal microbiota [79], so that vitamin K metabolism may represent another promising area of research in the field of cognitive aging.

The putative biomarkers of cognitive aging derived by microbiota metabolism can be detected in several biological samples, ranging from blood to cerebrospinal fluid to feces. In fact, most of the substances produced by gut microbiota are absorbed into the systemic circulation and can be detected in blood. This phenomenon is particularly enhanced in the presence of a "leaky gut". This means that increased intestinal mucosa permeability is caused by inflammatory conditions of the gastrointestinal tract or by the presence of an extreme gut microbiota dysbiosis [80].

From the systemic circulation, some microbiota-derived substances may reach the central nervous system and may be best detected in cerebrospinal fluid samples. Some investigators have also studied metabolic byproducts of intestinal bacteria in stool samples, since their concentration may be directly related to the microbiota composition and functionality. SCFAs are among the most studied microbiota-derived biomarkers of disease in stool samples [81]. However, these molecules show low stability in fecal samples leading to huge intra-individual variability, depending on the timing of analyses after sample collection [81].

3.2 Structural and Functional Components of Bacteria as Biomarkers of Cognitive Aging

The structural and functional components of gut microbiota that have been detected in biological samples of the host and related with the onset of cognitive dysfunction or dementia, include lipopolysaccharide (LPS) and rhamnolipids (Table 8.3). LPS can be detected in human blood samples at low concentrations even in the absence of bacteremia or sepsis. This phenomenon is an expression of gut microbiota

Table 8.3 Overview of the main bacterial products or metabolites that may be potentially useful as biomarkers of cognitive aging and dementia, according to the current scientific literature

Possible biomarker	Category/Origin	Biological sample of detection	Comment
Lipopolysaccharide	Constituent of bacterial wall, exotoxin	Blood Cerebrospinal fluid Brain biopsies	Increased in case of altered gut mucosa permeability or gut microbiota dysbiosis; Enhances neuroinflammation
Rhamnolipids	Constituent of bacterial wall, exotoxin	Blood Cerebrospinal fluid	Found in cerebrospinal fluid and blood in only one study, promote inflammation
Kynurenine Kynurenic acid 3-hydroxy-kynurenine	Products of amino acid metabolism (tryptophan)	Blood	Only indirectly influenced by gut microbiota metabolism of tryptophan
Indole-3 acetic acid Indoxyl sulfate	Products of amino acid metabolism (tryptophan)	Blood	Products of microbiota-driven degradation of tryptophan; Uremic toxins found in advanced chronic kidney failure
NADH:Ubiquinone reductase	Bacterial enzyme	Feces	Enzyme related to bacterial synthesis of tryptophan through the shikimate pathway
Acetate, butyrate, propionate	Short-chain fatty acids	Blood Feces	Products of bacterial metabolism of carbohydrates; Show neuroprotective, anti-inflammatory and pro-anabolic effects
Deoxycholic acid	Bile acid	Blood Feces	Concentrations depend on the gut microbiota metabolism of bile acids
Trimethylamine-N oxide	Product of microbial metabolism of dietary choline	Blood Cerebrospinal fluid	Marker of increased cardiovascular and cerebrovascular risk
Polyphenol metabolites	Product of microbial metabolism of nutrients	Blood	Effect depends on the individual metabolotype (composition and functionality of gut microbiota)
Vitamin K	Bacterial cofactor	Blood	Possibly influencing cognitive function; role not yet assessed in relation to microbiota

dysbiosis or altered intestinal permeability, and causes chronic subclinical activation of inflammation that is involved in the pathophysiology of several non-communicable diseases, including atherosclerosis, diabetes and obesity [82]. Since inflammation is also an important mechanism triggering age-related cognitive impairment and the onset of dementia, some researchers have investigated the possible association between the presence of LPS in biological samples of the host and dementia [10].

In mice with diet-induced obesity, an association between reduced performance at recognition and spatial memory tasks and increased serum levels of LPS was detected [61]. These findings were confirmed by an intervention study where genistein was administered in association with a high-fat diet to mice [83], suggesting that LPS levels may be inversely correlated with cognitive performance. However, the intracerebral injection of LPS in mouse models of Alzheimer's disease did not induce significant alterations in cognitive function [84].

Human serum levels of LPS have not been associated with cognitive performance by any study to date. However, investigations on brain biopsies have demonstrated that lysates from the hippocampus and superior temporal lobe neocortex of patients with Alzheimer's disease had significantly higher concentrations of LPS than brain lysates from non-demented controls [85–87]. Therefore, the relationship between LPS and cognitive performance in humans deserves more investigations and LPS could represent a promising biomarker of cognitive health.

Andreadou et al. have also demonstrated that rhamnolipids, other bacterial virulence factors possibly derived from the gut microbiota, exhibit higher serum and cerebrospinal fluid levels in patients suffering from Alzheimer's disease than in non-demented controls [88]. These findings have not been replicated in other studies but the role of rhamnolipids as a possible biomarker of cognitive aging and pathophysiology of dementia should be investigated.

3.3 Microbiota, Amino Acid Metabolism and Cognitive Aging

Studies performed in mice have demonstrated that the decline of cognitive performance is associated with a distinct metabolic profile in serum and in the brain [44, 60]. In mouse genetically prone to dementia, an overabundance of ketone bodies, lactate and amino acids and depletion of unsaturated fatty acids and choline, was demonstrated in serum and feces, suggesting a role of the intestinal microbiota metabolism in driving these changes [60, 65]. Brain metabolomics of aged mice showed significantly lower concentrations of amino acids (including methionine, phenylalanine, cysteine and creatine) and lipidic cofactors (including hydroxycholesterol, prostaglandins, phosphocholine and docosapentaenoate) than control young mice [44]. Part of these brain metabolic signatures may be directly influenced by the gut microbiota. In fact, older mice with signs of cognitive impairment had significantly higher brain levels of two metabolites related to microbial metabolism of the amino acid tryptophan, i.e., 3-indoxyl-sulfate and phenol sulfate,

compared to young mice [44]. Interestingly, these metabolites have been associated with neurological toxicity and inflammation [89]. In patients who underwent bone marrow transplantation, the levels these molecules were predictive of clinical outcomes, reflecting the presence of gut microbiota dysbiosis [90].

The metabolism of tryptophan has also been associated with brain function in humans. Aging is associated with reduced serum levels of tryptophan and increased activation of the main human metabolic pathway of tryptophan degradation, i.e. the kynurenine pathway [91]. The serum levels of some kynurenine pathway intermediates, such as kynurenic acid and 3-hydroxykynurenine, have also shown a positive association with the level of cognitive impairment [91]. In a recent large population-based study, the kynurenine-tryptophan ratio was inversely associated with the performance at the Kendrick Object Learning Test and Controlled Oral Word Association Test [92]. These findings can be explained by a possible neurotoxic effect of kynurenine pathway intermediates.

Gut microbiota can contribute to tryptophan degradation with its own metabolic pathways. The most studied intermediate is indole-3 acetic acid (IAA), which is known as one of the main uremic toxins in patients suffering from chronic kidney failure [93]. Serum IAA levels were found to be negatively associated with Mini-Mental State Examination test score in patients undergoing chronic hemodialysis [94] and with depressive symptoms in subjects with severe chronic kidney disease not undergoing hemodialysis [95]. Another intermediate of microbial tryptophan degradation is indoxyl sulfate, which showed serum concentrations that were associated with poor executive functions in a group of 199 patients with early-stage chronic kidney disease [96]. Interestingly, indoxyl sulfate is able to induce apoptosis in human astrocytes, suggesting a possible involvement of this microbiota-derived metabolite in the pathophysiology of dementia [97].

Moreover, tryptophan is autonomously produced by bacteria through the shikimate pathway, a seven-step metabolic route allowing the synthesis of aromatic amino acids from two intermediates in carbohydrate metabolism, i.e., phosphoenolpyruvic acid and erythrose 4-phosphate. In a study performed on 20 patients with Alzheimer's disease and 5 healthy controls, Paley et al. were able to identify gut bacterial gene sequences unique to patients with Alzheimer's disease, belonging to the enzyme NADH:Ubiquinone reductase that is related to the optimal functioning of the shikimate pathway [98]. These findings suggest that the gut microbiota of patients with Alzheimer's disease may have an enhanced production of tryptophan through the shikimate pathway and that this phenomenon may have relevance in the physiopathology of dementia.

In summary, the current scientific literature does not provide sufficient data to recommend the adoption of bacterial products of amino acid metabolism as biomarkers of cognitive aging. However, the complex interplay between the gut microbiota and the host in tryptophan metabolism may have relevance in the field of cognitive impairment and should be further investigated in the future. Kynurenine, kynurenic acid, 3-hydroxykynurenine, IAA and indoxyl sulfate could represent good candidates as biomarkers of cognitive aging.

3.4 *Microbiota-Derived SCFAs and Cognitive Aging*

SCFAs, namely acetate, butyrate and propionate, are among the most studied metabolic products of the gut microbiota. They are derived from dietary carbohydrates and absorbed into the systemic circulation, where they can exert a wide range of physiologic functions, including control of body weight, regulation of insulin sensitivity, regulation of inflammation and immune system activation [99, 100]. These mechanisms may have particular relevance for central nervous system diseases, in which inflammation is also involved in the pathogenesis of Alzheimer's disease [101]. Butyrate has been implicated as a central mediator of the possible gut-brain axis, and the effects of the administration of butyrate or butyrate-producing bacteria on brain functions have been investigated through several animal studies, recently reviewed by Stilling and colleagues [102]. However, few of these studies were focused on dementia or cognitive impairment and, therefore, their clinical relevance remains uncertain.

In a study performed in mice, Fröhlich and colleagues demonstrated that the administration of antibiotics to induce a deep gut microbiota dysbiosis, was associated with cognitive dysfunction and lower colonic concentrations of SCFAs compared to administration of placebo [45]. Conversely, the administration of a symbiotic (*Enterococcus faecium* plus inulin) in a mouse model of cognitive aging was associated with an increase in the fecal concentration of butyrate and better cognitive performances than the placebo [103]. The administration of a butyrate-producing species, *Clostridium butyricum*, as a probiotic to mouse models of vascular dementia and cerebral ischemia/reperfusion injury resulted in improved cognitive function or reduced neurologic deficits [104, 105]. In another study, the administration of *Bifidobacterium breve* strain A1, a metabolically active strain able to produce acetate, to an Alzheimer's disease mouse model resulted in improvements in cognitive function or in a less pronounced cognitive decline [106].

These data globally indicate that SCFAs, and particularly butyrate, could play an important physiopathological role in cognitive impairment, and thus may represent good biomarkers of cognitive aging. Fecal samples of patients with Alzheimer's disease are generally abundant in butyrate-producing bacteria [107] but no comparison with healthy controls is currently available on this specific point. The role of SCFAs as biomarkers of cognition in older subjects should thus be more investigated in future studies. Unfortunately, the volatile nature of these compounds makes them difficult to detect in human samples, and analyses generally show a low degree of reproducibility [81].

3.5 *Other Microbiota-Derived Compounds and Cognitive Aging*

3.5.1 **Bile Acids**

Bile acids are not a primary product of intestinal microbiota but their metabolism is influenced by the microbiome composition and functionality. In fact, dysbiosis can be associated with important alterations of bile acid metabolism, contributing to the

pathogenesis of several diseases [108]. Tauroursodeoxycholic acid, a bile acid found in bears and subject to gut microbiota metabolism, showed neuroprotective properties especially in animal models of Huntington's disease [109]. These properties have also been recently demonstrated in mouse models of dementia, in which the administration of tauroursodeoxycholic acid was able to slow down amyloid precursor protein processing and amyloid- β deposition [110, 111].

These data have raised speculations that other bile acids produced by humans and subject to gut microbiota metabolism, may have a role in the pathophysiology of dementia and could serve as biomarkers of cognitive aging. Olzarán and colleagues were able to identify a metabolic fingerprint of Alzheimer's disease by analyzing plasma samples of a large group of patients with mild cognitive impairment or dementia [112]. Interestingly, they found that the concentrations of one bile acid (deoxycholic acid) were independently associated with the presence of cognitive symptoms [112]. Another recent study showed that specific bile acid profiles in serum were associated with other well-established biomarkers of Alzheimer's disease normally found in the cerebrospinal fluid (amyloid β_{1-42} and p-tau₁₈₁) and with imaging markers of brain atrophy [113], reinforcing a possible role of bile acids as microbiota-derived biomarkers of cognitive aging.

3.5.2 TMAO

TMAO is a metabolic product derived from microbial metabolism of dietary choline and serum levels of this molecule have been associated with an increased risk of atherosclerosis in animal models and human beings [78]. Thus, it has been considered as a marker of risk of vascular dementia [78]. However, recent studies have highlighted that it may also have relevance in the pathogenesis of Alzheimer's disease. First, the administration of exogenous TMAO to mice genetically prone to dementia resulted in an increased number of senescent cells in hippocampus, reduced synaptic plasticity-related protein expression and reduced cognitive performance [114]. Moreover, in a large sample of older patients, either with Alzheimer-type dementia, mild cognitive impairment or no cognitive symptoms, the levels of TMAO detected in cerebrospinal fluid were significantly different according to cognitive status and related with other biomarkers of Alzheimer's disease (i.e., phosphorylated tau, total tau and neurofilament light chain protein) [115]. Thus, the elevation of TMAO in cerebrospinal fluid may represent a promising biomarker of cognitive dysfunction.

3.5.3 Polyphenols

Dietary polyphenols have been associated with reduced risk of a large number of cardiovascular disorders, based mainly on studies *in vitro* [116]. These compounds are generally metabolized by the gut microbiota into a large number of substances that may exert a protective function against neurodegeneration, and there is

interest in these molecules as potential biomarkers of cognitive aging. For example, 3-hydroxybenzoic acid and 3-(3'-hydroxyphenyl)propionic acid, two metabolites derived from microbiota degradation of anthocyanidins contained in grape seeds, accumulate in brain tissues of rats and exhibit the capacity of interfering with the assembly of β -amyloid into neurotoxic aggregates [117]. Polyphenol metabolites can also modulate cognitive resilience in mice, but this capacity is dependent on the gut microbiota composition and functionality, the so-called metabotype [118]. Therefore, the administration of polyphenols as food supplements or nutraceuticals may have different effects in different individuals, depending on the gut microbiota.

An example of this inter-individual variability of polyphenol metabolism, depending on gut microbiota composition, is the ellagitannins, a group of polyphenol compounds found mainly in pomegranates and walnuts [119, 120]. In human beings, two different gut microbiota metabotypes (A and B) have been identified, and each of these is able to produce different metabolites from ellagitannins, called urolithin-A and urolithin-B, respectively [119, 120]. Urolithin-A has been associated with reduced cardiometabolic risk factors and with beneficial health effects, unlike urolithin-B [119]. Thus, the gut microbiota urolithin-related metabotype may contribute to the observed variability of health benefits of pomegranate extracts found in humans [120].

A recent study performed in APP/PS1 mouse models of Alzheimer's disease has demonstrated that the administration of urolithin A ameliorated cognitive performance and positively influenced several pathophysiological mechanisms of dementia, including amyloid- β deposition, neuronal apoptosis and neuroinflammation [121]. Urolithin A also seems to be able to enhance mitophagy, which is a mechanism protecting against cognitive impairment [122]. In a small human randomized trial, the administration of 8 ounces of pomegranate juice for 4 weeks to older patients reporting cognitive complaints resulted in a significant improvement in verbal memory tasks, which was paralleled by a significant increase in plasma concentrations of urolithin A-glucuronide [123]. These data underline the point that urolithin A and urolithin A-metabotype of gut microbiota may represent interesting biomarkers of cognitive aging via identification of a subset of patients that are susceptible to nutritional intervention.

3.5.4 Vitamin K

Vitamin K metabolism and the administration of vitamin K antagonists as oral anti-coagulants have been recently studied as possible risk factors for cognitive decline in older individuals [124, 125]. Some studies support a positive association between vitamin K levels and cognitive performance [79, 124], while the administration of vitamin K antagonists to rats resulted in altered cognition [126]. However, the effect of vitamin K antagonists on cognitive function may depend on the pathophysiological mechanism of dementia, as it may be protective in cerebrovascular forms of dementia [125] and probably detrimental in neurodegenerative forms [79, 124]. Patients with cognitive impairment who need the administration of vitamin K antagonists are more likely to have multimorbidity and more severe forms of cognitive

dysfunction at baseline, so that the putative association between vitamin K antagonists and progression to dementia may be spurious [127]. In this scenario, the intestinal microbiome could play an important role, since vitamin K is physiologically produced by intestinal bacteria [128]. However, no study has investigated the correlation between production of vitamin K by the gut microbiota and cognitive outcomes to date. Vitamin K could however represent another promising biomarker of cognitive aging meriting future investigations.

4 Conclusions

Gut microbiota composition and microbiota-derived metabolites or substances represent a promising area of research for the identification of novel biomarkers of cognitive aging. However, the current literature state-of-the-art does not support the implementation of microbiome-related biomarkers of cognitive aging for use in clinical practice. The study of the relationship between gut microbiota composition and functionality in mild cognitive impairment and different types of dementia should be translated from animal models to patients. In addition, these studies should be focused on alpha diversity, Firmicutes/Bacteroidetes ratio, abundance of specific key taxa and microbial metabolism of amino acids, SCFAs, bile acids, vitamin K and nutrients such as polyphenols and choline.

The use of new microbiome-related biomarkers of cognitive aging could bring to several advantages. If these biomarkers show alterations in the early phases of dementia, they could assist physicians in the diagnostic process, or even lead to early diagnosis. They could also help identifying those patients with a quicker evolution towards dementia, deserving more aggressive treatments and strict follow-up. From the patient's perspective, it could bring improved management of cognitive diseases and give important information on neurological diseases, facilitating a comprehensive classification of health status. Finally, it could also have economic relevance, since the microbiome analyses are generally less expensive than brain imaging examinations. For all these reasons, more research is urgently needed in this field.

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